Examples of select and categorise case studies

(based on the mock exams)

Qualified Patent Information Professional

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Please note: it is to be understood that the sample answers provided in this document are intended to serve as a guide and by no means represent definitive answers. It is entirely possible that additional answers not specifically disclosed in this document could be considered as satisfactory answers.

The general advice for all candidates

Candidates shall accept the facts given in the examination paper and limit themselves to those facts. Whether and to what extent those facts are used shall be the responsibility of each candidate. Candidates shall not use any special knowledge they may have of the technical field of the invention.

Case study 1 - Novelty

You have recently been employed by a global food company, HealthChoice. The company has spent $500,000 dollars developing a high fibre and great tasting bread that is marketed as SonnePan. The bread contains tiny encapsulated particles that release both live *Lactobacillus acidophilus* culture as well as the daily recommended dose of dietary fibre directly in the intestines of the person or animal that consumes it. The food scientists at HealthChoice have managed to create the nutritional particles for the bread by encapsulating a dietary fibre and pro-biotic bacteria within a sugar based shell using a spray-drying process.

On 19 December 2000, HealthChoice filed worldwide the enclosed patent application directed at SonnePan which claims priority from the enclosed priority document that was filed on 22 December 1999. The patent application is currently pending in all countries. Health Choice is about to close a $30 million dollar deal that would involve selling all its rights relating to SonnePan to Puritan Foods. Before Puritan Foods will sign the deal they have asked HealthChoice's CEO for supporting evidence of his assertion that the claims will be granted as filed because in the CEO's opinion "there is no relevant prior art". The CEO has approached you to conduct a novelty search to verify his assertion. You have conducted the search and the final results of your search are attached as Annex 3.

Please report your findings to the CEO by categorising the results, according to whether you consider each document relevant or irrelevant, on the basis of novelty only. Please explain the reasons for how each document has been categorised.

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Annex 1 (Sonnepan Patent Application)

Encapsulated Multifunctional Biologically Active Food Component

The invention relates to a multifunctional encapsulated biologically active food component which consists of a core that comprises at least one dietary fiber, which core is surrounded by at least one biologically active substance and in which the core and the biologically active substance are surrounded by at least one shell-forming substance. The stability of the multifunctional food component is based on interactions of the components with one another.

BACKGROUND OF THE INVENTION

[0002] Biologically active substances in nutrition are physiologically important components. They can have the most varied functions in the organism and as a result make a positive contribution to health. Biologically active substances can act, for example, as classical nutrients, can stimulate immune activity or have protective activity or intervene in physiological processes in the body. Biologically active substances can include, inter alia, probiotic microorganisms, prebiotic substances, nutrients or secondary plant constituents. Enrichment of the diet with components of this type in a stable and in particular bioavailable form is therefore desirable from the nutritional aspect.

[0003] Dietary fibers are a heterogeneous product group. Many dietary fiber preparations are based on plant fibers and consist predominantly of water-insoluble polysaccharides in addition to pectin, lignin and plant gums (for example wheat fibers, oat dietary fibers, rice dietary fibers, apple fibers, citrus dietary fibers etc.). In addition there are also soluble dietary fibers which are mostly made up of complex carbohydrates (for example fructo-or galactooligosaccharides, β-glucans etc.). Dietary fibers taken in via the diet are distinguished by the fact that they are indigestible constituents for humans. Because of their inert character, dietary fibers reside in the intestine and can there optimally exert their physiological effects, for example increasing intestinal peristalsis, effects on cholesterol absorption, prebiotic activities etc. An increased intake of dietary fibers is desirable for nutritional reasons. A daily intake of 25-30 g of dietary fiber is recommended by nutritionists.

[0004] For the reasons described it is expedient to provide dietary fibers and biologically active substances in a stable and nutritionally utilizable form via the diet or other delivery route to the organism. An optimal release of the biologically active substances, for the reasons described above, is not desirable until after passage through the stomach in the lower digestive tract. Furthermore, it is desirable that adverse sensory perceptions of nutritionally valuable substances in foods do not occur. This is, in the case of insoluble dietary fibers, frequently a marked sensory perception of particles in the food matrix ("scratchy off-taste").

[0005] The technique of microencapsulation has long been used commercially predominantly in the pharmaceutical industry. For some time, however, there have also been studies on the use of encapsulation in food technology (Jackson, Lee, 1991, Kanawija et al. 1992, Hegenbart, 1993, Arshady, 1993, Dewettinck, 1997, Pegg, Shahidi, 1999). The spray-drying process is one of the most frequently used processes for encapsulating various

substances in the food industry. It can be considered as one of the essential advantages here that spray-drying is suitable for processing heat-sensitive materials. In addition, the process is inexpensive and offers the advantage that an existing technology can be utilized. In order to make possible targeted utilization for the various application sectors in the food industry, studies of the customary materials in different combinations would have to be carried out, since single materials cannot comply with the complex requirements which a food makes of the capsule material. Studies to date were concerned predominantly with decreasing the volatility of substances and their oxidation by embedding them into a suitable material. The effects resulting from the physicochemical properties of the capsule materials and of the physical conditions of this process require further study (Re, M. I., Drying Technology, 1998, 16(6), 1195-1236).

[0006] Most patents or patent applications relate to fields of application in the pharmaceutical industry. The major roles are taken here by the capsule materials used (generally in combination with specific activities or effects), the controlled release of substances via the application of the encapsulating technique and the stabilization of substances. In the food sector there are far fewer patents, which, however, are essentially determined by these three directions. In the case of microencapsulation of cells or cell free extracts (CFE), physiological stability in combination with their use as a pharmaceutical product play the major roles.

[0007] Microencapsulation with the purposes of a) use of dietary fibers, in particular fibers as a support material for biologically active substances, in particular microorganisms with simultaneous increase of the nutritional value, b) support material/microorganism interactions, c) prevention of support material/capsule material interactions, d) stabilization of the biologically active substances in the product and in the food with correspondingly extended shelf life, has not been described to date.

[0008] Immobilization of lactococcus, which are less sensitive than lactobacillus species, is possible in a matrix made of alginate/polyamino acids. In this experiment a study was to be made as to what extent the stabilization, handling and storage of microorganisms may be improved by the immobilization. Lactic acid production, as an indicator of metabolic activity, was reduced, however, after handling and storage of the microorganisms in comparison with microorganisms which had not been embedded. No information was provided, however, on interactions of the capsule material with its direct environmental surroundings (for example foods) or with the microorganisms or the use of support materials (Larisch, B. C., Poncelet, D., Champagne, C. P., Neufeld, R. J., J. Microenc., 1994, Vol. 11, No. 2, 189-195).

[0009] The encapsulation of lactic acid bacteria of the genera Streptococcus, Lactobacillus, Pediococcus, has also been achieved in various materials using extrusion. In this case a study was made of the viability of the encapsulated organisms in acidic media simulating the gastrointestinal tract and of the shelf life and stability of the encapsulated microorganisms at various temperatures. It was found in this case that the survival rates depend on the physicochemical properties of the capsule materials. The shelf-life studies at different temperatures found increased survival rates of the encapsulated organisms at temperatures above 22° C. in comparison with the unencapsulated bacteria. No statements were made about metabolic performance and/or metabolic activity. (Kim, H. S., Kamara, B. J., Good, I. C., Enders Jr., G. L., J. Indust. Microbiol., 1988, 3, 253-257).

[0010] Encapsulation techniques for lactic acid bacteria are also described in various patents. WO-A 9716077 refers to probiotic formulations which can be used as food ingredients. In this case the microorganisms are mixed with a second substance as carrier or shell substance, which in the latter case leads to an improved stability to passage through the stomach. Production processes for formulations to increase the stability of such probiotic microorganisms in the gastrointestinal tract are also described in CN-A 1113515, CN-A 1124773, WO-A 9920745 or WO-A 9952511. In these cases, especially, encapsulation techniques are used in order to protect the microorganisms against gastric acid. A disadvantage of these processes is that the resultant formulations are not stable in most food applications.

[0011] WO-A 9608261, WO-A 9734615 and WO-A 9734592 describe the microencapsulation of probiotic microorganisms with modified and unmodified starches. In these cases the starch acts as transport medium for the probiotic microorganisms into the stomach. WO-A 9826787 describes a method in which improved passage through the gastrointestinal tract for probiotic microorganisms is achieved using β-glucan as support.

[0012] The spray-drying process can also be used to increase the stability and storage life of bacteria. Thus in the agricultural field, in the case of seed material, by spray-drying a strain of rhizobacteria, improved preservation and protection of the seed material against infection with disease and premature germination are achieved. Encapsulation was achieved using spray-drying with the use of various materials all of which except for one combination (modified starches) are not permitted for the food sector. (Amiet-Charpentier, C., Gadille, P., Digat, B., Benoit, J. P., J. Microenc., 1998, Vol. 15, No. 5, 639-659).

[0013] In the food sector, lactic acid bacteria were also stabilized via various drying processes. Thus WO-A 9957242 describes a process which gives preparations suitable for foods made from lactic acid bacteria with additional carbon-dioxide-generating additives via various drying processes. Increased stability of encapsulated microorganisms was demonstrated when algal polysaccharides were used as capsule material. In this case the aerobic microorganisms were embedded into the capsule material by crosslinking. The resultant microorganisms can be used in the environmental sector and displayed similarly good performance with respect to PCP degradation as non-embedded microorganisms. (Hammill, T. B. , Crawford, R. L., Can. J. Microbiol., 1997, 43, 1091-1095).

[0014] A disadvantage of the above described processes and substances is that they are not stable in most food applications. When in particular microorganisms are added to foods, the resulting survival rates of the microorganisms are still too low to develop nutritional effects. Furthermore, with many biologically active formulations, adverse sensory perceptions occur. In addition, it is disadvantageous that the biologically active formulations, although they can pass to their destination (intestine), because of the pH, they cannot fully develop their activity there.

[0015] The object of the present invention was therefore to provide a system which simultaneously

[0016] prevents an interaction with the surrounding food (for example in some cases prevents unwanted swelling properties of the dietary fibers)

[0017] provides nutritionally valuable substances without adverse sensory perceptions,

[0018] ensures increased storage stability of nutritionally valuable substances and

[0019] optimizes the quantitative supply and localization of release of the biologically active substances at the desired site (optimized bioavailability).

DESCRIPTION OF THE INVENTION

[0020] This object is achieved by a multifunctional encapsulated biologically active food component which consists of a core which comprises at least one dietary fiber, which core is surrounded by at least one biologically active substance, the core and the biologically active substance being surrounded by one or more shell-forming substances, which preferably form stable complexes with the core materials and/or the biologically active substances. Since in most cases the biologically active substances are labile compounds whose activity decreases during storage as the pure substance, during processing and during storage in the processed state, the universal stabilization method described below and the resultant substances are a considerable improvement compared with the prior art. In addition, the bioavailability of the abovementioned substances is frequently a problem. Using the method described, biologically active substances may be formulated such that the bioavailability and thus the utility to health is considerably increased.

[0021] For the purposes of the present invention, food components are natural and synthetic constituents of the human and/or animal diet. In addition, the food components are taken to mean constituents which are added specifically to the preparations and which supplement the human and/or animal diet (dietary supplements). This term also includes substances which are used in pharmaceuticals as nutritional components.

[0022] "Multifunctional" for the purposes of the invention means that the encapsulated food component fulfills two or more nutritional functions. These also include technical functions, for example delayed release of nutritionally active substances at the site of action or an improved sensory perception of the components in the food.

[0023] Encapsulated means that the substance in question is surrounded on all sides by a shell. Shell substances which can be used are in particular compounds which are able to form stable complexes with the core materials and/or the biologically active substances. Examples of these are mono-, di-and polysaccharides (hydrolyzed starches, microbial polysaccharides, plant polysaccharides, acidic plant gums, pectins, celluloses), emulsifiers, peptides, proteins and prebiotic substances/substrates.

[0024] Stable complexes with the core materials and/or the biologically active substances are formed, in particular, when said materials interact with one another. Interactions here are taken to mean molecular and particulate interactions.

[0025] A dietary fiber is a substance defined by food law as a nutrient which is not metabolized at all or only to a small extent by the organism in question. Because of its inert character, dietary fibers reside in the intestine and can there exert optimally their physiological effects, such as increasing intestinal peristalsis, affecting cholesterol absorption, prebiotic effects etc. Examples of inventively usable dietary fibers are plant

fibers (wheat fibers, oat fibers, rice dietary fibers, apple fibers, citrus fibers etc.), water-insoluble celluloses and hemicelluloses, but also water-soluble polysaccharides (for example β-glucans, fructo-and galactooligosaccharides), pectins, lignins or plant gums.

[0026] Hereinafter, "biologically active substances" are taken to mean materials which have the most varied nutritional functions in the organism and as a result make a positive contribution to the state of health. Biologically active substances can act, for example, as classical nutrients, can have immune-stimulating activity or protective activity or else can intervene in physiological processes in the organism. Substances which can act as biologically active substances are, inter alia, probiotic microorganisms, prebiotic substances, enzymes, nutrients (vitamins, minerals, trace elements, proteins, amino acids etc.), natural or synthetic secondary plant constituents (for example carotenoids) or substances having antioxidant activity (for example flavonoids).

[0027] The encapsulated food components are spherical or polygonal structures having a mean diameter, in the unprocessed state, of from 1 µm to 200 µm, preferably from 20 to 100 µm, in particular <50 µm. In the processed state, the particle diameter remains unchanged, but it can also increase up to 5 fold.

[0028] The core content in the food component is, depending on the sought-after effect in the product in which the food components are to be used, from 10 to 90% by weight, preferably greater than 50% by weight. The content of the biologically active substance in the food component depends on its dose-dependent physiological activity and can be from less than 1% by weight to more than 50% by weight, preferably from 10 to 20% by weight. The content of the shell materials of the food component is determined by the target-product-oriented functionality and is up to 50% by weight, but preferably below 10% by weight.

[0029] To produce the inventive food components, expediently a procedure is followed such that the biologically active substance or the mixture of two or more biologically active substances is introduced into a medium which comprises one or more shell-forming substances. The resultant mixture is then enriched with the dietary fiber or the dietary fibers and homogeneously mixed and then freed from the solvent or dispersion medium.

[0030] If the biologically active substance is a microorganism suspension, it is produced by a fermentation, in which it must be ensured that sufficiently high cell densities are achieved, preferably $>1 \cdot 10^{9}$ per ml CFU (colony forming units). If necessary, the microorganism suspension can also be concentrated by centrifugation, filtration or other concentration processes corresponding to the prior art. This step is necessary, in particular, if, at the customarily achievable cell densities, an adequately high concentration in the encapsulated food components cannot be achieved. Concentration can be carried out by two powers of ten to approximately 10^{11} CFU per ml, but preferably by one power of ten.

[0031] In addition, it is expedient that components of the fermentation medium make a contribution to shell formation. Such substances can be, inter alia, proteins, peptides, carbohydrates or minerals.

[0032] When the biologically active substances are introduced into the solvent or dispersion medium, it must be ensured that a homogeneous distribution is achieved and, after the

partial or complete removal of the solvent or dispersion medium, the sought-after quantitative ratio between dietary fiber, shell materials and biologically active substances is formed. If expedient, the shell-forming substance can also be charged first and the biologically active substances added to it.

[0033] When the mixture is produced, the sequence of addition of the individual components is of no importance, but care must be taken to ensure that unwanted aggregations do not occur. This applies in particular in the case of addition of minerals which dissociate in solution. Not until the following drying process, as a consequence of specifically intended interactions between the components of the shell materials, the biologically active substances and the dietary fibers, does formation of complexes occur, which complexes are of importance for stabilizing the encapsulated food components. The solvent or dispersion medium is removed by known drying processes, for example spray-drying, fluidized-bed drying, freeze drying etc., but preferably by spray-drying. In the cases where all constituents of the food component to be encapsulated are present in a dispersion, a single-component nozzle is used for spraying, which ensures the formation of sufficiently small particles during the spraying operation. Preferably, nozzles having a nozzle diameter of from 0.1 to 2. 0 mm are used. However, it can also prove to be expedient that the shell material is not to come into contact with the mixture until immediately after encapsulation, so that they are combined in the drier via a two-component nozzle.

[0034] The advantage of the invention is that bioactive substances, by using dietary fibers, preferably fiber materials, can be processed to form food components in such a manner that they achieve high stability after the drying process, in the food in which they are incorporated, during storage of the food and in the gastrointestinal tract. The release of the food components with their physiologically multifunctional properties does not take place until at the optimum position in the gastrointestinal tract. Furthermore, technologically functional properties may be achieved in the food by incorporating the food components which lead to sensory enhancement, for example due to increased creaminess of the end product.

[0035] The invention can be used in very many food groups, such as milk products (fermented milk products, fresh cheese, cheese preparations), meat processing products (uncooked sausage, scalded-emulsion sausage, cooked-meat sausage, meat pies, meat salads), fruit and vegetable products (jams, jellies, fruit juices, vegetable purees, vegetable juices), bakery products (bread, rolls, patisserie products), beverages, but also in food supplements in animal nutrition (domestic and small animals; farm animals) and in cosmetics and in pharmaceuticals etc.

[0036] The invention is illustrated below on the basis of Examples.

EXAMPLE 1

[0037] 1% by weight of wheat fibers is suspended in water, MRS broth is added and the mixture is autoclaved. This mixture is inoculated with a microorganism culture (Lactobacillus acidophilus) and fermented for 24 hours at 37° C. until a cell count of 10^{9} CFU ml^{-1} is achieved. Culture and wheat fibers are centrifuged off and rinsed once with a 0.1% strength by weight maltose solution. The supernatant is removed and the residue is taken up with 0. 1% strength by weight maltose solution. In a second batch, the capsule material B, in this

example 4% by weight of gum arabic, is suspended in water. By adding the microorganism/wheat fiber mixture to the capsule material, a sprayable dispersion is produced. This dispersion, during the subsequent spray-drying is vigorously stirred at 500 rpm to ensure uniform distribution of the material to be dispersed. The drying process was carried out using the following parameter settings: 1 Drying air temperature:170-185° C.Exhaust air temperature:55-60° C.Spraying pressure: 1 barIntake pressure:0.01 bar

[0038] The resultant fine white powder was suspended in aqueous solution to determine the survival rate of the encapsulated microorganisms. The survival rate was >60% by weight.

[0039] In this example, the wheat fiber serves as a multifunctional food ingredient, firstly owing to its dietary fiber character, and to its simultaneous function as a support material for the microorganisms. Gum arabic acts as capsule material and maltose as processing aid and also as an additional C source for the bacteria.

EXAMPLE 2

[0040] The growth and fermentation conditions for the microorganisms are similar to those of Example 1. The suspension of the capsule materials is supplemented in this example by a network-forming protein with 2% by weight of gelatin, so that a copolymer of fixed capsule structures is formed. After production of the dispersion, consisting of microorganism suspension and capsule material suspension, this is dried as in Example 1.

EXAMPLE 3

[0041] The capsule material of this example is composed of a plurality of substances as followed: 3% by weight of gum arabic, 1% by weight of gelatin, 0.5% by weight of xanthan, 0.3% by weight of citric acid. The substances were dispersed in water with constant stirring and mixed with the suspension of microorganisms prepared according to Example 1. This mixture is dried under the same conditions as described in Example 1. The result is a finely crystalline powder having a microorganism density of >60% by weight, based on the starting amount.

[0042] Gum arabic and gelatin form a copolymer whose formation is supported by adding xanthan and citric acid. Xanthan can act simultaneously as energy source for the microorganisms, due to the amounts of acetate of pyruvate present therein.

EXAMPLE 4

[0043] In this example, in a targeted manner individual constituents of the culture medium (MRS broth) were integrated into the formation of a stable capsule/microorganism complex. The substances used here are ®Tween 80 at a concentration of 0.1% by weight as growth promoter for the bacteria, in addition 1% by weight of maltose, replacing glucose as C source, and, as complexing aid, 0.09% by weight of calcium acetate are used instead of sodium acetate. The bacterial suspension prepared according to Example 1 is taken up with a dispersion of the abovementioned substances in water. An aqueous 1-2% strength by weight alginate solution is then injected into the resultant mixture. The product obtained in this manner is dried in the spray tower as described in Example 1.

EXAMPLE 5

[0044] Similarly to the procedure in Example 4, certain constituents of the culture medium are replaced by substances which firstly can serve for capsule formation and secondly can serve as substrate for the microorganism. In this case the following were used: albumin as capsule material and as N source, lecithin as emulsifier and binding aid between protein and sugar, and as P source and maltose as aid during capsule formation and as C source. The substances are dissolved in water in the following concentrations: albumin 4% by weight, lecithin 0.5% by weight and maltose 0.5% by weight. The bacterial suspension produced as in Example 1 is added to this mixture. The dispersion is sprayed under the standard conditions specified in Example 1. A voluminous finely crystalline powder is obtained as a result of this process.

EXAMPLE 6

[0045] The microorganisms were cultured and fermented as in Example 1. To form the protective shell, in a first step, 3% by weight of pectins containing 0.5% by weight of inulin are suspended in water. The prepared bacterial suspension is added to this mixture. In a third step approximately 0.1% by weight of calcium chloride is added with constant stirring. The resultant mixture is spray-dried under standard conditions. In this example, pectin acts as capsule material, inulin is used as processing aid with prebiotic properties. By adding calcium chloride, the pectin forms what is termed a calcium-bridged gel.

EXAMPLE 7

[0046] A high-viscosity dispersion is given using 2.5% by weight of maltodextrin, 0.5% by weight of lecithin and 1% by weight of guar gum as capsule materials. This dispersion is mixed with the bacterial suspension produced according to Example 1 and sprayed under standard conditions. The substances maltodextrin and lecithin form a gel-like network, the gelation capacity of the polysaccharide used being increased by the guar gum used.

EXAMPLE 8

[0047] As described under Example 1, in this case also a microorganism suspension is prepared containing wheat fibers as support material. This suspension is taken up as follows using an aqueous 0.5% strength by weight xanthan solution for stabilization. The resultant mixture is mixed with a previously prepared dispersion of 2.5% by weight of albumin and 1% by weight of carboxymethylcellulose in water with constant stirring. The albumin used forms a complex with the carboxymethylcellulose, which complex acts as capsule material.

CLAIMS (ENGLISH)

What is claimed is:

1. A multifunctional encapsulated biologically active food component consisting of a core which comprises at least one dietary fiber, which core is surrounded by at least one biologically active substance, in which the core and the biologically active substance(s) are encapsulated by one or more shell-forming substance(s).

2. The food component as claimed in claim 1, wherein the dietary fiber is selected from plant fibers (wheat fibers, apple fibers, oat fibers etc.), water-insoluble polysaccharides (celluloses) and water-soluble polysaccharides, pectins, lignin and plant gums.

3. The food component as claimed in claim 1, wherein the shell substance(s) is (are) able to form a stable complex with the core material or the biologically active substance(s) or the core material and the biologically active substance(s).

4. The food component as claimed in claim 3, wherein the shell substance is selected from one or more of the following substances: mono-, di-and polysaccharides (hydrolyzed starches, microbial polysaccharides, plant polysaccharides, acidic plant gums, pectins, celluloses), emulsifiers, peptides, proteins and prebiotic substances.

5. The food component as claimed in claim 1, wherein the dietary fiber is selected from one or more of the following substances: plant fibers (wheat fibers, oat fibers, rice dietary fibers, apple fibers, citrus fibers etc.), water-insoluble celluloses and hemicelluloses, water-soluble polysaccharides (for example β-glucans, fructo-or galactooligosaccharides), pectins, lignins or plant gums.

6. The food component as claimed in claim 1, wherein the biologically active substance is selected from one or more of the following substances: probiotic microorganisms, prebiotic substances, enzymes, nutrients (vitamins, minerals, trace elements, proteins, amino acids), natural or synthetic secondary plant constituents (for example carotenoids) and substances having antioxidant activity (for example flavonoids).

7. The food component as claimed in claim 1, which has a spherical or polygonal shape having a mean diameter, in the unprocessed state, of from about 1 µm to about 200 µm.

8. The food component as claimed in claim 1, wherein the core content of the food component is from about 10 to about 90% by weight.

9. The food component as claimed in claim 1, wherein the content of the biologically active substance in the food component is from <1% by weight to >50% by weight.

10. The food component as claimed in claim 1, wherein the content of shell materials in the food component is ≦50% by weight.

11. A process for producing a food component as claimed in claim 1, which comprises introducing a biologically active substance or a mixture of two or more biologically active substances into a medium which comprises one or more shell-forming substances, then enriching the resultant mixture with one or more dietary fiber(s) and homogeneously mixing the mixture and then freeing it from solvents or dispersion media.

Annex 2 (Sonnepan Priority Document)

Multifunctional Food Particle

The invention relates to a multifunctional encapsulated biologically active food component which consists of a core that comprises at least one dietary fiber, which core is surrounded by at least one biologically active substance and in which the core and the biologically active substance are surrounded by at least one shell-forming substance. The stability of the multifunctional food component is based on interactions of the components with one another.

BACKGROUND OF THE INVENTION

Biologically active substances in nutrition are physiologically important components. They can have the most varied functions in the organism and as a result make a positive contribution to health. Biologically active substances can act, for example, as classical nutrients, can stimulate immune activity or have protective activity or intervene in physiological processes in the body. Biologically active substances can include, inter alia, nutrients or secondary plant constituents. Enrichment of the diet with components of this type in a stable and in particular bioavailable form is therefore desirable from the nutritional aspect.

Dietary fibers are a heterogeneous product group. Many dietary fiber preparations are based on plant fibers and consist predominantly of water-insoluble polysaccharides in addition to pectin, lignin and plant gums (for example wheat fibers, oat dietary fibers, rice dietary fibers, apple fibers, citrus dietary fibers etc.). In addition there are also soluble dietary fibers which are mostly made up of complex carbohydrates (for example fructo- or galactooligosaccharides, .beta.-glucans etc.). Dietary fibers taken in via the diet are distinguished by the fact that they are indigestible constituents for humans. Because of their inert character, dietary fibers reside in the intestine and can there optimally exert their physiological effects, for example increasing intestinal peristalsis, effects on cholesterol absorption, prebiotic activities etc. An increased intake of dietary fibers is desirable for nutritional reasons. A daily intake of 25-30 g of dietary fiber is recommended by nutritionists.

For the reasons described it is expedient to provide dietary fibers and biologically active substances in a stable and nutritionally utilizable form via the diet or other delivery route to the organism. An optimal release of the biologically active substances, for the reasons described above, is not desirable until after passage through the stomach in the lower digestive tract. Furthermore, it is desirable that adverse sensory perceptions of nutritionally valuable substances in foods do not occur. This is, in the case of insoluble dietary fibers, frequently a marked sensory perception of particles in the food matrix ("scratchy off-taste").

The technique of microencapsulation has long been used commercially predominantly in the pharmaceutical industry. For some time, however, there have also been studies on the use of encapsulation in food technology (Jackson, Lee, 1991, Kanawija et al. 1992, Hegenbart, 1993, Arshady, 1993, Dewettinck, 1997, Pegg, Shahidi, 1999). The spray-drying process is one of the most frequently used processes for encapsulating various substances

in the food industry. It can be considered as one of the essential advantages here that spray-drying is suitable for processing heat-sensitive materials. In addition, the process is inexpensive and offers the advantage that an existing technology can be utilized. In order to make possible targeted utilization for the various application sectors in the food industry, studies of the customary materials in different combinations would have to be carried out, since single materials cannot comply with the complex requirements which a food makes of the capsule material. Studies to date were concerned predominantly with decreasing the volatility of substances and their oxidation by embedding them into a suitable material. The effects resulting from the physicochemical properties of the capsule materials and of the physical conditions of this process require further study (Re, M. I., Drying Technology, 1998, 16(6), 1195-1236).

Most patents or patent applications relate to fields of application in the pharmaceutical industry. The major roles are taken here by the capsule materials used (generally in combination with specific activities or effects), the controlled release of substances via the application of the encapsulating technique and the stabilization of substances. In the food sector there are far fewer patents, which, however, are essentially determined by these three directions. In the case of microencapsulation of cells or cell free extracts (CFE), physiological stability in combination with their use as a pharmaceutical product play the major roles.

Microencapsulation with the purposes of a) use of dietary fibers, in particular fibers as a support material for biologically active substances b) support material interactions, c) prevention of support material/capsule material interactions, d) stabilization of the biologically active substances in the product and in the food with correspondingly extended shelf life, has not been described to date.

The object of the present invention was therefore to provide a system which simultaneously prevents an interaction with the surrounding food (for example in some cases prevents unwanted swelling properties of the dietary fibers) provides nutritionally valuable substances without adverse sensory perceptions, ensures increased storage stability of nutritionally valuable substances and optimizes the quantitative supply and localization of release of the biologically active substances at the desired site (optimized bioavailability).

DESCRIPTION OF THE INVENTION

This object is achieved by a multifunctional encapsulated biologically active food component which consists of a core which comprises at least one dietary fiber, which core is surrounded by at least one biologically active substance, the core and the biologically active substance being surrounded by one or more shell-forming substances, which preferably form stable complexes with the core materials and/or the biologically active substances. Since in most cases the biologically active substances are labile compounds whose activity decreases during storage as the pure substance, during processing and during storage in the processed state, the universal stabilization method described below and the resultant substances are a considerable improvement compared with the prior art. In addition, the bioavailability of the abovementioned substances is frequently a problem. Using the method described, biologically active substances may be formulated such that the bioavailability and thus the utility to health is considerably increased.

For the purposes of the present invention, food components are natural and synthetic constituents of the human and/or animal diet. In addition, the food components are taken to mean constituents which are added specifically to the preparations and which supplement the human and/or animal diet (dietary supplements). This term also includes substances which are used in pharmaceuticals as nutritional components.

"Multifunctional" for the purposes of the invention means that the encapsulated food component fulfills two or more nutritional functions. These also include technical functions, for example delayed release of nutritionally active substances at the site of action or an improved sensory perception of the components in the food.

Encapsulated means that the substance in question is surrounded on all sides by a shell. Shell substances which can be used are in particular compounds which are able to form stable complexes with the core materials and/or the biologically active substances. Examples of these are mono-, di- and polysaccharides (hydrolyzed starches, microbial polysaccharides, plant polysaccharides, acidic plant gums, pectins, celluloses), emulsifiers, peptides, proteins and prebiotic substances/substrates.

Stable complexes with the core materials and/or the biologically active substances are formed, in particular, when said materials interact with one another. Interactions here are taken to mean molecular and particulate interactions.

A dietary fiber is a substance defined by food law as a nutrient which is not metabolized at all or only to a small extent by the organism in question. Because of its inert character, dietary fibers reside in the intestine and can there exert optimally their physiological effects, such as increasing intestinal peristalsis, affecting cholesterol absorption etc. Examples of inventively usable dietary fibers are plant fibers (wheat fibers, oat fibers, rice dietary fibers, apple fibers, citrus fibers etc.), water-insoluble celluloses and hemicelluloses, but also water-soluble polysaccharides (for example .beta.-glucans, fructo- and galactooligosaccharides), pectins, lignins or plant gums.

Hereinafter, "biologically active substances" are taken to mean materials which have the most varied nutritional functions in the organism and as a result make a positive contribution to the state of health. Biologically active substances can act, for example, as classical nutrients, can have immune-stimulating activity or protective activity or else can intervene in physiological processes in the organism. Substances which can act as biologically active substances are, inter alia, enzymes, nutrients (vitamins, minerals, trace elements, amino acids etc.), natural or synthetic secondary plant constituents (for example carotenoids) or substances having antioxidant activity (for example flavonoids).

The encapsulated food components are spherical or polygonal structures having a mean diameter, in the unprocessed state, of from 1 μm to 200 μm, preferably from 20 to 100 μm, in particular <50 μm. In the processed state, the particle diameter remains unchanged, but it can also increase up to 5 fold.

The core content in the food component is, depending on the sought-after effect in the product in which the food components are to be used, from 10 to 90% by weight, preferably greater than 50% by weight. The content of the biologically active substance in the food component depends on its dose-dependent physiological activity and can be from less than

1% by weight to more than 50% by weight, preferably from 10 to 20% by weight. The content of the shell materials of the food component is determined by the target-product-oriented functionality and is up to 50% by weight, but preferably below 10% by weight.

To produce the inventive food components, expediently a procedure is followed such that the biologically active substance or the mixture of two or more biologically active substances is introduced into a medium which comprises one or more shell-forming substances. The resultant mixture is then enriched with the dietary fiber or the dietary fibers and homogeneously mixed and then freed from the solvent or dispersion medium.

When the biologically active substances are introduced into the solvent or dispersion medium, it must be ensured that a homogeneous distribution is achieved and, after the partial or complete removal of the solvent or dispersion medium, the sought-after quantitative ratio between dietary fiber, shell materials and biologically active substances is formed. If expedient, the shell-forming substance can also be charged first and the biologically active substances added to it.

When the mixture is produced, the sequence of addition of the individual components is of no importance, but care must be taken to ensure that unwanted aggregations do not occur. This applies in particular in the case of addition of minerals which dissociate in solution. Not until the following drying process, as a consequence of specifically intended interactions between the components of the shell materials, the biologically active substances and the dietary fibers, does formation of complexes occur, which complexes are of importance for stabilizing the encapsulated food components. The solvent or dispersion medium is removed by known drying processes, for example spray-drying, fluidized-bed drying, freeze drying etc., but preferably by spray-drying. In the cases where all constituents of the food component to be encapsulated are present in a dispersion, a single-component nozzle is used for spraying, which ensures the formation of sufficiently small particles during the spraying operation. Preferably, nozzles having a nozzle diameter of from 0.1 to 2.0 mm are used. However, it can also prove to be expedient that the shell material is not to come into contact with the mixture until immediately after encapsulation, so that they are combined in the drier via a two-component nozzle.

The advantage of the invention is that bioactive substances, by using dietary fibers, preferably fiber materials, can be processed to form food components in such a manner that they achieve high stability after the drying process, in the food in which they are incorporated, during storage of the food and in the gastrointestinal tract. The release of the food components with their physiologically multifunctional properties does not take place until at the optimum position in the gastrointestinal tract. Furthermore, technologically functional properties may be achieved in the food by incorporating the food components which lead to sensory enhancement, for example due to increased creaminess of the end product.

The invention can be used in very many food groups, such as milk products (fermented milk products, fresh cheese, cheese preparations), meat processing products (uncooked sausage, scalded-emulsion sausage, cooked-meat sausage, meat pies, meat salads), fruit and vegetable products (jams, jellies, fruit juices, vegetable purees, vegetable juices), bakery products (bread, rolls, patisserie products), beverages, but also in food supplements in

animal nutrition (domestic and small animals; farm animals) and in cosmetics and in pharmaceuticals etc.

Claims

1. A multifunctional encapsulated biologically active food component consisting of a core which comprises at least one dietary fiber, which core is surrounded by at least one biologically active substance, in which the core and the biologically active substance(s) are encapsulated by one or more shell-forming substance(s).

2. The food component as claimed in claim 1, wherein the dietary fiber is selected from plant fibers (wheat fibers, apple fibers, oat fibers), water-insoluble polysaccharides (celluloses) and water-soluble polysaccharides, pectins, lignin and plant gums.

3. The food component as claimed in claim 1 or 2, wherein the shell substance(s) is (are) able to form a stable complex with the core material and/or the biologically active substance(s).

4. The food component as claimed in one or more of claims 1 to 3, wherein the biologically active substance is selected from one or more of the following substances: enzymes, nutrients (vitamins, minerals, trace elements, amino acids), natural or synthetic secondary plant constituents (for example carotenoids) and substances having antioxidant activity (for example flavonoids).

5. The food component as claimed in one or more of claims 1 to 4, which has a spherical or polygonal shape having a mean diameter, in the unprocessed state, of from 1 μm to 200 μm.

6. A process for producing a food component as claimed in claim 1, which comprises introducing a biologically active substance or a mixture of two or more biologically active substances into a medium which comprises one or more shell-forming substances, then enriching the resultant mixture with one or more dietary fiber(s) and homogeneously mixing the mixture and then freeing it from solvents or dispersion media.

Annex 3 (Search Results)

Document 1 (D1)

Publication number: JP2002522403
Publication date: 2002-04-16
Also published as:
BRPI9909153A (on 2000-12-05)
EP10673986A1 (on 2001-01-03)
US6515427BA (on 2003-02-04)
WO9952311A1 (on 1999-10-21)

English abstract: The invention relates to starch capsules which protect various substances, such as living microbes or enzymes, against the effect of the environment or the intestines, and to a method for manufacturing such capsules. A fraction of a suitable size category is chosen from the starch granules, the porosity of the granules is improved by hydrolyzing, and the granules are filled with desired substances, such as living microbes and/or enzymes. When desired, the starch granules can be coated with a suitable biopolymer, such as starch or amylose.

Machine translation of JP JP2002522403 claims 1-10:

1. The starchy capsule which features that it possessed porous structure, as a result of hydrolysis the microbe or the microbe and/or filled up with the polypeptide, or the protein includes the starchy granule.

2. The starchy granule, by using the enzyme adding water in the claim 1 which features that it is disassembled the starchy capsule of statement.

3. The starchy granule, α-[amiraze] and beta - the amylase and/or in the claim 1 which features that with the gluco amylase adding water it is disassembled or 2 the starchy capsule of statement.

4. The starchy granule, being biopolymer, coating from the claim 1 which features that it is done either of 3 in one section the starchy capsule of statement.

5. The starchy granule, the cellulose, the pectin and the protein, the starch and/or with the amylose coating from the claim 1 which features that it is done either of 4 in one section the starchy capsule of statement.

6. The starchy granule, the cellulose, the pectin and the protein, the starch and/or with the blend of the amylose and the membrane coating material which can be allowed medicine coating from the claim 1 which features that it is done either of 5 in one section the starchy capsule of statement.

7. The starchy granule, the barley, the potato and the wheat, the oats, the pea bean and the corn, the tapioca and the sago, the United States or the similar tuber vegetable, or the corn

crop, desirably the potato, the barley, the wheat or the corn, to be most desirable from the claim 1 which features that it does from the potato either of 6 in one section the starchy capsule of statement.

8. Size of the starchy granule 10~100 micro m, desirably from the claim 1 which features that it is 50~100 micro m either of 7 in one section the starchy capsule of statement.

9. The starchy granule, the bacterium, the yeast or from the claim 1 which features that it has filled up with the microbe like the Hyphomycetes either of 8 in one section the starchy capsule of statement. less than DP N=0003 greater than less than TXF FR=0001 HE=246 WI=152 LX=0300 LY=0300 greater than

10. The starchy granule, lactic acid bacillus being attached, streptococcus being attached, [pedeiokotsukasu] being attached, [rakutokotsukasu] being attached, [roikonosutotsuku] being attached and [korinebakuteriumu] being attached, from the claim 1 which features that it has filled up with the lactobacillus the [enterokotsukasu] being attached way or the lactobacillus which belongs to [bihuidobakuteriumu] being attached either of 9 in one section the starchy capsule of statement.

Document 2 (D2)

Company News – 15 May 2000
From our correspondent

The US-company Procter & Gamble has announced the introduction of a special kind of energy drink for people and animals suffering from autoimmune diseases like rheumatoid arthritis (RA).

Phosphatidylinositol and phosphatidylcholine can alleviate the symptoms of RA and pharmaceuticals with these compounds are available on the market. Yet, these compounds are also available in the average diet of people that eat healthy foods, such as milk, fruits, yoghurt and probiotics. Scientists at P&G found that the human body is not able to take full advantage of the presence of the compounds in these food products since they are excreted without being extracted from the food. They have now found a revolutionary way to make use of other food components, such as fibers to enable the uptake of these compounds into the body.

Mary Roseblum (head of Animal Nutrition Researchat P&G) explains: "In essence it was a simple idea. We used pectin (formed as little globules) to let phosphatidylinositol and phosphatidylcholine precipitate on those globules. In this way we were able to overconcentrate these compounds. The next step was to disperse these globules in drinking liquid, such as milk".

Jeff Richmaster of the Formulations Department added: "This was only half of the solution, since it appeared that the globules did not cross the stomach, but were degraded there, which prevented the advantageous effect of the compound. Thus we had to coat these globules with cellulose to enable them to get through the stomach unharmed"

Once P&G had found how to stabilize the active ingredients and to shield them from degradation in the stomach, they could start to develop the current product; a milk- based solution in which the little globules are dispersed, and which by the presence of these globules has a smooth mouth-feel, like yoghurts or creams.

It is envisaged that this health drink will alleviate the symptoms of RA and patients suffering from other auto-immune diseases. And that simply by drinking a yoghurt-like product. This truly is 'nutraceutics' in the way it should be.

Document 3 (D3)

[11] **Patent/Publication Number: US'414**
[45] **Publication Date: Aug, 13 1996**

[21] **Application Number: US1995XXXXXXA**
[22] **Application Date: Mar, 22 1995**
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[51] **Int. Cl.[8]:** A23L000130 A23L000100 A23L000105 A23L00010526 A23L0001164 A23L0001305 A23L0001308 A61K000900
[52] **ECLA: A23L000100P4** A23L00010526 ; A23L0001164B ; A23L0001164C ; A23L0001308 ; A61K000900M18B
[58] **Field of Search:**

424439
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[57] **ABSTRACT**
A nutritional product having a solid matrix containing protein, fat and carbohydrate has disposed therein particles of dietary fiber encapsulated in zein. The preferred dietary fiber is guar. Such a nutritional product may be used for reducing the serum cholesterol in a mammal.

DETAILS

The present invention relates to a nutritional product with a solid matrix containing encapsulated dietary fiber, which reduces serum cholesterol in mammals.

Atherosclerosis is a disease of the arteries which begins as a lipid filled lesion in the intima of the arterial wall and progresses gradually with the eventual formation of a fibroatheromatous plaque over a period of years. The disease often affects the coronary arteries which perfuse the heart. Once significant encroachment on the vessel lumen occurs, coronary flow may be insufficient to meet myocardial oxygen demands, causing thoracic pain (stable angina pectoris). Eventually, the plaque may fissure or rupture, with or without overlying thrombosis. Plaque disruption may cause an abrupt reduction in coronary perfusion, leading to unstable angina, myocardial infarction (necrosis of the heart muscle resulting from interruption of the blood supply to the area) or ischemic sudden death, presumably due to ventricular arrhythmia. Heart disease can be the result of several

etiologies, but it is most often due to atherosclerotic obstruction of large coronary arteries. More than half the deaths related to heart disease can be attributed to atherosclerosis.

The risk factor hypothesis of atherosclerosis has become well accepted in the medical world: the majority of people who die or are disabled as a result of atherosclerosis exhibit one or more identifiable characteristics called risk factors. If a person has a risk factor, he or she is more likely to develop clinical manifestations of atherosclerosis and is likely to do so earlier than is a person with no risk factors. The following parameters have been shown to be associated with coronary heart disease (CHD) in the Framingham study and other large epidemiological studies and are now well accepted: age (the relation of age to CHD is also dependent on sex) and family history of premature CHD, hypercholesterolemia and specifically high blood levels of low density lipoprotein (LDL) cholesterol, low levels of high density lipoprotein (HDL) cholesterol, cigarette smoking, hypertension, and diabetes each contributes to increasing the risk of disease over baseline rates by a factor of 2 to 6-fold. When these characteristics are combined, the combined risks of coronary heart disease are additive (Dauber, "The Epidemiology of Atherosclerotic Disease", THE HARVARD UNIVERSITY PRESS, 1980; Kannel, "New Perspectives on Cardiovascular Risk Factors", AMERICAN HEART JOURNAL, 114:213-219, 1987; Matthews et al., "Menopause and Risk Factors for Coronary Heart Disease", THE NEW ENGLAND JOURNAL OF MEDICINE, 321(10):641-646, 1989; "Report of the National Cholesterol Education Program Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults", ARCHIVES OF INTERNAL MEDICINE, 148:36-69, 1988)

Just as important as the identification of cholesterol as a risk factor is the fact that when blood cholesterol and specifically LDL cholesterol levels are decreased in hypercholesterolemic subjects, there is a decrease in risk of heart disease. The results of the Lipid Research Clinic trials indicate that for every percentage point decrease in cholesterol levels, the risk of coronary heart disease decreases by 2%. ("Lipid Research Clinics Program. The Lipid Research Clinics Primary Prevention Trial Results I. Reduction in incidence of coronary heart disease", JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, 251(3)351-364, 1984; "Lipid Research Clinics Program. The Lipid Research Clinics Coronary Primary Prevention Results II. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering", JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, 251(3)365-374, 1984)

The blood cholesterol raising effects of dietary saturated fat and cholesterol are well accepted. Therefore, the American Heart Association and the National Cholesterol Education Program recommend as their "Step 1" diet a cholesterol-lowering program consisting of a reduction of total fat to less than 30% of calories as fat, a reduction of saturated fatty acids to less than 10% of calories and a reduction of cholesterol to less than 300 mg per day. It is also accepted that polyunsaturated fat lowers blood cholesterol, but because of the relatively small amount of data on the long term use of diets with very high polyunsaturated fat content, the American Heart Association and the National Academy of Sciences do not recommend that polyunsaturates exceed 10% of calories. (Expert Panel, "Summary of the Second Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II)", JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, 269(23) :3015-3023, 1993; Nutrition Committee of the American Heart Association, "Dietary Guidelines for Healthy American Adults", CIRCULATION, 77(3):721A-724A, 1988; Food and

Nutrition Board, National Research Council, RECOMMENDED DIETARY ALLOWANCES, 10TH EDITION, National Academy Press, Washington, D.C., 1989). The National Cholesterol Education Program guidelines also state that monounsaturates should make up 10-15% of the diet, protein 10-20%, carbohydrate 50-60%, and dietary fiber 15-25 g/day. The type of dietary fiber is not specified.

For people who are eating an average American diet, switching to a Step 1 diet means decreasing their intake of fat. In the Multiple Risk Factor Intervention Trial, dietary changes according to a Step 1 diet were initiated leading to decreases in serum cholesterol in the range of 5-7%. (Banks et al., "Dietary Management of the Patient with Atherosclerosis: Are the New National Cholesterol Education Panel Recommendations Enough?", JOURNAL OF THE NATIONAL MEDICAL ASSOCIATION, 81(5):493-495, 1989). That means that if the ultimate goal is to reduce total cholesterol levels to less than 200 mg/dL, individuals who are consuming an average American diet and have serum cholesterol levels over 215-220 mg/dL will need to rely on more than a Step 1 diet.

A more stringent dietary recommendation of the National Cholesterol Education Program is the "Step 2 diet" which further restricts saturated fat to 7% of calories and cholesterol to less than 200 mg per day. One drawback of the Step 2 diet and other very low fat diets in that in addition to lowering LDL they lower HDL. (Jones et al., "Effect of dietary fat selection on plasma cholesterol synthesis in older, moderately hypercholesterolemic humans", ARTERIOSCLEROSIS AND THROMBOSIS, 14(4):542-548, 1994; Grundy et al., "Comparison of monounsaturated fatty acids and carbohydrates for reducing raised levels of plasma cholesterol in man", AMERICAN JOURNAL OF CLINICAL NUTRITION, 47:965-969, 1988)

The Step 1 diet does not provide specific recommendations for any other components of the diet which might enhance its cholesterol-lowering or antiatherogenic potential. Additional cholesterol-lowering components include vegetable oils that contain non-saponifiable components, cholesterol-lowering dietary fibers, and vegetable proteins. Rice bran oil contains a sizeable unsaponifiable fraction, i.e., non-acyl glycerol portion that contains 2 general classes of compounds: (a) sterols, and triterpene alcohols and (b) tocotrienols, which are similar to tocopherols, but with 3 double bonds in the side chain. The sterols and triterpene alcohols in rice bran oil are often esterified to ferulic acid and are known as "oryzanols". Studies in rats, primates and humans indicate that rice bran oil lowers serum cholesterol and may lower serum triglycerides. (Nicolosi, et al., "Rice bran oil lowers serum total and low density lipoprotein cholesterol and Apo B levels in nonhuman primates", ATHEROSCLEROSIS, 88:133-142, 1991; Lichenstein et al., "Rice bran oil consumption and plasma lipid levels in moderately hypercholesterolemic humans", ARTERIOSCLEROSIS AND THROMBOSIS, 14(4):549-546, 1994) Two different mechanisms may be involved. First, plant sterols and oryzanols may interfere with cholesterol or saturated fat absorption and/or the absorption of bile acids. Second, in studies in chicks, pigs, and quail, tocotrienols have been reported to reduce cholesterol synthesis in the liver. It is also possible that plant sterols may prevent atherosclerosis by other mechanisms. (Mattson et al., "Optimizing the Effect of Plant Sterols on Cholesterol Absorption in Man", THE AMERICAN JOURNAL OF CLINICAL NUTRITION, 35:697-700, 1982; Qureshi et al., "The Structure of an Inhibitior of Cholesterol Biosynthesis Isolated from Barley", THE JOURNAL OF BIOLOGICAL CHEMISTRY, 261(23):10544-10550, 1986)

The cholesterol-lowering effects of dietary fiber have been summarized in several recent reviews. (Jenkins et al., "Fiber in the treatment of hyperlipidemia", Handbook of Dietary Fiber in Nutrition, G. Spiller, Ed., CRC Press, 1986 pp. 327-344; Sugano et al., "Dietary Fiber and Lipid Absorption", Dietary Fiber: Chemistry, Physiology, and Health Effects, Kritchevsky et al., Ed. Plenum Press, 1988 pp. 137-155; Anderson et al., "Dietary Fiber and Coronary Heart Disease", CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION, 29(2):95-147, 1990. Viscous soluble fibers are effective cholesterol-lowering agents when compared to non-viscous insoluble fibers or digestible carbohydrates, but the effect is variable. Table 1 summarizes data from over 50 studies of human subjects. As indicated in Table 1, one can expect a decrease in serum cholesterol in the range of 10% to 15% with doses of an appropriate source of fiber ranging from 6 g/day to 50 g/day. The variability of the response could be due to differences in the dose, timing of administration, types of subjects enrolled, and purities and chemical compositions of the fiber sources. In general, guar gum has advantages over the other fibers listed in Table 1 as it is more consistently high level of dietary fiber than pectin, more readily available at higher quality than psyllium, and much more consistently effective than oat and soy products.

TABLE 1

_____

CHOLESTEROL LOWERING EFFECT

OF VARIOUS FIBER SOURCES

Total Cholesterol

LDL Cholesterol

Number

Mean decrease or

Mean decrease or

of

Fiber Source

range range Studies

_____

Guar Gum-11.2%-17% 22

Pectin-12.4%--14

Psyllium-13.1%-20% (one study)

10

Soy-6.5%--2

Poly-

saccharide

Oat Products

-3 to-36% 0 to-58% 13

_____

The most likely mechanisms for the cholesterol lowering effect of fiber according to Anderson et al., "Dietary fiber and coronary heart disease", CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION, 29 (2):95-147, (1990) are: (1) modification of bile acid reabsorption in terminal ileum (interruption of the entero-hepatic cycle of bile acids); (2) interference with lipid absorption; and (3) down-regulation of the liver's capability to synthesize cholesterol.

Many soluble fibers are extensively or completely degraded by bacteria in the cecum, yet bile acids are not well reabsorbed once they are released from dietary fiber. This may be partly due to the products of fermentation. The production of short chain fatty acids (SCFA) causes a drop in colonic pH which may decrease the solubility and the passive reabsorption of bile acids. (Remesy et al., "Cecal fermentations in rats fed oligosaccharides (insulin) are modulated by dietary calcium levels", AMERICAN JOURNAL OF PHYSIOLOGY, 264:G855-G862, 1993)

Cholesterol biosynthesis in the liver is known to be regulated by intracellular cholesterol levels, but dietary fiber does not cause an increase in cholesterol biosynthesis in the liver that is commensurate with the requirements for bile acid synthesis. Several studies support the hypothesis that propionate generated by bacterial fermentation of fiber could exert a rate-controlling effect on liver cholesterol synthesis. (Chen et al., "Propionate may mediate the hypocholesterolemic effects of certain soluble plant fibers in cholesterol-fed rats", PROCEEDINGS OF THE SOCIETY OF EXPERIMENTAL BIOLOGY AND MEDICINE, 175:215-218, 1984; Ebihara et al., "Hypocholesterolemic effect of cecally infused propionic acid in rats fed a cholesterol-free, casein diet", NUTRITION RESEARCH, 13:209-217, 1993) Other data dispute the validity of this concept. (Evans et al., "Relationship between structure and function of dietary fibre: a comparative study of the effects of three galactomannans on cholesterol metabolism in the rat", BRITISH JOURNAL OF NUTRITION, 68:217-229, 1992; Nishina et al., "Effects of propionate on lipid biosynthesis in isolated rat hepatocytes", JOURNAL OF NUTRITION, 120:668-673, 1990)

Plant proteins such as zein protein can lower cholesterol. The cholesterol-lowering

mechanism of zein protein is unclear. Part of the effect can be explained by the amino acid

composition of proteins. (Huff et al., "Plasma cholesterol levels in rabbits fed low fat,

cholesterol-free, semipurified diets: Effects of dietary proteins, protein hydrolysates and amino acid mixtures", ATHEROSCLEROSIS 28:187-195, 1977) Although the substitution of a supplement containing 5-10 g of plant protein for part of the animal protein in the diet would be unlikely by itself to cause a medically significant decrease in blood cholesterol levels, the use of zein protein as part of a combination of dietary cholesterol-lowering ingredients might contribute to a medically significant decrease in LDL cholesterol.

There is very little published scientific information on diets that combine known cholesterol lowering ingredients.

There is provided in accordance with the present invention a nutritional product having a solid matrix comprising protein, fat and carbohydrate, said matrix having disposed therein dietary fiber encapsulated in zein. In one embodiment, the matrix is a food bar. The preferred dietary fiber in the food bar is guar encapsulated with a coating of at least about 20% add-on zein. The protein is preferably soy protein and may further include calcium caseinate, and/or oat protein. The fat is preferably selected from the group consisting of vegetable oils containing less than 25% saturated fatty acids, by weight. Examples of such vegetable oils are rice bran oil, canola oil, and corn oil.

FOOD BAR EXAMPLE 1

Many attempts were made to manufacture an acceptable food bar matrix containing unencapsulated guar gum and free of partially or fully hydrogenated fat. For example the order of adding ingredients and mixing times was varied, but without satisfactory results. Food Bar Prototype Number 1 is typical of these attempts.

_____

RECIPE FOR FOOD BAR PROTOTYPE NUMBER 1

CONCENTRATION

BY PERCENT

INGREDIENT WEIGHT OF BAR

_____

High Fructose Corn Syrup

25.71

Oat Bran.sup.1 21.17

Guar.sup.2 12.35

Soy Protein 11.44

Rice Bran Oil 10.13

Polydextrose 6.62

Glycerin 6.18

Crisp Rice 4.45

Dicalcium Phosphate

0.97

Lecithin 0.59

Citric Acid 0.39

_____

.sup.1 The "oat bran" used was actually a mixture comprising, by weight,

26.25% oat fiber, 62.128% oat flour and 11.622% soy protein.

.sup.2 The guar was obtained from TIC Gums and was designated by their

product code "8/22A", which is described below in the paragraph preceding

"ENCAPSULATION EXPERIMENT 1".

Manufacturing Procedure:

Food Bar Prototype Number 1 was prepared in a Hobart mixer. All ingredients were placed in the mixer and mixed at room temperature (24. degree..+-. 10° C.). The first ingredients placed in the mixer were the soy protein, dicalcium phosphate, and citric acid and they were mixed until blended. The rice bran oil, and lecithin were then added to the other ingredients and mixed until blended. The guar was then added to the ingredient blend and mixed therewith until blended. The polydextrose, oat bran, and crisp rice, were then added and mixed until blended. The final ingredients added to the blend were the high fructose corn syrup, and glycerin which were mixed with the other ingredients until blended. The batch was then dumped on to the bench top and rolled out using a typical rolling pin to a uniform thickness. The batch was cut into bars with a spatula then cooled in a refrigerator to between 0. degree. and 10° C. At no time were the food bars-or the blend of ingredients subjected to elevated temperatures for cooking or baking. Of course, friction due to mixing could elevate the temperature of the blend a few degrees. The bars were then packaged in a low density polyethylene/foil wrap.

The texture of this prototype food bar and all of the other prototype food bars described herein was determined using a Stevens L.F. R.A. Texture Analyzer. This instrument measures the amount of "grams of force"[that it takes to move a probe 3 mm into a bar at a speed of 0.2 mm/sec. The sample size is one bar, with five measurements taken per bar. The five measurements are averaged together and recorded as grams of force. The texture of food bar prototype number 1 was determined several times over a period of weeks and the results are presented in TABLE 5.

TEXTURE TESTING FOR FOOD BAR PROTOTYPE

NUMBER 1

FOOD BAR

WEEK HARDNESS

---

0 82

2 342

4 454

6 531

8 478

Inasmuch as a hardness of 400 or greater is unacceptably difficult to chew, this prototype and others containing unencapsulated guar and desirable levels of hydrogenated fat were not acceptable as a commercial product. Other problems which were observed were food bars becoming dried out, hardened, crumbling, or even turning into a powder.

ENCAPSULATION EXPERIMENT 2

The purpose of this experiment was to determine if the use of a different plasticizer with the zein would allow thinner coatings which would be as good of a moisture barrier as thicker coatings while giving the acceptable mouth feel of a thinner coating (smaller particles) when incorporated in a food product.

A solution of coating material was prepared comprising zein F4000 plus Captex® 355 equaling 20% of the zein, as a 12.5% by weight solution of ethanol/water at a 90/10 weight/weight ratio. In a 4"/6" fluid bed unit, the 8/22 guar gum (small guar particles) was initially granulated with a bottom spray nozzle and then coated using a bottom spray with a Wurster column insert. The coating solution was applied to 1000 g of the guar gum at a rate

of 9 g/min. The atomizing air pressure for the spray nozzle was 15 psig. The fluidizing inlet air temperature varied between 44.4° and 50.9° C. with a corresponding air discharge temperature of about 21.1° to 27.2° C. After 10% zein by weight of the weight of the guar gum was applied, the guar gum was sieved to remove particles above 840 µm and below 125 µm. The guar gum was then coated using the Wurster column insert with the same processing conditions. Samples were removed at zein levels of 20% and 40% by weight of the guar gum. At each sampling point the coated guar gum was sieved to remove particles greater than 840 µ m before being returned to the unit for more coating. The encapsulation process was stopped after 60% zein by weight of the guar was applied. This process resulted in less agglomeration than encapsulation experiment 1, but the powder flow within the chamber was slower which may have been due to the higher oil content in the coating solution.

ENCAPSULATION EXPERIMENT 3

This experiment was conducted to evaluate the coatability of larger size guar particles.

Guar gum was encapsulated in 20% add on zein using a 18" Wurster coater. The guar gum 8/22A used in this experiment has a slightly larger particle size, as described above. A solution of a coating material was prepared comprising zein F4000 plus Durkex® 500 equaling 20% of the zein, as a 15% by weight solution of ethanol/water at a 90/10 weight/weight ratio. The coating solution was applied to 35 kg of guar gum at an initial rate of 200 g/min and was gradually increased to 250 g/min over a 40 minute period. The atomizing air pressure for the spray nozzle was 80 psig. The fluidizing inlet air temperature varied between 44.4° and 46.7° C. with a corresponding air discharge temperature of between 26.1° to 38.9° C. After 20% zein by weight of the weight of the guar gum was applied, the process was stopped. The product was dried for 5 minutes and then removed from the column. 99% of the product was less than 40 mesh.

It was determined that larger size guar particles yielded better encapsulated particles of more uniform size than those obtained by coating the smaller size guar particles.

ENCAPSULATION EXPERIMENT 4

The objective of this experiment was to attempt to produce a final product of smaller encapsulated particles by using a series of sieving steps.

Guar gum was encapsulated in different levels of zein using a 18" Wurster coater. Guar gum 8/22 (small guar particles) was used in this experiment. A solution of a coating material was prepared comprising zein F4000 plus Durkex® 500 equaling 20% of the zein, as a 23.5% by weight solution of ethanol/water at a 90/10 weight/weight ratio. The coating solution was applied to 35 kg of the guar gum at a rate of 250 g/min. The atomizing air pressure for the spray nozzle was 80 psig. The fluidizing inlet air temperature varied between 43.9° and 46.7. degree. C. with a corresponding air discharge temperature of between 24. 4° to 40° C. After 10% zein by weight of the weight of the guar gum was applied, the process was stopped. The product was sieved to remove product greater than 420 µm and less than 150 . mu.m. The sieved guar gum was returned to the Wurster column insert and coated with the same processing conditions. After a zein level of 20% add on was applied, the system was

stopped. The product was dried for 5 minutes and then removed from the column. 97.5% of the product was less than 40 mesh.

While the yield of acceptable end product was high, this procedure would be cost prohibitive because of extra processing steps.

ENCAPSULATION EXPERIMENT 5

The objective of this experiment was to evaluate the use of rice bran oil as a hydrophobic material in the zein coating.

For this experiment the larger size guar gum (8/22A) was encapsulated in 25% add on zein with rice bran oil as the plasticizer. A solution of a coating material was prepared comprising zein F4000 plus rice bran oil equaling 20% of the zein by weight, as a 23.5% by weight solution of ethanol/water at a 90/10 weight/weight ratio. In a 4"/6" fluid bed unit, the guar gum was coated using a bottom spray with a Wurster column insert. The coating solution was applied to 500 g of the guar gum 8/22A at a rate of 9 g/min. The atomizing air pressure for the spray nozzle was 15 psig. The fluidizing inlet air temperature varied between 43.9° and 45° C. with a corresponding air discharge temperature of between 26.9° and 34.4° C. After 25% zein by weight of the weight of the guar gum was applied, the guar gum was sieved to remove particles above 420 µm and below 125 µm. 85.3% of the product was in the correct size range.

Rice bran oil did not appear to facilitate as good a coating process as the other plasticizers, but this could possibly be improved with changes in process and/or formulation.

ENCAPSULATION EXPERIMENT 6

The objective of this experiment was to evaluate the coating of larger guar particles with increased levels of zein.

For this experiment, the larger size guar gum particles (8/22A) were encapsulated in 30% add on zein with Durkex® 500 as the plasticizer. A solution of a coating material was prepared comprising zein F-4000 plus Durkex® 500 equaling 20% of the zein, as a 23.5% by weight solution of ethanol/water at a 90/10 weight/weight ratio. In a 4"/6" fluid bed unit, the guar gum was coated using a bottom spray with a Wurster column insert. The coating solution was applied to 500 g of the guar gum 8/22A at a rate of 9 g/min. The atomizing air pressure for the spray nozzle was 15 psig. The fluidizing inlet air temperature varied between 42.8° and 46.1° C. with a corresponding air discharge temperature of between 29.4° to 35. 6° C. After 30% zein by weight of the weight of the guar gum was applied, the guar gum was sieved to remove particles above 420 µm and below 125 µm. 89.4% of the product was in the correct size range.

When the microencapsulated guar manufactured in this experiment was incorporated into food bars, the bars were crumbly and had an unacceptable "sandy" mouth feel.

ENCAPSULATION EXPERIMENT 7

The purpose of this experiment was to evaluate the use of carnauba wax as a coating material to reduce processing time with a dual coating process.

For this experiment, some of the product from experiment 3 was overcoated with carnauba wax. The carnauba (No. 120, Frank B. Ross Co. Inc., Jersey City, N.J., U.S.A.) was melted in a beaker and held at a temperature of 104. 4° C. In a 4"/6" fluid bed unit, 500 g of the product from example 4 was coated using a bottom spray without a Wurster column insert. The molten wax was pumped at a temperature between 98.9. degree. and 104.4° C. The atomizing air pressure was 15 psig. The fluidizing inlet air temperature varied between 51.6° and 53.3. degree. C. with a corresponding outlet temperature of 39.4° to 41. 7° C. After 75 g of the wax was applied the coating process was stopped.

When the microencapsulated particles manufactured in this experiment were incorporated into food bars, the resultant food bars became unacceptably hard within two months after manufacture.

ENCAPSULATION EXPERIMENT 8

The objective of this experiment was to evaluate zein particles coated only with carnauba wax.

For this experiment, the larger size guar gum particles (8/22A) were encapsulated in 44.8% add on carnauba wax. The carnauba wax (No. 120) was melted in a beaker and held at a temperature of 104.4° C. In a 4"/6" fluid bed unit, the guar gum was coated using a bottom spray without a Wurster column insert. The molten wax was applied to 500 g of the guar gum 8/22A. The atomizing air pressure for the spray nozzle was 15 psig. The fluidizing inlet air temperature varied between 53.9° and 72.2° C. with a corresponding air discharge temperature of between 33.1° and 36.7° C. After the carnauba wax was applied, the product was removed.

The microencapsulated guar manufactured in this experiment was not used in food bars because of the results of experiment 7.

ENCAPSULATION EXPERIMENT 9

The objective of this experiment was to evaluate the use of beeswax as a coating material.

For this experiment, the larger size guar gum was encapsulated in 23% add on beeswax. The beeswax (Frank B. Ross Co. Inc., Jersey City, N. J. U. S.A. was melted in a beaker and held at a temperature of 107.2. degree. C. In a 4"/6" fluid bed unit, the guar gum was coated using a bottom spray without a Wurster column insert. The molten wax was applied to 500 g of guar gum 8/22A (large guar gum particles). The atomizing air pressure for the spray nozzle was 15 psig. The fluidizing inlet air temperature varied between 21.1° and 32.2° C. with a corresponding air discharge temperature of between 28.3° to 29.4. degree. C. After the 5 minutes, the guar gum was starting to agglomerate so the inlet air temperature was reduced to 21° C. The process was stopped after 23% add on because of flow problems within the chamber.

When the encapsulated guar manufactured in this experiment was incorporated in food bars, the bars were unacceptably hard and crumbly and caused packing around the teeth of persons eating the bar.

ENCAPSULATION EXPERIMENT 10

The objective of this experiment was to evaluate the use of paraffin wax as a coating material.

For this experiment, the larger size guar gum particles (8/22A) were encapsulated in 40% add on paraffin wax. The wax (Paraffin 150/160, Frank B. Ross Co., Inc., Jersey City, N.J. U.S.A.) was melted in a beaker and held at a temperature of 104.4° C. In a 4"/6" fluid bed unit, the guar gum was coated using a bottom spray without a Wurster column insert. The molten wax was applied to 500 g of the guar gum 8/22A. The atomizing air pressure for the spray nozzle was 15 psig. The fluidizing inlet air temperature varied between 26.1° and 27.2. degree. C. with a corresponding air discharge temperature of between 25. 5° and 29.4. degree. C. After 40% add on was applied the process was stopped.

When the encapsulated guar manufactured in this experiment was incorporated in food bars the bars hardened very quickly and caused packing around the teeth of persons eating the bar.

ENCAPSULATION EXPERIMENT 11

The purpose of this experiment was to evaluate the prospect of coating xanthan gum, which is a soluble high viscosity fiber.

For this experiment, xanthan gum was encapsulated in 20% add on zein with Durkex® 500 as the plasticizer. A solution of a coating material was prepared comprising zein F4000 plus Durkex® 500 equaling 20% of the zein, as a 23.5% by weight solution of ethanol/water at a 90/10 weight/weight ratio. In a 4"/6" fluid bed unit, the xanthan gum was coated using a bottom spray with a Wurster column insert. The coating solution was applied to 500 g of the xanthan gum at a rate of 9 g/min. The atomizing air pressure for the spray nozzle was 15 psig. The fluidizing inlet air temperature varied between 45° and 52.2. degree. C. with a corresponding air discharge temperature of between 27. 2° and 32.2° C. After 20% zein by weight of the weight of the xanthan gum was applied, the process was stopped.

To date the encapsulated xanthan gum has not been incorporated into a food product, but the coating process appears to have yielded a satisfactory product.

ENCAPSULATION EXPERIMENT 12

This experiment was conducted to evaluate the feasibility of larger scale (bigger batch size) coating of guar with zein using larger capacity coating equipment and a different plasticizer.

Guar gum was encapsulated in different levels of zein using a 18" Wurster coater. The small guar gum particles (8/22) were used in this experiment. A solution of a coating material was prepared comprising zein F4000 plus partially hydrogenated vegetable oil (Durkex. RTM. 500, Van den Bergh Foods Co., Lasle, Ill. U.S.A.) equaling 20% of the zein, as a 23.5% by

weight solution of ethanol/water at a 90/10 weight/weight ratio. The coating solution was applied to 50 kg of the guar gum at an initial rate of 175 g/min and was gradually increased to 215 g/min over a 30 minute period. Periodically the liquid line was flushed with 90/10 ethanol/water, if the liquid line pressure increased. The atomizing air pressure for the spray nozzle was 80 psig. The fluidizing inlet air temperature varied between 45.6° and 46.7. degree. C. with a corresponding air discharge temperature of between 25. degree. and 33.3. degree. C. After 10% zein by weight of the weight of the guar gum was applied, the process was stopped to remove a sample. The guar gum (35 kg) was returned to the Wurster column insert and coated with the same processing conditions. After a zein level of 15% add on was applied, the system was stopped again, and a sample was removed. The encapsulation process was stopped after 20% zein by weight of the guar was applied. The product was dried for 5 minutes and then removed from the column. The product was sieved to remove product over 40 mesh (420 µm). 84% of the product was less than 40 mesh.

It was determined that a scale-up of the coating process if feasible and that the hydrogenated vegetable oil is a good plasticizer that did not have any substantial effect on product taste.

ENCAPSULATION EXPERIMENT 13

The objective of this experiment was to further refine the coating process.

Guar gum was encapsulated in 25% add on zein using a 18" Wurster coater. A solution of a coating material was prepared comprising zein F4000 plus Durkex® 500 equaling 20% of the zein, as a 23.5% by weight solution of ethanol/water at a 90/10 weight/weight ratio. The coating solution was applied to 35 kg of large guar gum particles (8/22A) at a rate of 240 g/min. The atomizing air pressure for the spray nozzle was 80 psig. The fluidizing inlet air temperature varied between 45° and 47.2° C with a corresponding air discharge temperature of between 28.9° to 37.8° C. After 25% zein by weight of the weight of the weight of the guar gum was applied, the process was stopped. The product was dried for 5 minutes and then removed from the column. The product was sieved to remove product over 40 mesh and underneath 140 mesh. 89.8% of the product was in the right range.

The microencapsulated guar manufactured with this procedure was employed in food bar prototype number 4 which was used in the "HUMAN CLINICAL STUDY OF FOOD BAR" which is described below.

ENCAPSULATION EXPERIMENT 14

The objective of this experiment was to improve the coating process and produce better microencapsulated guar for use in a solid food product.

Large guar gum particles (8/22A) were encapsulated in 25% add on zein using a 18" Wurster coater. A solution of a coating material was prepared comprising zein F4000 plus Durkex® 500 equaling 20% of the zein, as a 15% by weight solution of ethanol/water at a 90/10 weight/weight ratio. The coating solution was applied to 35 kg of the guar gum particles at a rate of 240 g/min. The atomizing air pressure for the spray nozzle was 80 psig. The fluidizing inlet air temperature varied between 38.9° and 47.2° C. with a corresponding air discharge

temperature of between 24.4° and 35.6° C. After 25% zein by weight of the weight of the guar gum was applied, the process was stopped. The product was dried for 5 minutes and then removed from the column. The product was sieved to remove product over 40 mesh. 97.2% of the product was less than 40 mesh.

CLAIMS (ENGLISH)
We claim:

1. A nutritional product comprising a solid matrix comprising fat, carbohydrate, and at least one protein selected from the group consisting of vegetable proteins and milk proteins, said solid matrix having dispersed therein particles comprising a dietary fiber which lowers Serum cholesterol in humans encapsulated in zein.

2. A nutritional product according to claim 1 wherein the dietary fiber is guar.

3. A nutritional product according to claim 1 wherein said particles comprise guar encapsulated in about 20% add-on zein.

4. A nutritional product according to any one of claims 1-3 wherein a source of protein is soy protein.

5. A nutritional product according to any one of claims 1-3 wherein a source of fat is selected from the group consisting of vegetable oils containing, by weight, less than 25% saturated fatty acids.

6. A nutritional product according to any one of claims 1-3 wherein the protein is soy protein and the fat is selected from the group consisting of vegetable oils containing, by weight, less than 25% saturated fatty acids.

7. A nutritional product according to any one of claims 1-3 wherein the protein is soy protein and oat protein.

8. A nutritional product according to any one of claims 1-3 wherein the protein is soy protein and calcium caseinate.

9. A nutritional product according to any one of claims 1-3 wherein the protein is soy protein, oat protein and calcium caseinate.

10. A nutritional product for lowering serum cholesterol in humans comprising a solid matrix comprising fat, carbohydrate, at least one protein selected from the group consisting of vegetable proteins and milk proteins, and vitamins and minerals, said solid matrix having dispersed therein a serum cholesterol reducing quantity of particles comprising guar encapsulated in zein.

11. A nutritional product according to claim 10 wherein the protein is soy protein.

12. A nutritional product according to claim 10 wherein the fat is selected from the group consisting of vegetable oils containing, by weight, less than 25% saturated fatty acids.

13. A nutritional product according to claim 11 wherein the fat is selected from the group consisting of vegetable oils containing, by weight, less than 25% saturated fatty acids.

14. A nutritional product for lowering serum cholesterol in humans comprising a solid matrix of soy protein, rice bran oil, and carbohydrate, said solid matrix having dispersed therein a serum cholesterol reducing quantity of particles comprising guar encapsulated in zein.

15. A nutritional product according to claim 14 wherein said particles comprise guar encapsulated by at least about 20% add-on zein.

16. A nutritional product according to claim 14 wherein said solid matrix further comprises oat protein.

17. A nutritional product according to claim 14 wherein said solid matrix further comprises calcium caseinate.

18. A nutritional product according to claim 14 wherein said solid matrix further comprises calcium caseinate and oat protein.

19. A nutritional product according to claim 14 wherein the solid matrix further comprises an acidulant selected from the group consisting of citric acid, malic acid, and fumeric acid.

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Document 4 (D4)

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Sodium-Alginate Beads Coated with Polycationic Polymers: Comparison of Chitosan and DEAE-Dextran

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The retention capacity of alginate beads coated by two polycationic polymers, chitosan or diethylaminoethyl-dextran (DEAE-dextran) was studied. When beads were stored in latex, the chitosan coating was stable for less than 2 years, whereas the DEAE-dextran was stable for 5years. The greater the concentration of the polycationic polysaccharides in the formation solution of the beads, the greater the stability of the coated beads. Further the stability depended on the pH conditions of bead formation. With chitosan, the greatest stability was observed at pH 5.4. With DEAE-dextran the greatest stability was observed at pH 4.

INTRODUCTION

Alginate is a polysaccharide, extracted from brown algae, which contains guluronic and mannuronic acids. The alginate gelation process has its origin in a capacity of the polysaccharide molecules specifically to bind divalent cations and this results in conformational/ aggregational changes. To improve stability, the micro-capsules are sometimes coated with a polycationic polymer that forms a membrane at the bead surface. In fact, the formation of a polyelectrolyte complex has been demonstrated to occur when an anionic and a cationic polymer are simultaneously present in aqueous solution. Such a complex between two oppositely charged polymers has been studied by several groups, 2-5 and it was recognized that it could be formed between alginate (or any other anionic polysaccharide) and chitosan which is a polycationic polysaccharide derived from the natural polymer, chitin. However, chitosan presents the drawback of being insoluble at pH higher than 5.4 and this property limits its use when pigments that are unstable at low pH, have to be encapsulated. Therefore, we used another polycationic polymer, diethylaminoethyl-dextran (DEAEdextran), and the resulting DEAE-dextran coated beads were compared to those prepared with chitosan. DEAE-dextran is soluble at any pH and its amine functions are capable of interacting with alginate. In this study, we report on the stability of coated and non-coated beads in aqueous based resins.

METHODS

Bead formation

Sodium alginate was dissolved in a solution of the material to be encapsulated (Trypan blue) to obtain an alginate final concentration of 1.8% (w/v). This viscous solution was introduced in a 10 ml syringe and extruded through a 0.15 mm diameter needle using compressed air. The droplets were pulled off in 150 ml of a 0.1% HC1 chitosan (2-8 g/litre)-0.05 M $CaCl_2$ or

DEAE-dextran (8-20 g/litre)-0.05 M $CaCl_2$ stirred solution whose pH was adjusted at a given value (2, 4, 5.4, 6 or 7) with 1 M NaOH. The beads were allowed to harden for 30 min. They were rinsed with distilled water, then transferred into a latex.

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Document 5 (D5)

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[57]
ABSTRACT
A particulate fibre composition containing at least one first dietary fibre, coated by an insoluble dietary fibre or a dietary fibre with low solubility, serving to prevent dissolution of the fibre composition in the oral cavity and during passage through the oesophagus. The fibre composition has one or several inserted additional layers of at least one second dietary fibre between the at least one first dietary fibre and the coating of the insoluble dietary fibre/dietary fibre of low solubility. This fibre composition can be produced and made for individual and special purposes and applications in as much as the different properties in relation to solubility and fermentability of the fibres are utilized for the production of multilayer particles. The dietary fibre supplement can be applied as pharmaceuticals and in food products where high fibre content and small calorie content is given high priority. Furthermore, the dietary fibre supplement can be applied for replacement of part of the sugar in sugar coatings of generally known cereals.

DETAILS

Particulate fibre composition

The invention relates to a particulate fibre composition of such type containing at least one first dietary fibre surrounded by an insoluble dietary fibre or a dietary fibre of low solubility serving to prevent dissolution of the fibre composition in the oral cavity as well as during passage through the oesophagus.

In recent years, ready-made food has become an increasing part of the diet. As little as 50 years ago, the quantity of fibres in the diet was approximately 5 times higher than in today's Western World diets. This gradual change of food habits and the increased level of welfare, particularly in the Western World, has resulted in an increasing number of persons with diseases such as diabetes mellitus, gastrointestinal diseases, obesity, obstipation, hiatal hernia, cardiovascular diseases, intestinal polyps, arteriosclerosis and colon cancer and rectal cancer as well as ordinary digestive trouble.

So far, it is a well-known fact that a diet containing sufficient quantities of fibres facilitates the support of normal healthy body functions, thus decreasing the number of gastrointestinal diseases considerably.

Natural vegetable fibres are high-molecular polymers that form part of the vegetable cell wall such as e.g. cellulose, hemicellulose, pectin, etc. Vegetable fibres are indigestible or digest slowly in human beings. Consequently, no calories or a very small amount of calories are added to the food. Fibres are known to be a valuable contribution to the food, as they contain e.g. anti-oxidants and vitamins.

The vegetable fibres become voluminous at contact with liquid, resulting in a sense of satiety and reducing the desire for further intake of food. When the fibres absorb liquid, the vegetable fibres act as a lubricant for the passage of food through the alimentary canal, thus protecting the mucosa. Hence, intake of food with high fibre content offers the possibility of adjusting digestion and reducing calorie intake.

Attempts to utilize this knowledge in various ways are made, e.g. by ingestion of unprocessed fibres directly via the food or as a dietary supplement, or ingestion of more or less processed fibres.

Frequently, however, the taste of unprocessed fibres is very unpleasant. The mouthfeel becomes sticky when the fibres swell and consequently they are very difficult to swallow. Hence, unprocessed fibres are extremely difficult to ingest and their useful effect difficult to utilize.

US Patent No. 4,619,831 discloses a composition of dietary fibres produced by coating an insoluble fibre with an easily soluble fibre. The insoluble fibre is chemically and enzymatically purified to provide a concentration of insoluble dietary fibre.

Subsequently, the concentrated fibre is encapsulated in an easily soluble fibre. Easily soluble vegetable fibres are inclined to absorb liquid. They therefore dissolve at the first contact with liquid, e.g. water, and the insoluble vegetable fibres will quickly begin to swell. When e.g. the humidity of air is absorbed, the nutritional supplement will gradually become soft and spongy and may offer favourable conditions of growth for microbial activity, hence a poor durability of the dietary fibre composition; on top of that, the vegetable fibres expand quickly.

Such disadvantages make heavy demands on storage facilities and reduce the applications of the product.

Another disadvantage is created when the composition of dietary fibres is consumed together with food, in as much as the fibres begin to swell at the first contact with saliva in the oral cavity. Such swelling quickly causes the fibres to grow to such a considerable degree that it gives an unpleasant sensation when the person swallows the food. Possible utilization of fibres in colon cannot be monitored.

Japanese patent application JP 6015163 discloses microcapsules or pearls comprising fibres or drugs released at controllable speed.

To prevent decomposition of the microcapsules while standing in strong saline solutions, the capsules contain alginic acid fibres or an alginic acid salt. The microcapsules are furthermore characterized by good physical stress properties.

Such microcapsules are produced by mixing a sodium alginate solution with another substance, e.g. a fibre. The compound is shaped into pearls and after a fall from a height of 5cm into a calcium chloride solution, it is subjected to subsequent drying.

The microcapsules comprise only two fibres. The capsules are produced in such a way that the previous mixing of the fibres will not cause a complete surrounding of the remaining substance by fibres of alginic acid or alginic acid salt. Hence, it will be liberated gradually to the surroundings as early as at the first contact with a liquid. Furthermore, the design of the microcapsules is stress-proof which make them extremely unpleasant to chew.

The energy content of vegetable fibres is very low and utilization involves some difficulties. However, particularly water-soluble vegetable fibres are more or less fermentable, although such process involves considerable energy consumption.

It has only recently become known within technical science that fibres are combined of various components, the result of which is that different fibres have individual compositions which however only have been identified in very few cases. As an example, the effect of water-soluble dietary fibres of e.g. fruits, oat and legumes on the content of glucose and cholesterol in the blood is known today.

Generated through own experiments, the inventors of this invention have now succeeded in applying this new know-how for the manufacture of a number of various fibre compositions with unique positive effect on health as well as applications so far unknown.

The object of the invention is to provide a particulate fibre composition of the kind mentioned in the opening paragraph, which is applicable for preventive treatment of diseases, for direct treatment of diseases, or for consumption as a beneficial dietary supplement without essential change of eating habits.

A second object of the invention is the making of a particulate fibre composition for adjustment of the retention time of food in one or several sections of the gastrointestinal tract.

A third object of the invention is to provide a multilayer particulate fibre composition, each layer having its own unique effect on or in a previously identified spot in the gastrointestinal tract.

A fourth object of the invention is to provide a fibre composition rich in fibre and low in carbohydrate.

A fifth object of the invention is to provide a method to produce such particulate fibre composition.

The novel and unique features, whereby this is achieved according to the invention, is the insertion of one or several additional layers of at least one other dietary fibre between the at least one first dietary fibre and the coating of the insoluble/ slightly soluble dietary fibre.

Insoluble and soluble dietary fibres will absorb liquid at contact. To prevent dissolution and swelling of fibres e.g. already during storage of the finished product or immediately after initial fibre intake, the fibres may he encapsulated in at least one vegetable fibre coating which has insolubility or slight solubility by nature or through processing.

Production of compositions of fibre combinations with numerous therapeutic and/or healthful possibilities and effects is rendered possible by structuring the particulate fibre composition of layers of different fibres.

The fibre composition is made up of several different fibres, thus according to the invention enabling the design of a particulate fibre composition, partly consisting of fibres whose properties allow the conveyance of one or several fibres to one or several prefixed spots in the gastrointestinal tract, partly consisting of fibres whose purpose is to act in such spots.

By using the fact e.g. that various insoluble fibres or fibres with low solubility are more or less dissolved at various rates and at various pH values, it is possible to apply such fibres for encapsulation of other components such as easily soluble fibres that are fermented in colon, or fibres with low solubility that swell and fill the stomach for a prolonged period of time before passing on in the system.

Other advantageous effects may be e.g. swelling to increase the sense of satiety, to release vitamins and to adjust transit time through the gastrointestinal tract. In addition, there is by fermentation generated acetate supplying energy to the organism (corresponding to approx. 50% carbohydrate), butyrate directly nourishing epithelial cells in colon, and propionate supposedly reducing the content of cholesterol in the blood.

In addition, the soluble fermentable fibres change the bowel flora in colon in such a way that the quantity of bifido bacteria is increased to the detriment of bacteria such as Clostridium, Escherichia coli and Klebsiella. It is a well-known fact that bifido bacteria reduce certain initial stages and markers of colon cancer and reduce the risk of gastrointestinal infections as well as various infections in the bowel, e. g. Crohn's disease and ulcerative colitis.

The particulate fibre composition can advantageously comprise one or several inserted layers of fibres designed to gradually dissolve and/or be released and/or be fermented in the course of conveyance of the fibre composition through the gastrointestinal tract and its stay in the various sections such as the stomach, the jejunum, the duodenum, the ileum or the colon.

A preferred embodiment of the invention may include at least one first dietary fibre in the fibre composition, accounting for between 65% and 98% of the total fibre content of the fibre composition, and this fibre can advantageously be selected as the fibre required to be conveyed to and utilized in the desired part of the gastrointestinal tract.

The outermost layer of fibre can advantageously be selected as a fibre which does not dissolve until at contact with the gastric juice. When the fibre composition is encapsulated by such a layer of insoluble fibres or fibres of low solubility, the coating will form a protective barrier against absorption and penetration of humidity from the surroundings to the inner layers of fibre.

Consequently, the durability and retention time of the packed fibre composition can advantageously be increased, and the costs of expensive packing techniques and storage conditions be kept down.

At the same time, the advantage is obtained in that the fibre composition will not begin to swell on ingestion, but gradually be dissolved on the desired spot in the stomach or the intestine.

Consequently, it is far more pleasant to eat than e.g. unprocessed fibres of e.g. wheat bran or psyllium. As previously mentioned, such are very difficult to swallow and give an unpleasant, sticky sensation in the mouth.

A particularly advantageous embodiment of the invention offers an outermost coating to the fibre composition, e.g. containing a natural colouring agent to give the composition an attractive appearance. Alternatively, the coating may be a thin natural layer of fibres, sweet to the taste, such as inulin or Raftilose. This makes appearance, taste and texture of the fibre composition attractive to e.g. children for eating on e.g. sour-milk products which children typically eat for breakfast.

Inulin is not hydrolyzed by enzymes in the gastrointestinal tract and therefore presents no metabolisable carbohydrate source.

Consequently, it is excreted in a non-metabolised manner.

In cases where the only sweetener of the fibre composition is a non-decomposable dietary fibre, the fibre composition is also an attractive dietary supplement for diabetes patients.

Alternatively, an outer layer of the fibre composition may be either a glazing or a coating of a monosaccharide such as fructose, glucose or sucrose, adding a pleasantly sweet taste with a prompt taste sensation to the fibre composition and making it even easier to swallow.

Additionally, the fibre composition may have one or several inserted layers or an outermost coating of a protein, such as casein containing all normal amino acids as well as a beneficially large number of the essential amino acids.

The at least one first dietary fibre is preferably selected from the group of psyllium, citrus pulp, apple pulp, black currant pulp, cherry pulp, grape pulp, modified starch, wheat bran, cellulose, acacia gum, alginate and fibres from pulp originating from other vegetables and fruits. However, this invention is not limited to such dietary fibres in as much as other types of fibres will be within the scope of this invention.

Furthermore, similar encapsulation of other nutritive components in fibres will also be possible.

As example of the fibre content in pulp, it can be mentioned that apple pulp from production of apple juice analysed to have a dietary fibre content of approximately 58 per cent, of this approximately 25 per cent is raw cellulose; the pulp from production of black-currant juice analysed a dietary fibre content of approximately 65 per cent, of this approximately 25 per cent is raw cellulose; and pulp from production of cherry juice analysed a dietary fibre content of approximately 60%, of this approximately 23 per cent is raw cellulose.

Such residual or side products from juice production are a low-priced raw material, containing minerals and vitamins and being particularly well suited for adjustment of the dietary fibre content of food. Frequently, such residual or side products are waste products which are removed either by expensive disposing or by incineration. Consequently, such products are advantageously low-priced and useful ingredients of the fibre composition according to this invention.

When the dietary fibres come from industrial residual products, prior ultrasound processing may be advantageous, e.g. 15-40 kHz, partly to give raw material containing vegetable fibres, such as pulp and pulp fibres from vegetables and fruits, a larger surface, and partly to ensure that the natural germs on pulp and fibres are completely destroyed.

The at least one other dietary fibre can advantageously be selected from the fibre group consisting of pectin, guar gum, acacia gum, dextran, inulin, Raftilose, alginic acid, alginate, mainly K-alginate or Ca-alginate, or combinations of these.

In a preferred embodiment the at least one first dietary fibre is encapsulated in a coating of K-alginate or a coating of Ca-alginate, the insolubility of such combinations at neutral pH value being well-known to the expert, or that the combinations can easily be processed with a view to becoming insoluble at neutral pH value. (Edvar Onsoyen, Commercial applications of alginates, Carbohydrates in Europe No. 14, May 1996, pp. 26-31). The combinations are very robust against exposure to liquid and do not dissolve until exposure to a liquid with a low pH number, e.g. when exposed to the hydrochloric acid of the stomach. Such coating may also act as an inserted dietary fibre layer.

Alternatively, the encapsulating coating or one or several of the inserted dietary fibre layers may be a combination of K-alginate, Ca-alginate or pectin.

In addition, the fibre composition may include at least one additive, comprising between 0.1 and 5 per cent of the total weight of the finished fibre composition. Such additive has been selected from the fibre group with non-oxidizing properties such as tomatoes and grapes, vitamins, colouring agents, flavouring agents or from the group of sweeteners with low caloric content, mainly from the group of inulin, neohesperidine and steviolglycos ides. Steviolglycoside sweetens up to 300 times more per weight unit and neohesperidine up to 1500 times more per weight unit compared to sucrose which makes this group of sweeteners highly applicable to keep the dietary supplement low in caloric content.

In an alternative embodiment, an additive with anti-oxidizing properties may be added to the particulate fibre composition.

Examples of such additives may be synthetic or natural vitamins such as vitamin C or E. The durability of the finished product will be further ensured by addition of anti-oxidants, or if an essential part of the fibre composition consists of fibres with anti-oxidizing effect.

Furthermore, this produces a good effect on the fibre composition in as much as anti-oxidants inhibit the formation of free oxygen radicals, thus producing an anti-inflammatory effect as well as preventing cardiovascular diseases.

For adjustment of the relation between the fibre content of the fibre and the volume of the finished product, the fibre composition may advantageously additionally include at least one filler, preferably from the group of guar gum, starch, maltodextrin or their breakdown products and/or derivations. In addition, such filler makes for the unification of fibres.

Lucrative applications of this fibre composition may be addition to or coating of corn products, bread, health bars and similar products in as much as addition of the composition will not affect the normal characteristics of the end product.

In addition, the invention relates to a method for producing a particulate fibre composition as described above.

The method may include one or several of the following steps:

-solution/ suspension of the at least one first dietary fibre in water,

-filtration of the solution/ suspension of the at least one first dietary fibre through a filter with a fixed mesh size preferably not exceeding 0.2 mm,

-evaporation of fibres to dryness,-trituration of evaporized fibre paste to a particulate fibre sphere with a spherical particle size preferably not exceeding 0.2 mm,

-coating of the particulate fibre substance with one or several layers of a second dietary fibre, and

-drying of the resultant particulate fibre composition at approximately 60'C.

If the fibres originate from industrial production of e.g. juice, such fibres may produce an undesired microbiological activity. In such cases, the method may advantageously include an initial step where the fibres are ultrasound processed for a period sufficiently long to inactivate microbiological activity. The fibres may further be autoclaved to obtain optimum guarantee for elimination of all germs.

Furthermore, it may be appropriate to treat the evaporized fibres with a solution containing cation, such as CaCl2, to crosslink and unify the fibres in the fibre composition. To reduce drying time and production time it may be appropriate to apply a CaC1, solution with a relatively high concentration, e.g. 5% (5 grams/100 ml).

In an especially preferred embodiment, the method can also include the step of adding sweetener exclusively or together with one or several additives to the nutritional supplement.

When the at least one first dietary fibre and one or several inserted layers of fibre are sprayed and/or coated with a fibre, e.g. an alginate which is insoluble until contact with liquid with a low pH, or pectin which has low solubility at neutral pH, the gelating, coating and stabilising properties of the fibre will cause the fibre to surround the remaining fibres forming a coating, entirely covering the remaining fibre layers.

Furthermore, the invention relates to the application of the fibre composition in food processing, e.g. cereals, cakes, snacks, health bars, healthy candy, drinks as well as health food products in general. Depending on the applied fibres, the energy of such food will be low, as will the optional content of natural or added vitamins, minerals and/or anti-oxidants. The intake of such food products can contribute positively to e.g. adjustment of the cholesterol in the blood stream, adjustment of the uptake of calcium, increase of the number of bifido bacteria in colon as well as adjustment of digestion.

The fibre composition may form part of such food products by way of coating or in the form of added granulates or powders in as much as swelling of the fibre composition is prevented when added to a liquid-containing medium with neutral pH value.

By suspension of the finished particulate fibre composition in an aqueous solution, the suspension can easily be sprayed onto or over any type of cereal, followed by subsequent drying by well-known techniques. In this way, a food product rich in fibre and low in caloric value is produced. Consequently, the fibre composition is extremely suitable for substitution of at least part of the sugar in sugar coatings of generally known cereals.

The fibre present in such a cereal comprises as much as 30 w%.

Particularly beneficial applications of fibre compositions according to this invention is in the form of dietary supplements or pharmaceuticals, e.g. for adjustment of emptying time of the stomach, for adjustment of transit time of food through the intestines, for adjustment of calcium uptake by the gastrointestinal tract, for treatment of insulin resistance, lipaemia, obstipation, overweight or infection in the gastrointestinal tract.

Within the scope of this invention, the fibres for the production of the fibre composition may be fermented or synthesised dietary fibres as well.

Within the scope of this invention, the fibre composition may be applied for numerous purposes in food products, dietary products as well as health food products, and is consequently not limited to the above mentioned applications.

The dietary fibres of the particulate fibre composition may include any combination of various soluble, insoluble, easily fermentable dietary fibres or dietary fibres which are not easily fermentable and particularly beneficial embodiments will be described in the enclosed examples.

In the following examples, the coating unit is a rotary mill, type Mansfield Ltd. UK.

13 C expiratory test was carried out by ingestion of 150mg "C-marked sodium acetate together with the apportioned quantity of dietary fibres or blind test. The 13C content of

the expiratory air was measured every third minute for two hours and every fifteenth minute for four hours.

Alternative embodiments of this invention have been produced and tested in the following tests.

EXAMPLES

Test 1:

Production of particulate fibre composition according to the invention with one first dietary fibre and two additional fibre layers.

Transfer of 50 grams psyllium to coater and heating to 60'C.

Crosslinking of fibres by spraying with 10ml of a 1% CACl2, solution for a 60-second period. Drying of fibres by conveyance in coater at 60'C for 5 minutes. Spraying of the dried crosslinked psyllium fibres with 5ml 5% pectin solution for 10 minutes. Subsequent drying of the fibre composition by conveyance in coater for additionally 5 minutes at 600C. Final spraying of the pectin-coated psyllium fibres with 10ml 10% inulin, and drying of the fibre composition by conveyance in coater for 5 minutes at 60'C.

This fibre composition has a long retention time in the stomach and contains 50 grams of psyllium, 0.1 gram of CACl2 0.25 grams of pectin and 1 gram of inulin, giving an end product with a composition of the substance by percentage as follows: 97.37% psyllium, 0.19% CACl2 2 1 0. 49% pectin and 1.95% inulin, based on the final weight of the finished product.

Test 2:

Production of a-particulate fibre composition according to the invention with one first dietary fibre and two additional fibre layers.

As test 1, however 10ml 5% pectin solution and 20ml 10% inulin suspension are applied.

This fibre composition has long retention time in the stomach and the content of psyllium results in neutralisation and stabilisation of the blood sugar level at ingestion of the fibre composition. The fibre composition contains 50 grams of psyllium, 0.1 gram of CACl2 0.5 grams of pectin and 2 grams of inulin. The composition by percentage of the final product is 95.06% psyllium, 0.19% CaC1, 0.95% pectin and 3.80% inulin, based on the final weight of the finished product.

Test 3:

Production of a particulate fibre composition according to the invention with one first dietary fibre and two additional fibre layers.

Transfer of 100 grams of psyllium to coater and heating to 600C.

Crosslinking of fibres by spraying with 10ml of a 1% CACl2 solution for a 60-second period. Drying of fibres by conveyance in coater at 60'C for 5 minutes. Spraying of the dried crosslinked psyllium fibres with 25ml 5% pectin solution for 3 minutes. Subsequent drying of the fibre composition by conveyance in coater for additionally 5 minutes at 600C. Final spraying of the pectin-coated psyllium fibres with 50ml 10% Raftilose, and drying of the fibre composition by conveyance in coater for 5 minutes at 600C.

The organoleptic experience of the testees was that this fibre composition was pleasant to the taste, it was pleasant to consume as well as gave a long sense of satiety. It contains 100 grams of psyllium, 0.1 gram of CaCl2 1.25 grams of pectin and 5.0 grams of Raftilose, giving an end product with a composition of the substance by percentage as follows: 94.03% psyllium, 0.09% CaCl2, 1.18% pectin and 4.70% Raftilose, based on the final weight of the finished product.

Test 4:

Production of a particulate fibre composition according to the invention with one first dietary fibre of citrus pulp and two additional fibre layers.

Transfer of 500 grams of citrus pulp to 100ml water and ultrasound-processing for a 15-minute period. Filtration of the fibre composition and autoclave treatment at 112'C for 10 minutes and drying overnight. Microbiological control in the form of cultivation on nutrient substrate showed no occurrence of germs.

Transfer of 250 grams of citrus pulp to coater and heating to 600C.

Crosslinking of fibres by spraying with 25ml of a 1% CaCI, solution for a 120-second period. Drying of fibres by conveyance in coater at 600C for 5 minutes. Spraying of the dried crosslinked citrus pulp with 50ml 5% pectin solution for 3 minutes. Subsequent drying of the fibre composition by conveyance in coater for additionally minutes at 60'C. Final spraying of the pectin-coated citrus pulp with 50ml 10% Raftilose, and drying of the fibre composition by additional conveyance in coater for 5 minutes at 600C.

This fibre composition contains 250 grams of psyllium, 0.25 grams of CACl2, 2.5 grams of pectin and 5.0 grams of Raftilose, giving an end product with a composition of the substance by percentage as follows: 96. 99% psyllium, 0.10% CaCl2, 0.97% pectin and 1.94% Raftilose, based on the final weight of the finished product.

For control of the ability of the particulate fibre composition to prevent liquid absorption, 5 grams of unprocessed fibres and 5 grams of the particulate fibre composition according to the invention respectively were transferred to centrifugal bottle containing 50 ml water and agitated for 60 seconds. Subsequent centrifugation at 1000 rpm for 120 seconds and measurement of supernatant. The test was repeated 5 times and showed significantly less absorption of liquid by the particulate fibre composition-up to 77%-compared with unprocessed fibres.

In addition, this fibre composition was applied for the stomach emptying test, shown in Fig. 3. A testee was given 15 grams of water and 15 grams of unprocessed citrus pulp respectively as well as 15 grams of the fibre composition according to the invention for

comparison. The rate of stomach emptying was determined by means of 13 C expiration test and the content of glucose in the blood was monitored.

The test shows that coating of citrus pulp with a pectin layer results in an increase of the half life period for stomach emptying (T/2) by approximately 60%. This fibre composition is rich in vitamins and well suited for prolongation of the sense of satiety. Furthermore, it will contribute to a reduction of the content of cholesterol and triglyceride in the blood.

Consequently, it is particularly suitable for reduction of the risk of arteriosclerosis, development of arteriosclerotic heart disease and cerebral haemorrhage.

Test 5:

Production of a particulate fibre composition according to the invention with one first dietary fibre of apple pulp and two additional fibre layers.

Conducted as Test 4, however with apple pulp in stead of citrus pulp.

This fibre composition was applied for the stomach emptying test, shown in Fig. 4. A testee was given 30 grams of water and 30 grams of unprocessed apple pulp respectively and for comparison 30 grams of the fibre composition according to the invention. The rate of stomach emptying was determined by means of "C expiration test and the content of glucose in the blood was monitored.

This test reveals surprising new information and shows that apple pulp single-handedly reduces the rate of stomach emptying, and that coating of apple pulp with a pectin layer results in a reduction in the half life period for stomach emptying (T/2) by approximately 33%. Consequently, this fibre composition is suitable for treatment of persons with problems of too long passage time through the gastrointestinal tract as well as persons suffering from obstipation. Apple pulp is rich in C vitamins. In addition, it is easily fermentable and thus has a positive effect in colon due to stimulation of the generation of bifido bacteria.

Test 6:

Production of a particulate fibre composition according to the invention with one first dietary fibre and two additional fibre layers.

Conducted as Test 4, however with wheat bran in stead of citrus pulp.

This fibre composition was applied for the stomach emptying test, shown in Fig. 5. A testee was given 30 grams of water and 30 grams of unprocessed wheat bran respectively, and for comparison 30 grams of the fibre composition according to the invention. The rate of stomach emptying was determined by means of "C expiration test and the content of glucose in the blood was monitored.

This fibre composition enables increase of the half life period for stomach emptying by approximately 50%. Consequently, this fibre composition is suitable for prolongation of e.g. the sense of satiety and is well suited as a dietary product as well as a health product.

Test 7:

Production of a particulate fibre composition according to the invention with two first dietary fibres and three additional fibre layers.

Dissolution of 1000 grams of psyllium in 1000ml boiling water and filtration through a filter with mesh size 0.05mm. Pouring of this compound over 1000 grams of oat bran and evaporation and grinding to particles of less than 0.02mm. Transfer to heated coater (rotary mill). Crosslinking of fibres by spraying with 50ml of a 5% CaCl2 solution for a 60-second period. Drying of fibres by conveyance in coater at 60'C for 5 minutes. Spraying of the dried crosslinked fibre composition with 100ml 3% pectin solution for 10 minutes. Subsequent drying of the fibre composition by conveyance in coater for additionally 5 minutes at 600C. Spraying of the pectin-coated fibres with 100ml 5% alginate solution which is insoluble at neutral pH value, and drying of the fibre composition by conveyance in coater for 5 minutes at 60'C. Final coating of the fibre composition with 20 grams of inulin in a 10% solution and drying of the fibre composition by conveyance in coater at 60'C for minutes.

This fibre composition contains 1000 grams of psyllium, 1000 grams of oat bran, 2.5 grams of CaCl2, 3.0 grams of pectin, 5.0 grams of alginate and 20 grams of inulin, giving an end product with a composition of the substance by percentage as follows: 49.25% psyllium, 49.25% oat bran, 0.12% CaCl2, 0.15% pectin, 0.25% alginate and 0.98% inulin, based on the final weight of the finished product.

The final product is sweet to the taste, is partially soluble in the stomach and contributes to prevention of the rate of stomach emptying by approximately 50%. Psyllium and oat bran is fermented in colon, and ingestion of the fibre composition results in reduced insulin response.

Test 8:

Production of a particulate fibre composition according to the invention with two first dietary fibres and three additional fibre layers as well as an outer coating of glucose.

Production of fibre composition as in Test 7, however with a glucose coating.

This fibre composition has a higher energy content of easily metabolisable monosaccharids, and the outer sweet-tasting layer is pleasant to the taste promptly.

Test 9:

Production of a simple fibre composition according to the invention with one first dietary fibre and one additional fibre layer.

Transfer of 100 grams of psyllium to coater and heating to 60'C.

Crosslinking of fibres by spraying with 10ml of a 1% CaC1, solution for a 60-second period. Drying of fibres by conveyance in coater at 600C for 5 minutes. Spraying of the dried crosslinked psyllium fibres with 25ml 5% pectin solution for 3 minutes. Subsequent drying of the fibre composition by conveyance in coater for additionally 5 minutes at 600C.

This fibre composition contains 100 grams of psyllium, 0.1 gram of CaC1, and 1.25 grams of pectin, giving an end product with a composition of the substance by percentage as follows: 98.67% psyllium, 0.10% CaCl2 and 1.23% pectin, based on the final weight of the finished product.

CLAIMS (ENGLISH)

Patent claims

1. A particulate fibre composition of the kind that comprises at least one first dietary fibre, coated by an insoluble dietary fibre or a dietary fibre with low solubility serving to prevent dissolution of the fibre composition in the oral cavity and during passage through the oesophagus, characterised by the insertion of one or several layers of at least one second dietary fibre between the at least one first dietary fibre and the coating of the insoluble dietary fibre/dietary fibre of low solubility.

2. A particulate fibre composition according to claim 1, characterised by the first primary dietary fibre accounting for between 65 and 98% of the weight of the finished fibre composition.

3. A particulate fibre composition according to claim 1 or 2, characterised by at least one fibre of the particulate fibre composition having a therapeutic effect.

4. A particulate fibre composition according to claim 1, 2 or 3, characterised by the at least one first dietary fibre being a soluble, easily fermentable fibre.

5. A particulate fibre composition according to any of claims 1-4, characterised by the selection of the at least one first dietary fibre from the group of psyllium, citrus pulp, apple pulp, grape pulp, modified starch, wheat bran, oat bran, cellulose, gum arabic, alginate and pulp fibres from vegetables and fruits.

6. A particulate fibre composition according to any of claims 1-5, characterised by the selection of the at least one second dietary fibre from the group of pectin, guar gum, acacia gum, dextran, inulin, Raftilose, alginic acid, alginate, preferably K alginate or Ca alginate, or combinations of these.

7. A particulate fibre composition according to any of claims 1-6, characterised by the inclusion of additionally at least one additive to the fibre composition, selected from the group of fibres with anti-oxidizing properties, vitamins, colouring agents, flavouring agents or from the group of sweeteners with low calorie value, preferably from the group of inulin, neohesperidine and steviolglycosides.

8. A particulate fibre composition according to claim 8, characterised by the at least one additive being a layer of monosaccharides, oligosaccharides or proteins.

9. A particulate fibre composition according to claim 7 or 8, characterised by the at least one additive being added in a quantity of between 0.1% to 5% of the weight of the finished fibre composition.

10. A method for producing a particulate fibre composition of the kind that comprises at least one first dietary fibre surrounded by a coating of an insoluble dietary fibre or a dietary fibre with low solubility, serving to prevent dissolution of the fibre composition in the oral cavity and during passage through oesophagus, characterised by the method comprising one or several of the following steps:

dissolution/ suspension of the at least one first dietary fibre in water, filtration of the fibre solution/ suspension through a filter with fixed mesh size, evaporation of fibres, trituration of evaporated fibre mass to a particulate fibre matter, encapsulation or coating of the particulate fibre matter in a rotary mill by one or several layers of a second dietary fibre, and drying of the resultant particulate fibre composition.

11. A method according to claim 10, characterised by the inclusion of an initial step, namely ultrasound processing of the dietary fibres for a sufficient period to inactivate microbiological activity.

12. A method according to claim 10 or 11, characterised by the additional inclusion of a step for treatment of the evaporated fibres with a CaCl2 solution.

13. A method according to claim 10, 11 or 12, characterised by the additional inclusion of a step for adding of at least one sweetener exclusively or together with one or several additives.

14. Application of a particulate fibre composition according to any of claims 1-8, characterised by the application of the fibre composition for coating of cereals or for coating of food products produced of or containing cereals.

15. Application of a particulate fibre composition according to any of claims 1-8, characterised by the application of such quantity of the fibre composition, applied for coating of cereals or for coating of food products produced of or containing cereals, which will give the finished product a fibre content above 30% and especially above 40% of the weight of the finished particulate fibre composition.

16. Application of a particulate fibre composition according to claims 1-8, characterised by the application of the fibre composition as a dietary supplement.

17. A particulate fibre composition according to any of claims 1-8, characterised by the application of the fibre composition as a pharmaceutical.

18. A particulate fibre composition according to any of claims 1-8, characterised by the application of the fibre composition for adjustment of rate of stomach emptying.

19. Application of a particulate fibre composition according to claims 1-8 for the production of a pharmaceutical for treatment of insulin resistance, lipaemia, obstipation, overweight or infection in the gastrointestinal tract.

20. Application of a particulate fibre composition according to claims 1-8 for the production of a pharmaceutical for adjustment of uptake of calcium by the gastrointestinal tract or for adjustment of the intestinal transit time of food.

* * * * *

Case study 2 - Infringement

Your client is active in the field of tissue bio-engineering. They have now found a production process for tissue that has the function of heart valves, which can be used to replace any malfunctioning heart valve *in situ*.
The production process starts by seeding smooth muscle fibroblast cells that are derived from the patient (which is referred to as being 'homologous') on a scaffold, after which homologous endothelial cells are seeded thereupon. This scaffold is made of a biocompatible and biodegradable polymer such as PGA, PLA, polycaprolactone and/or the polyhydroxyalkanoate, P4HB, wherein the structure of the scaffold is obtained by electrospinning these materials. The tissue is then grown under steady flow-rate and pressure conditions in a bioreactor (pulsatile flow chamber), that makes use of bovine plasma as a source of nutrients, and the necessary growth factors. When the tissue has grown sufficiently, it is harvested and implanted into the patient. Once implanted, the extracellular matrix will continue to form as the scaffold gradually degrades.

Your client would like to sell the heart valves, as described above, in the United States and in various countries in Europe. The client has asked you to conduct a patent infringement/patent clearance search in order to identify any potential patent infringement risks. The results of your search are Documents 1-9. A copy of each has been attached. Which of these documents would you cite in a search report as potentially relevant from a patent infringement perspective and for what reason(s)?

There is no need to use Espacenet (or any other external database) to obtain status information for these documents. You may assume that all annuity fees for the patents and patent applications have been paid. All the information you need to answer the question is included herewith.

List of Documents:
Document 1- US20080233162
Document 2- US5192312
Document 3- US5855610
Document 4- EP1077072
Document 5- US6514515
Document 6- Extract from "Artificial Heart Valves"
Document 7- EP1339356
Document 8- WO2006/099334
Document 9- EP1878451

Document 1

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(54) **FIBROUS 3-DIMENSIONAL SCAFFOLD VIA ELECTROSPINNING FOR TISSUE REGENERATION AND METHOD FOR PREPARING THE SAME**

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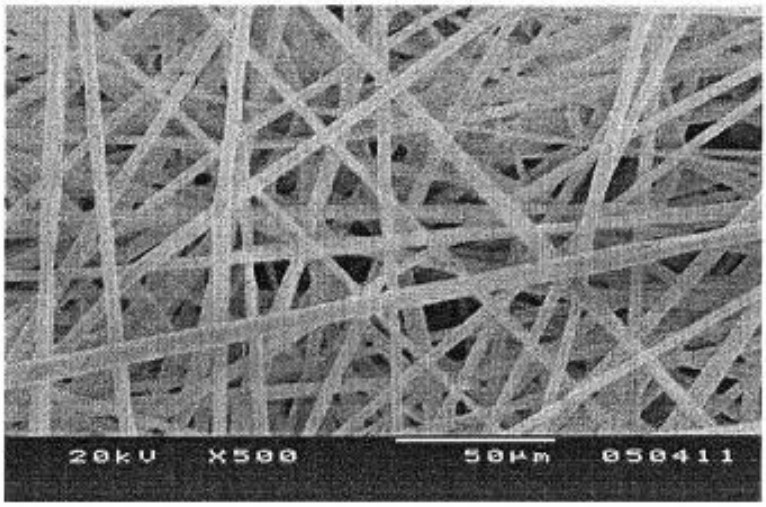
(57) **ABSTRACT**

The present invention relates to a fibrous 3-dimensional porous scaffold via electrospinning for tissue regeneration and a method for preparing the same. The fibrous porous scaffold for tissue regeneration of the present invention characteristically has a biomimetic structure established by using electrospinning which is efficient without wasting materials and simple in handling techniques. The fibrous porous scaffold for tissue regeneration of the present invention has the size of between nanofiber and microfiber and regular form and strength, so that it facilitates 3-dimensional tissue regeneration and improves porosity at the same time with making the surface area contacting to a cell large. Therefore, the scaffold of the invention can be effectively used as a support for the cell adhesion, growth and regeneration.



Document 1
Claims of US2008/233162

1. A fibrous porous 3-dimensional scaffold for tissue regeneration comprising a polymer and/or a low molecular fiber, which is formed in a 3-dimensional network structure by electrospinning.
2. The fibrous porous 3-dimensional scaffold for tissue regeneration according to claim 1, wherein the polymer is one or more synthetic polymers selected from a group consisting of representative bio-degradable aliphatic polyesters such as polylactic acid (PLA), polyglycolic acid (PGA), poly(D,L-lactide-co-glycolide) (PLGA), poly(caprolactone), diol/diacid aliphatic polyester, polyester-amide/polyester-urethane, poly(valerolactone), poly(hydroxyl butyrate) and poly(hydroxyl valerate) or one or more natural polymers selected from a group consisting of chitosan, chitin, alginic acid, collagen, gelatin and hyaluronic acid.
3. The fibrous porous 3-dimensional scaffold for tissue regeneration according to claim 2, wherein the polylactic acid (PLA) is a low molecular and/or a polymer poly-L-lactic acid (PLLA).
4. The fibrous porous 3-dimensional scaffold for tissue regeneration according to claim 1, wherein the fiber is 1-15 < in diameter.
5. A method for preparing the fibrous porous 3-dimensional scaffold for tissue regeneration of claim 1 by using electrospinning.
6. The method for preparing the fibrous porous 3-dimensional scaffold for tissue regeneration using electrospinning according to claim 5, which comprises the following steps:
(i) preparing a spinning solution by dissolving a polymer and/or a low-molecular compound singly or together in an organic solvent; and
(ii) spinning the polymer solution by using an electro-spinner and volatilizing the organic solvent at the same time to form a 3-dimensional network structure.
7. The method for preparing the scaffold for tissue regeneration according to claim 5, which additionally includes the step of molding the fiber to fit defective area.
8. The method for preparing the scaffold for tissue regeneration according to claim 5, wherein the polymer and/or low molecular compound is PLLA.
9. The method for preparing scaffold for tissue regeneration according to claim 5, wherein the organic solvent is one or more compounds selected from a group consisting of chloroform, dichloromethane, dimethylformamide, dioxane, acetone, tetrahydrofurane, trifluoroethane and hexafluoroisopropylpropanol.
10. The method for preparing the scaffold for tissue regeneration according to claim 9, wherein the organic solvent is a mixture of dichloromethane and propylpropanol or a mixture of dichloromethane and acetone.
11. The method for preparing the scaffold for tissue regeneration according to claim 5, wherein the organic solvent has a boiling point of 0-40[deg.] C. and a viscosity of 25-35 cps.
12. The method for preparing the scaffold for tissue regeneration according to claim 5, wherein the polymer and low molecular compounds are dissolved in 5-20 weight % organic solvent to prepare a spinning solution.
13. The method for preparing the scaffold for tissue regeneration according to claim 5, wherein the step (ii) is carried out under the following conditions; temperature: 15-25[deg.] C., humidity: 10 40%, spinning distance: 10-20 cm, voltage: 10-20 kV, releasing speed: 0.050 < 0.150 ml/min and the internal diameter of the syringe: 0.5-1.2 mm.
14. An implantation material for cell adhesion, growth and regeneration comprising the fibrous porous 3-dimensional scaffold for tissue regeneration of claim 1.

15. The implantation material for cell adhesion, growth and regeneration according to claim 14, wherein the cell is cartilage cell, endothelial cell, skin cell, osteocyte, bone cell or stem cell.

Document 2

US005192312A

United States Patent [19]

Orton

[11] Patent Number: 5,192,312

[45] Date of Patent: Mar. 9, 1993

[54] **TREATED TISSUE FOR IMPLANTATION AND METHODS OF TREATMENT AND USE**

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[52] **U.S. Cl.** **623/2**; 623/11; 623/66; 427/2

[58] **Field of Search** 623/66, 11, 1, 2; 427/2

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,407,787	10/1983	Stemberger	424/28
4,485,096	11/1984	Bell	424/95
4,539,716	9/1985	Bell	623/1
4,546,500	10/1985	Bell	623/1
4,609,551	9/1986	Caplan	424/95
4,642,120	2/1987	Nevo et al.	623/16
4,785,079	11/1988	Gospodarowicz	530/399
4,828,563	5/1989	Müller-Lierheim	623/66

(List continued on next page.)

FOREIGN PATENT DOCUMENTS

0296475	12/1988	European Pat. Off. .
0361957	4/1990	European Pat. Off. .
WO86/02273	4/1986	PCT Int'l Appl. .
WO89/00198	1/1989	PCT Int'l Appl. .
WO89/01286	2/1989	PCT Int'l Appl. .
WO89/08117	9/1989	PCT Int'l Appl. .
2136533	9/1984	United Kingdom 623/2

OTHER PUBLICATIONS

O'Brien, et al., *A Comparison of Aortic Valve Replacement with Viable Cryopreserved and Fresh Allograft Valves, with a Note on Chromosomal Studies*, J. Thoracic & Cardiovascular Surg. 94:812–823 (1987).

Slavkin, et al., *Concepts of Epithelial–Mesenchymal Interactions During Development: Tooth and Lung Organogenesis*, J. Cellular Bioch. 26:117–125 (1984).

Manu-Tawiah and Martin, *Peat Extract as a Carbon Source for the Growth of Pleurotus ostreatus Mycelium*, J. Sci. Food Agric. 47:243–247 (1989).

Nichols, et al., *Cytogenetic Evaluation of Human Endothelial Cell Cultures*, C. Cellular Phys. 132:453–462 (1987).

Nanchahal, et al., *Cultured Composite Skin Grafts: Biological Skin Equivalents Permitting Massive Expansion*, The Lancet 2 (1989) 22:191–193 (Jul. 22, 1989).

Shiogama, et al., *An Improved Cryopreservation Procedure for Human Fetal Pancreas Tissues*, Biological Abstracts, vol. 85, Abstract No. 46563 (1988).

Shingh, et al., *Binding of Tumor-Derived Angiogenic Factor to High Affinity Receptor on Endothelial Cells*, J. Cell Biology 103:299a, Abstract No. 1107 (1986).

Bell, et al., *Living Tissue Formed in vitro and Accepted as Skin-Equivalent Tissue of Full Thickness*, Science 211:1052–1054 (1981).

(List continued on next page.)

Primary Examiner—David Isabella
Assistant Examiner—Dinh X. Nguyen
Attorney, Agent, or Firm—Kenyon & Kenyon

[57] **ABSTRACT**

Tissue which is suitable for transplant is treated with a growth factor and cells which populate the tissue and native cells must be removed, they cannot be "masked" reduce immunogenicity; this increases the longevity of the tissue upon transplant. The preferred growth factor is basic fibroblast growth factor, and the preferred cells are fibroblasts. The tissue can be an allograft or xenograft taken from a cow, pig or other mammal.

24 Claims, 2 Drawing Sheets

Document 2
Claims for US 5,192,312 (only independent claims are shown)

1. An implantable human heart valve treated with growth factor effective on fibroblast cells and populated with fibroblast cells in an amount and for a time period effective for rendering the heart valve substantially non-immunogenic upon implant into a mammal.

2. An implantable non-human mammalian heart valve treated with growth factor effective on fibroblast cells and populated with fibroblast cells in an amount and for a time period effective for rendering the heart valve substantially non-immunogenic upon implant into a mammal.

11. A method of reducing the immunogenicity or improving the longevity of an implantable mammalian heart valve comprising: treating the heart valve with growth factor effective on fibroblast cells, and populating the heart valve with fibroblasts in an amount effective for reducing the immunogenicity of the heart valve upon implant into a patient.

18. A method of reducing transplant tissue rejection of an implantable mammalian heart valve comprising: treating the heart valve with growth factor effective on fibroblast cells, and populating the treated heart valve with fibroblasts to reduce tissue rejection upon transplant into a patient.

Document 3

US005855610A

United States Patent [19]

Vacanti et al.

[11] **Patent Number: 5,855,610**

[45] **Date of Patent: Jan. 5, 1999**

[54] **ENGINEERING OF STRONG, PLIABLE TISSUES**

[75] Inventors: **Joseph P. Vacanti**, Winchester; **Christopher K. Breuer**, Brighton; **Beverly E. Chaignaud**; **Toshiraru Shin'oka**, both of Brookline, all of Mass.

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[21] Appl. No.: **445,280**

[22] Filed: **May 19, 1995**

[51] **Int. Cl.**[6] **A61F 2/02**

[52] **U.S. Cl.** **623/11**

[58] **Field of Search** 623/1, 2, 11, 12, 623/66; 424/425, 426

[56] **References Cited**

U.S. PATENT DOCUMENTS

1,995,970	3/1935	Dorough	260/2
2,609,347	9/1952	Wilson	260/2.5
2,653,917	9/1953	Hammon	260/2.5
2,659,936	11/1953	Hammon	18/55
2,664,366	12/1953	Wilson	117/138.8
2,676,945	4/1954	Higgins	260/45.7
2,683,136	7/1954	Higgins	260/78.3
2,703,316	3/1955	Schneider	260/78.3
2,758,987	8/1956	Saizberg	260/78.3
2,846,407	8/1958	Wilson	260/2.5
2,951,828	9/1960	Zeile et al.	260/77.5
3,531,551	9/1970	Trehu	264/210
3,826,241	7/1974	Bucalo	128/18
3,880,991	4/1975	Yolles	424/22
3,883,393	5/1975	Knazek et al.	195/1.8
3,902,497	9/1975	Casey	128/296
3,935,065	1/1976	Doerig	195/1.7
3,949,073	4/1976	Daniels et al.	424/177
3,960,150	6/1976	Hussain et al.	128/260
3,974,526	8/1976	Dardik et al.	3/1.4
3,992,726	11/1976	Homsy	3/1
3,996,444	12/1976	Clark et al.	62/306
4,026,304	5/1977	Levy	128/419
4,060,081	11/1977	Yannas et al.	128/156
4,069,307	1/1978	Higuchi et al.	424/22
4,137,921	2/1979	Okuzumi	128/335.5
4,141,087	2/1979	Shalaby et al.	3/1
4,144,126	3/1979	Burbidge	195/1.1
4,186,448	2/1980	Brekke	3/1.9
4,192,827	3/1980	Mueller et al.	525/123
4,205,399	6/1980	Shalaby et al.	3/1
4,228,243	10/1980	Ikuta	435/285
4,239,684	12/1980	Teag et al.	260/17.4
4,243,775	1/1981	Rosensaft et al.	525/415
4,277,682	7/1981	Mueller et al.	525/421
4,280,954	7/1981	Yannas et al.	260/123.7
4,304,591	12/1981	Mueller et al.	71/93
4,304,866	12/1981	Green et al.	435/240
4,328,204	5/1982	Wasserman et al.	424/19
4,347,847	9/1982	Usher	128/334
4,348,329	9/1982	Chapman	260/403
4,352,883	10/1982	Lim	435/178
4,356,261	10/1982	Kuettner	435/68
4,391,797	7/1983	Folkman et al.	424/19

(List continued on next page.)

FOREIGN PATENT DOCUMENTS

24245/88	2/1989	Australia .
0 248 247	6/1986	European Pat. Off. .
0 248 248	6/1986	European Pat. Off. .
0 153 895	9/1986	European Pat. Off. .
0 226 061	6/1987	European Pat. Off. .
0 282 746	9/1988	European Pat. Off. .
0 344 924	5/1989	European Pat. Off. .
0 361 957	9/1989	European Pat. Off. .
0 339 607	11/1989	European Pat. Off. .
28 53 614	7/1979	Germany .
33 18 150	10/1986	Germany .
62-011 458	1/1987	Japan .
63-074 498	4/1988	Japan .
63-196 273	8/1988	Japan .
63-196 595	8/1988	Japan .
WO 87/06120	10/1987	WIPO .
WO 88/03785	8/1988	WIPO .
WO 89/00413	1/1989	WIPO .
WO 89/07944	9/1989	WIPO .
WO 90/12603	11/1990	WIPO .
WO 90/12604	11/1990	WIPO .
WO 91/01720	2/1991	WIPO .
WO 92/06702	4/1992	WIPO .
WO 92/07525	5/1992	WIPO .
WO 93/07913	4/1993	WIPO .
WO 93/08850	5/1993	WIPO .
WO 93/16687	9/1993	WIPO .
WO 94/21299	9/1994	WIPO .
WO 94/25079	11/1994	WIPO .

OTHER PUBLICATIONS

Allcock, H.R. et al., "Synthesis of Poly[(Amino Acid Alkyl Ester)Phosphazenes][1–3]," Macromolecules, 10(4) (Jul./Aug., 1977).

Allcock, H.R., et al., "Hydrolysis Pathways for Aminophosphazenes[1]," Inorg. Chem. 21(1):515–521 (Jan. 1982).

Allcock, H. R., et al., "Amphilphille Polyphosphazenes as Membrane Materials: Influence of Side Group on Radiation Cross Linking," Biomaterials 9(6):500–508 (Nov. 1988).

(List continued on next page.)

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[57] **ABSTRACT**

It has been discovered that improved yields of engineered tissue following implantation, and engineered tissue having enhanced mechanical strength and flexibility or pliability, can be obtained by implantation, preferably subcutaneously, of a fibrous polymeric matrix for a period of time sufficient to obtain ingrowth of fibrous tissue and/or blood vessels, which is the removed for subsequent implantation at the site where the implant is desired. The matrix is optionally seeded prior to the first implantation, after ingrowth of the fibrous tissue, or at the time of reimplantation. The time required for fibrous ingrowth typically ranges from days to weeks. The method is particularly useful in making valves and tubular structures, especially heart valves and blood vessels.

9 Claims, No Drawings

Document 3
Claims for US 5,855,610

1. A cell-matrix structure comprising
a fibrous matrix formed of a biocompatible, biodegradable synthetic polymer, and seeded with dissociated human cells,
wherein the matrix is configured to form a tissue structure having mechanical strength and flexibility or pliability,
wherein the cell-matrix structure is formed by seeding the matrix, implanting the seeded matrix into a recipient human or animal for a period of time sufficient to form extracellular matrix; and harvesting of the resulting cell-matrix structure.

2. The cell-matrix structure of claim 1 wherein the matrix is configured to form a tube.

3. The cell-matrix structure of claim 1 wherein the matrix is configured to form a valve in a blood vessel, intestine, or heart.

4. The cell-matrix structure of claim 3 wherein the matrix is configured to form a heart valve.

5. The cell-matrix structure of claim 1 wherein the cells are selected from the group of consisting of parenchymal and connective tissue cells.

6. A tissue-engineered heart valve formed of a porous polymeric matrix seeded with dissociated endothelial and fibroblast cells, wherein the cells form extracellular matrix following implantation into a human or animal recipient, and wherein the extracellular matrix is shaped to form a heart valve.

7. The heart valve of claim 6 wherein the matrix is formed of a polymer selected from the group consisting of poly(lactic acid), poly(glycolic acid), and combinations thereof.

8. The heart valve of claim 7 wherein the matrix is formed of polymer fibers having an interstitial spacing of between 100 and 300 microns and having pore sizes and structure to control the pattern and extent of fibroblastic tissue ingrowth following implantation.

9. The heart valve of claim 7 wherein the matrix was seeded with dissociated cells selected from the group consisting of fibroblasts, myofibroblasts, and endothelial cells and includes elastin fibers.

Document 4

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(54) **In vitro-Verfahren zum Herstellen einer homologen Herzklappen- oder Gefässprothese**

In vitro process for the preparation of heart valve or vessel prothese

Procédé de préparation in vitro de prothèse de valve cardiaque ou de vaisseaux

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(56) Entgegenhaltungen:
WO-A-94/25584
WO-A-97/49799
DE-A- 19 828 726
US-A- 5 855 610

- **SHINOKA T. ET AL: "Tissue engineering heart valves: valve leaflet replacement study in a lamb model" THE ANNALS OF THORACIC SURGERY, Bd. 60, Nr. 6, 1995, Seiten s513-s516, XP000993044**
- **HOERSTRUP S.P. ET AL: "New pulsatile bioreactor for in vitro formation of tissue engineered heart valves" TISSUE INGENEERING, Bd. 6, Nr. 1, Februar 2000 (2000-02), Seiten 75-79, XP000993059**
- **ZUND G. ET AL: "The in vitro construction of a tissue engineered bioprosthetic heart valve" EUROPEAN JOURNAL OF CARDIO-THORACIC SURGERY, Bd. 11, 1997, Seiten 493-497, XP000993050**
- **HOERSTRUP S.P. ET AL: "Fluorescence activated cell sorting: a reliable method in tissue engineering of a bioprosthetic heart valve" THE ANNALS OF THORACIC SURGERY, Bd. 66, Nr. 5, 1998, Seiten 1653-1657, XP000993051**
- **Sodian, R., et al.: TISSUE ENGINEERING, Vol. 5, No. 5, 1999, pp. 489-493**
- **Sodian R. et al.: Abstract Book, 2nd Bi-Annual Meeting of the Tissue Engineering Society 1998, p. 479, Abstract No. O-57, 1998.**

Bemerkungen:
Die Akte enthält technische Angaben, die nach dem Eingang der Anmeldung eingereicht wurden und die nicht in dieser Patentschrift enthalten sind.

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EP 1 077 072 B8

Document 4
Claims for EP 1 077 072

In vitro process for the production of a homologous heart valve prosthesis or vessel prosthesis for implantation in human patients, comprising the following steps:

- provision of a biodegradable carrier,
- colonization of the carrier with homologous fibroblasts and/or myofibroblasts to develop a connective tissue matrix,
- colonization of the carrier/matrix with endothelial cells,
- introduction of the carrier/matrix into a pulsatile flow chamber in which it can be exposed to increasing flow rates and/or pressure, and
- continuous or discontinuous increasing of the flow rate from an initial value of 50-100 ml/min up to a final value of 2,000-5,000 ml/min and/or of the pressure to 120-240 mm/Hg.

2. Process according to claim 1, characterized in that the biodegradable carrier is a biodegradable polymer matrix or an acellular biological matrix.

3. Process according to one of claims 1 or 2, characterized in that the carrier comprises a polyglycollic acid (PGA), polylactic acid (PLA), polyhydroxyalkanoate (PHA), poly-4-hydroxybutyrate (P4HB) or a mixture of two or more of these polymers.

4. Process according to one of claims 1 to 3, characterized in that the biodegradable carrier is preformed in the form of a heart valve.

5. Process according to one of claims 1 to 3, characterized in that the biodegradable carrier is preformed in the form of a blood vessel.

6. Process according to one of claims 1 to 4, characterized in that the carrier has a polymer density of 40 to 120 mg/cm^3, preferably 50 to 80 mg/cm^3.

7. Process according to one of claims 1 to 6, characterized in that the carrier is a porous polymer with a pore size of 80 to 240 µm.

8. Process according to one of claims 1 to 7, characterized in that the fibres of the carrier have a diameter of 6 to 20 µm, preferably 10 to 18 µm.

9. Process according to one of claims 1 or 2, characterized in that the carrier is a connective tissue skeleton of an animal heart valve.

10. Process according to one of claims 1 or 2, characterized in that the carrier is a connective tissue skeleton of an animal vessel.

11. Process according to one of claims 1 to 10, characterized in that the step of colonization with fibroblasts and/or myofibroblasts is repeated 3 to 14 times, preferably 5 to 10 times.

12. Process according to one of claims 1 to 11, characterized in that approx. 10^5 to 5 x 10^8, preferably 4-5 x 10^6 fibroblasts and/or myofibroblasts are employed per square centimetre of carrier/matrix and colonization step.

13. Process according to one of claims 1 to 12, characterized in that the step of colonization with endothelial cells is repeated 3 to 14 times, preferably 5 to 10 times.

14. Process according to one of claims 1 to 11, characterized in that approx. 10^5 to 5 x 10^8, preferably 4-5 x 10^6 endothelial cells are employed per square centimetre of carrier/matrix and colonization step.

15. Process according to one of claims 1 to 14, characterized in that the fibroblasts and/or myofibroblasts and/or endothelial cells are human cells.

16. Process according to one of claims 1 to 15, characterized in that the fibroblasts and/or myofibroblasts and/or endothelial cells are autologous cells.

17. Process according to one of claims 1 to 16, characterized in that flow rates of 50 ml/min to 5,000 ml/min, preferably 50 to 2,000 ml/min, are established in the pulsatile flow chamber.

18. Process according to one of claims 1 to 17, characterized in that the flow rate is increased over a period of time of 1 week to 12 weeks.

19. Process according to one of claims 1 to 18, characterized in that the initial flow rate is 50 to 100 ml/min.

20. Process according to one of claims 1 to 19, characterized in that the initial pulse frequency is 5 to 10 pulses/min.

21. Process according to one of claims 1 to 19, characterized in that the flow rate is increased up to max. 5,000 ml/min for vessel prostheses and for heart valve prostheses.

22. Process according to one of claims 1 to 20, characterized in that the pulse frequency is increased up to max. 180 pulses/min for vessel prostheses and for heart valve prostheses.

23. Process according to one of claims 1 to 17, characterized in that systemic pressures of 10 to 240 mm Hg are established in the pulsatile flow chamber.

24. Homologous heart valve which can be produced by the process according to one of claims 1 to 23.

25. Homologous heart valve according to claim 24 for implantation in a human patient, wherein the homologous heart valve has a connective tissue inner core surrounded by an endothelial cell layer, and a collagen density of 43 to 55% exists in the connective tissue inner core.

26. Homologous heart valve according to claim 24, characterized in that it withstands the flow conditions in the human heart.

27. Homologous vessel which can be produced with the process according to one of claims 1 to 23.

Document 5

US006514515B1

(12) **United States Patent**
Williams

(10) **Patent No.: US 6,514,515 B1**
(45) **Date of Patent: Feb. 4, 2003**

(54) **BIOABSORBABLE, BIOCOMPATIBLE POLYMERS FOR TISSUE ENGINEERING**

(75) Inventor: **Simon F. Williams**, Sherborn, MA (US)

(73) Assignee: **Tepha, Inc.**, Cambridge, MA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

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(22) Filed: **Mar. 3, 2000**

Related U.S. Application Data

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(51) **Int. Cl.**[7] **A61F 2/02**; A61K 9/50

(52) **U.S. Cl.** **424/424**; 424/425; 424/501; 424/502

(58) **Field of Search** 424/424, 425, 424/501, 502

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,982,543	A		9/1976	Schmitt et al.
4,711,241	A		12/1987	Lehmann
4,826,493	A		5/1989	Martini et al.
4,880,592	A		11/1989	Martini et al.
4,910,145	A		3/1990	Holmes et al.
5,245,023	A		9/1993	Peoples et al.
5,271,961	A		12/1993	Mathiowitz et al.
5,292,860	A		3/1994	Shiotani et al.
5,334,698	A		8/1994	Witholt et al.
5,468,253	A		11/1995	Bezwada et al.
5,480,794	A		1/1996	Peoples et al.
5,489,470	A		2/1996	Noda
5,502,116	A		3/1996	Noda
5,512,669	A		4/1996	Peoples et al.
5,516,883	A		5/1996	Hori et al.
5,536,564	A		7/1996	Noda
5,550,173	A	*	8/1996	Hammond et al. 523/122
5,563,239	A		10/1996	Hubbs
5,705,187	A		1/1998	Unger
5,711,933	A		1/1998	Bichon et al.
5,789,536	A	*	8/1998	Liggat et al. 528/503
6,245,537	B1	*	6/2001	Williams et al. 435/135

FOREIGN PATENT DOCUMENTS

DE	39 37 649	A1	5/1991
EP	0 258 781	A1	3/1988
EP	0 423 484	A1	4/1991
EP	0 601 885	A2	6/1994

(List continued on next page.)

OTHER PUBLICATIONS

Yagmurlu et al, sublactam–cefoperazone polyhydroxybutyrate–co–hydroxyvalerate Local Antibiotic Delivery System: In Vivo Effectiveness and Biocompatibility in the Treatment of Implant–Related Experimental Osteomyelitis, J. Biomed. Mater. Res. (1999), 46(4.*

(List continued on next page.)

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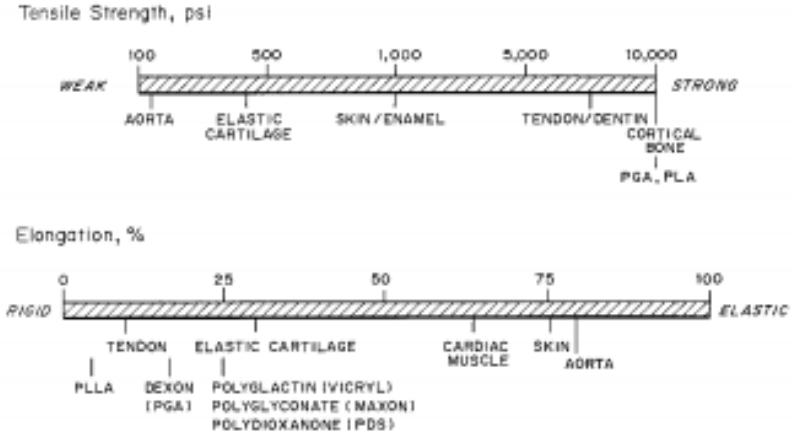
(57) **ABSTRACT**

Bioabsorbable biocompatible polymers which provide a good match between their properties and those of certain tissue structures are provided. The bioabsorbable biocompatible polymers can be prepared with tensile strengths, elongation to breaks, and/or tensile modulus (Young's modulus) values of the tissues of the cardiovascular, gastrointestinal, kidney and genitourinary, musculoskeletal, and nervous systems, as well as those of the oral, dental, periodontal, and skin tissues. Methods for processing the bioabsorbable biocompatible polymers into tissue engineering devices are also provided.

39 Claims, 2 Drawing Sheets



Document 5
Claims for US 6,514,515

1. A composition or device for use in tissue engineering comprising a bioabsorbable biocompatible polymer comprising polyhydroxyalkanoate, wherein the composition or device has one or more mechanical properties selected from the group consisting of stress, strain, stress-strain, stress-strain hysteresis, stress-strain relaxation, viscoelasticity, contraction stress, resting stress, Young's modulus, tensile strength, durability, yield point, failure strength, toughness, ductility, softness, hardness, creep, elastic deformation, wear resistance, shear failure, roughness, compressive strength, load capacity, modulus of elasticity, ultimate compressive strength, yield strength, stress-strain relationship, scratch resistance, abrasion resistance, flexural modulus, shear modulus, contact angle, surface tension, adhesive strength, surface free energy, bending strength, shear strength, bonding strength, bending strength, bending stiffness, compressive modulus, bending modulus, fracture toughness, elongation, fiber strength, fiber modulus, fiber elongation, thermal expansion coefficient, fracture toughness, static and dynamic elasticity, longitudinal stretch, radial stretch, stress and strain, circumferential stretch, ultimate elongation, viscosity, expansion, static and kinetic coefficients of friction, plasticity, axial tension, shock absorbance, bearing strength, formability, rigidity, stress rupture, bend radius, impact strength, and fatigue strength, equivalent to the same properties of a differentiated tissue or tissue structure.

2. The composition of claim 1 wherein the polymer degrades in vivo in less than one year.

3. The composition of claim 1 wherein the polymer has an extension to break of over 25%.

4. The composition of claim 3 wherein the polymer is in the form of a fiber and the extension to break is over 45%.

5. The composition of claim 1 wherein the polymer has a tensile strength less than 10,000 psi.

6. The polymer of claim 5 wherein the polymer is in the form of a fiber and the tensile strength is less than 50,000 psi.

7. The composition of claim 1 wherein the polymer has a Young's modulus of less than 100,000 psi.

8. The polymer of claim 7 wherein the polymer is in the form of a fiber and the Young's modulus is less than 200,000 psi.

9. The composition of claim 1 wherein the polymer has a melting temperature less than 190[deg.] C.

10. The composition of claim 1 wherein the polymer has a glass transition temperature less than 20[deg.] C.

11. The composition of claim 1 wherein the polymer has two or more properties selected from the group consisting of extension to break over 25%, tensile strength less than 10,000

psi, Young's modulus less than 100,000 psi, glass transition less than 20[deg.] C., and melting temperature less than 190[deg.] C.

12. The composition of claim 1 wherein the tissue is selected from the group consisting of cardiovascular, gastrointestinal, kidney, genitourinary, musculoskeletal, nervous, oral, breast, periodontal, and skin.

13. The composition of claim 1 wherein the mechanical property is selected from the group consisting of tensile strength, Young's modulus, elongation to break, hardness, compressive strength, burst strength, toughness, and impact strength.

14. The composition of claim 1 wherein the tissue is cartilage and the polymer has a tensile strength of 435 psi+-25%.

15. The composition of claim 1 wherein the tissue is skin and the polymer has a tensile strength of 1,100 psi+-25%.

16. The composition of clam 1 wherein the tissue is tendon and the polymer has a tensile strength of 7,700 psi+-25%.

17. The composition of claim 1 wherein the tissue is aorta and the polymer has a tensile strength of 160 psi+-25%.

18. The composition of claim 1 wherein the tissue is cardiac muscle and the polymer has a tensile strength of 16 psi+-25%.

19. The composition of claim 1 wherein the tissue is bone and a polymer has a tensile strength of 10,000 psi+-25%.

20. The composition of claim 1 wherein the tissue is enamel and the polymer has a tensile strength of 1,600 psi+-25%.

21. The composition of claim 1 wherein the tissue is skin and the polymer has an ultimate elongation of 78%+-25%.

22. The composition of claim 1 wherein the tissue is tendon and the polymer has an ultimate elongation of 10%+-25%.

23. The composition of claim 1 wherein the tissue is cartilage and polymer has an ultimate elongation of 30%+-25%.

24. The composition of claim 1 wherein the tissue is heart and the polymer has an ultimate elongation of 10-15%+-25%.

25. The composition of claim 1 wherein the tissue is aorta and the polymer has an ultimate elongation in the transverse and longitudinal directions of 77-81%+-25%.

26. The composition of claim 1 wherein the tissue is skin and the polymer has a Young's modulus of 2,000-18,000 psi+-25%.

27. A device comprising a bioabsorbable biocompatible polyhydroxyalkanoate polymer, wherein the device has one of more mechanical properties equivalent to a specific tissue or tissue structure, wherein the device is selected from the group consisting of a tissue engineering scaffold, guided tissue repair material, wound dressing, drug delivery vehicle, anti-adhesion material, cell encapsulation material, coating, implant, stent, orthopaedic device, prosthetic, adhesive, diagnostic, sutures, surgical meshes, staples, meniscus repair and regeneration devices, screws (interference screws and meniscal screws), bone plates and plating systems, cardiovascular patches, pericardial patches, slings, pins, anti-adhesion barriers, articular cartilage repair devices, nerve guides, tendon and ligament repair devices, atrial septal defect patches, bulking and filling agents, vein valves, bone marrow scaffolds, bone graft scaffolds, skin substitutes, dural substitutes, ocular implants, spinal fusion cages, and muscular implants (cardiac and skeletal), wherein the mechanical properties are selected from the group consisting of stress, strain, stress-strain, stress-strain hysteresis, stress-strain relaxation, viscoelasticity, contraction stress, resting stress, Young's modulus, tensile strength, durability, yield point, failure strength, toughness, ductility, softness, hardness, creep, elastic deformation, wear resistance, shear failure, roughness, compressive strength, load capacity, modulus of elasticity, ultimate compressive strength, yield strength, stress-strain relationship, scratch resistance, abrasion resistance, flexural modulus, shear modulus, contact angles, surface tension, adhesive strength, surface free energy, bending strength, shear strength, bonding strength, bending strength, bending stiffness, compressive modulus, bending modulus, fracture toughness, elongation, fiber strength, fiber modulus, fiber elongation, thermal expansion coefficient, fracture toughness, static and dynamic elasticity, longitudinal stretch, radial stretch, stress and strain, circumferential stretch, ultimate elongation, viscosity, expansion, static and kinetic coefficients of friction, plasticity, axial tension, shock absorbance, bearing strength, formability, rigidity, stress rupture, bend radius, impact strength, and fatigue strength.

28. The device of claim 27 wherein the device is a tissue engineering scaffold or matrix.

29. The device of claim 28 wherein the polymer degrades in vivo in less than two years.

30. The device of claim 28 wherein the tissue engineering scaffold which has different properties in different regions.

31. The device of claim 28 wherein the scaffold or matrix is flexible.

32. The device of claim 28 wherein the tissue is heart valve or blood vessel.

33. The device of claim 28 wherein the tissue engineering scaffold or matrix is for tissue engineering of musculoskeletal tissue.

34. The device of claim 28 wherein the tissue is selected from the group consisting of cartilage, tendon, ligament, and bone.

35. The device of claim 28 wherein the tissue engineering scaffold or matrix is for tissue engineering of genitourinary tissue.

36. The device of claim 28 wherein the tissue forms a structure selected from the group consisting of bladder, ureter, and urethra.

37. The device of claim 28 for tissue engineering of gingiva.

38. The device of claim 28 seeded with cells for implantation.

39. The device of claim 28 further comprising materials selected from the group consisting of other polymers, compounds, additives, biologically active substances, growth factors, cell attachment factors, and drugs.

Document 6

Extract from: “Artificial Heart Valves” by Simionescu, D.T., (2006) Wiley Encyclopedia of Biomedical Engineering, Copyright & 2006 John Wiley & Sons, Inc.

7. REGENERATIVE MEDICINE APPROACHES TO HEART VALVE REPLACEMENT

The field of regenerative medicine is based on the innovative and visionary principle of using the patient’s own cells and extracellular matrix components to restore or replace tissues and organs that have failed. This regenerative approach is a derivative of reconstructive surgery, where surgeons use the patient’s tissues to rebuild injured or aging body parts. Modern approaches to heart valve regenerative medicine include several research methodologies, collectively known as tissue engineering. The most intensely researched approaches are (1) the use of decellularized tissues as scaffolds for in situ regeneration, (2) construction of tissue equivalents in the laboratory before implantation, and (3) use of scaffolds preseeded with stem cells.

A widespread approach is to use native (uncrosslinked) decellularized valves obtained from processed human or animal tissues. Once implanted, decellularized tissues are expected to provide proper environment and sufficient stimuli for host cells to infiltrate, remodel, and eventually regenerate the valvular tissue. As antigenic determinants are mainly concentrated on the surface of cells, removal of the original cells (decellularization) is necessary for avoiding complications related to immune rejection, which can be satisfactorily attained using combinations of detergents and enzymes, leaving behind 3-D scaffolds comprising apparently intact matrix molecules. Experimental data obtained with decellularized porcine valves yielded spectacular results (35). In vitro hydrodynamic performance was excellent, and valves performed well after implantation in sheep for 5 months as replacement of pulmonary valves. Explanted valves showed good repopulation of porcine scaffolds with fibroblast-like cells as well as an almost complete re-endothelialization of valve surfaces.

These encouraging studies prompted several small scale studies in humans using a commercially available decellularized porcine heart valve. However, despite the initial enthusiasm, the results of a small study in children were catastrophic. In a breakthrough and intrepid study, a group of cardiac surgeons from Austria reported that three out of four children implanted with decellularized porcine heart valves had died within 1 year after implantation because of tissue rupture, degeneration, and calcification of the implant (36). Analysis of explanted decellularized porcine heart valves revealed lack of cell repopulation or endothelialization. The collagen matrix induced a severe inflammatory response and encapsulation of the graft and also served as a substrate for development of numerous calcification sites. The same group of researchers also recently identified the presence of the porcine cell-specific disaccharide galactose-alpha-1-3-galactose (alpha-Gal epitope) in decellularized porcine heart valves as the possible source of immunogenicity (37). Similarly, decellularized blood vessels also elicited inflammatory responses (38) and failed to maintain patency (39).

Evidently, more basicstudies are required for further development of these products as well as to reevaluate the relevance of animal models. Several academic groups, as well as a group of medical device companies, continue to pursue research and development of

decellularized cardiovascular tissues (40–42). A second approach involves construction of tissue equivalents in the laboratory prior to implantation, with the expectation that assembling the tissue-engineered valvular constructs from appropriate cells, and synthetic or natural matrix components, would create mechanically competent, nonthrombogenic, living tissues capable of adaptation and growth. Compared with decellularized tissues, this approach provides better control of the device properties before implantation. However, because of the enormity of this task, and because of possible early clinical failures of decellularized tissues, researchers in the field of heart valve tissue regeneration have taken a cautious, stepwise approach. The in vitro assembly of heart valve tissue from its individual components was pioneered by I. Vesely et al. (43,44). In this ingenious approach, a chemically crosslinked nonbiodegradable glycosaminoglycan gel was seeded with vascular cells and cultured in vitro, which resulted in the formation of a thin sheet of elastin at the interface between cells and the glycosaminoglycan gel. The collagen structural component was created by fibroblast- mediated compaction of soluble collagen, with the expectation that in vitro assembly of these building blocks would, at some point, create a valve-like structure. Formore details, please refer to the chapter on Tissue Engineering of Heart Valves in this Encyclopedia.

In an exemplary collaborative effort, clinicians, basic scientists, polymer chemists, and biomedical engineers focused on creating functional tissue-engineered heart valves in vitro using biodegradable scaffolds (45). These efforts included scaffold design and characterization, optimization of cell sources, finding adequate mechanisms for cell delivery, and optimizing in vitro culture of the seeded scaffolds, culminating with the surgical replacement of heart valves in sheep. A wide variety of scaffolding models created from biodegradable polymers have been tested for heart valve tissue engineering, including polyglycolic acid, polylactic acid, polycaprolactone, and biodegradable elastomers, which are manufactured into nonwoven textiles in shapes and conformations that mimic the natural architecture of the heart valve. These scaffolds are then seeded with cells that can be obtained from (1) fully differentiated cells such as myofibroblasts and endothelial cells derived from systemic arteries, or (2) pluripotent stem cells derived from adipose tissue, bone marrow, or peripheral blood (46). As mature cells have a limited lifespan, an attractive cell source was stem cells for heart valve tissue engineering. Recently, in a landmark experiment, mesenchymal stem cells obtained from ovine bone marrow were seeded onto biodegradable scaffolds and the constructs were cultured in vitro before implantation as a valve in the pulmonary position of sheep (47) for up to 8 months. Tissue-engineered valves performed well hemodynamically, with signs of slow degradation of the scaffolds, and concomitant deposition of new extracellular matrix. Moreover, cell types resembled those present in natural heart valves. Overall, these exciting results hold great promise for truly effective regenerative approaches to treatment of heart valve disease.

Document 7

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(54) TISSUE-ENGINEERED VASCULAR STRUCTURES

AUS GEWEBE HERGESTELLTE GEFÄSSSTRUKTUREN

STRUCTURES VASCULAIRES DE SYNTHESE

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WO-A-98/15237
WO-A-99/45775
US-A- 5 290 271
US-A- 5 880 090

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Document 7 (for Part 3 of the exam)
Claims for EP 1 339 356

1. A tissue-engineered vascular construct comprising a scaffold configured to form said construct and seeded with endothelial progenitor cells and collagen cells capable of forming vascular tissue, said scaffold comprising a biodegradable material.

2. The tissue-engineered vascular construct of claim 1, wherein the scaffold is configured to form a tube.

3. The tissue-engineered vascular construct of claim 1, wherein the scaffold is configured to form a trileaflet heart valve.

4. A method for making a tissue-engineered vascular construct comprising the steps of : (a) providing a substrate shaped to form the vascular construct, said substrate comprising a biodegradable material; (b) contacting said substrate with endothelial progenitor cells and collagen cells capable of adhering thereto and forming vascular tissue, thereby forming a primary cell-seeded construct; (c) maintaining said primary cell-seeded construct for a first growth period in a fluid media suitable for growth of said cells and imparting stresses in the construct during said first growth phase to stimulate the physiological conditions to be encountered by the construct once implanted to form the vascular construct.

5. The method of claim 4, wherein the step of imparting stresses comprises cyclical increases in pressure and flow within said construct.

6. The method of claim 4, wherein step of imparting stresses comprises a gradual increase in shear stress.

7. The method of claim 4, wherein said biodegradable material is a polymer.

8. A tissue-engineered trileaflet heart valve produced by the method of claim 4,5, or 6.

9. A tissue-engineered tubular construct produced by the method of claim 4, 5, or 6.

10. A tissue-engineered two-dimensional construct produced by the method of claim 4,5, or 6.

Document 8

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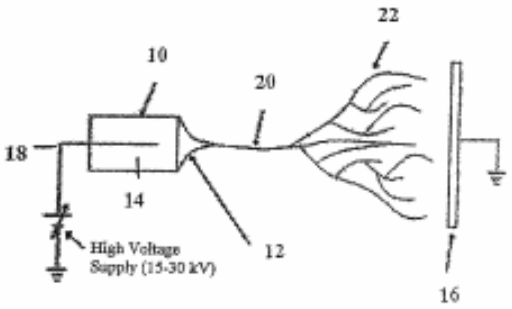
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) **Title:** PRODUCTION OF TISSUE ENGINEERED HEART VALVES



(57) **Abstract:** The invention is directed to methods for preparing artificial heart valves by preconditioning a matrix seeded with endothelial cells and smooth muscle cells differentiated from isolated progenitor cells. These cell seeded matrices are exposed to fluid conditions that mimic blood flow through the heart to produce tissue engineered heart valves that are analogous to native heart valves.

WO 2006/099334 A2

Document 8
Claims for WO2006/099334 (only independent claims are shown)

1. A method for producing a preconditioned heart valve, comprising: obtaining a population of endothelial cells differentiated from progenitor cells; seeding a matrix having a heart valve shape with the endothelial cells such the cells attach to the matrix to form an endothelial cell layer; obtaining a population of smooth muscle cells differentiated from progenitor cells; depositing the smooth muscle cells onto the endothelial cell layer such that the smooth muscle cells form a smooth muscle cell layer that joins to the endothelial cell layer; attaching seeded matrix to an attachment element in a preconditioning chamber, wherein the attachment element has a channel that is fluidly coupled to fluid flow system; and preconditioning the seeded matrix with the flow system in which a biological fluid is moved through the seeded matrix, wherein the flow-rate and pulse-rate of the biological fluid is controlled such that a preconditioned heart valve is produced.

25. A preconditioned tissue engineered heart valve, comprising: a biocompatible matrix having a heart valve shape seeded with a population of endothelial cells differentiated from progenitor cells, wherein the endothelial cells attach to the matrix to form an endothelial cell layer; a population of smooth muscle cells differentiated from progenitor cells seeded onto the endothelial cell layer, wherein the smooth muscle cells form a smooth muscle cell layer that attaches to the endothelial cell layer; and wherein the seeded cells have been preconditioned in a preconditioning chamber that exposes the seeded cells to a biological fluid that is passed through the seeded matrix at a flow-rate and pulse-rate equivalent to normal blood flow through the heart.

Document 9

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Remarks:
This application was filed on 20 - 09 - 2007 as a divisional application to the application mentioned under INID code 62.

(54) **Bioabsorbable, biocompatible polymers for tissue engineering**

(57) Bioabsorbable biocompatible polymers which provide a good match between their properties and those of certain tissue structures are provided. The bioabsorbable biocompatible polymers can be prepared with tensile strength, elongation to breaks, and/or tensile modulus (Young's modulus) values of the tissues of the cardiovascular, gastrointestinal, kidney and genitourinary, musculoskeletal, and nervous systems, as well as those of the oral, dental, periodontal, and skin tissues. Methods for processing the bioabsorbable biocompatible polymers into tissues engineering devices are also provided.

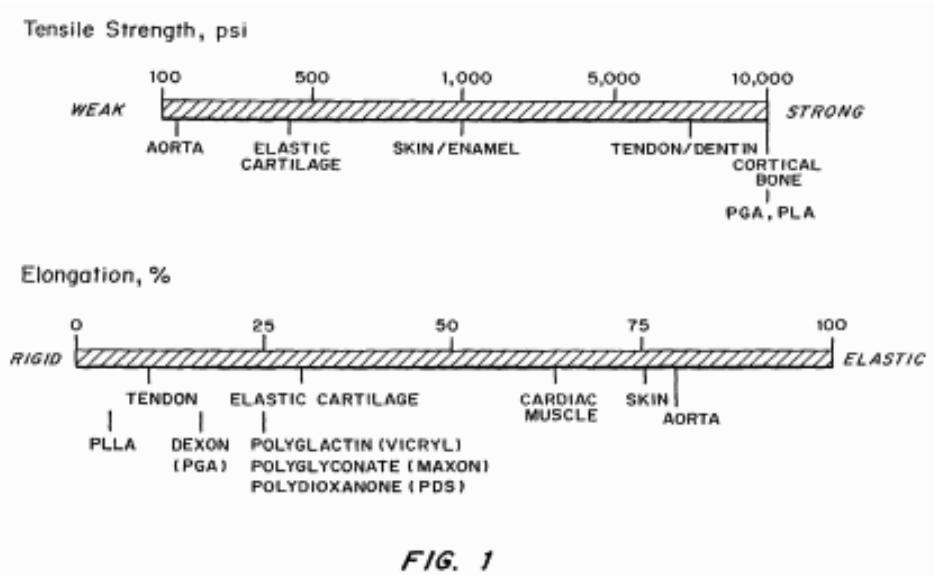

FIG. 1

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EP 1 878 451 A1

Document 9

Claims for EP 1 878 451 as currently pending:

Claims

1. A device for use in tissue engineering selected from the group consisting of a meniscus repair and regeneration device, an articular cartilage repair device, a tendon or ligament repair device and a bone graft scaffold,

the device comprising a bioabsorbable biocompatible polymer comprising polyhydroxyalkanoate, wherein the polymer has two or more mechanical properties selected from the group consisting of

an extension to break of over 25%,

a tensile strength of less than 10,000 psi (or, where the device is a bone graft scaffold, a tensile strength of 10,000 psi ± 25%), and

a Young's modulus of less than 100,000 psi,

and wherein the two or more of the extension to break, the tensile strength and the Young's modulus of the device and/or polymer are equivalent to the corresponding mechanical properties of cartilage where the device is a meniscus repair and regeneration device or an articular cartilage repair device, of tendon where the device is a tendon repair device, of ligament where the device is a ligament repair device, or of bone where the device is a bone graft scaffold.

2. The device of any preceding claim wherein the polymer has an extension to break of over 25%.

3. The device of Claim 2 wherein the polymer is in the form of a fibre and the extension to break is over 45%.

4. The device of any preceding claim wherein the polymer has a tensile strength of less than 10,000 psi.

5. The device of Claim 4 wherein the polymer is in the form of a fibre and the tensile strength is less than 50,000 psi.

6. The device of any preceding claim wherein the polymer has a Young's modulus of less than 100,000 psi.

7. The device of Claim 6 wherein the polymer is in the form of a fibre and the Young's modulus is less than 200,000 psi.

8. The device of Claim 1 wherein the device is a meniscus repair and regeneration device.

9. The device of Claim 1 wherein the device is an articular cartilage repair device.

10. The device of Claims 8 or 9 wherein the polymer has a tensile strength of 435 psi ± 25% and/or an ultimate elongation of 30% ± 25%.

11. The device of Claim 1 wherein the device is a tendon repair device.

12. The device of Claim 11 wherein the polymer has a tensile strength of 7,700 psi ± 25% and/or an ultimate elongation of 10% ± 25%.

13. The device of Claim 1 wherein the device is a ligament repair device.

14. The device of Claim 1 wherein the device is a bone graft scaffold.

15. The device of Claim 14 wherein the polymer has a tensile strength of 10,000 psi ± 25%.

16. The device of any preceding claim wherein the polymer degrades *in vivo* in less then two years.

17. The device of any preceding claim wherein the polymer degrades *in vivo* in less then one year.

18. The device of any preceding claim wherein the polymer has a melting temperature of less than 190°C.

19. The device of any preceding claim wherein the polymer has a glass transition temperature less than 20 °C.

20. The device of any preceding claim which is seeded with cells for implantation.

21. The device of any preceding claim further comprising materials selected from the group consisting of other polymers, compounds, additives, biologically active substances, growth factors, cell attachment factors, and drugs.

Case study 3 - Patentability

Company Z wants to continue the prosecution of a patent by filing a European Patent Application for an invention, validly claiming priority from a French Application with a filing date of 27 November 2007. P works in the R&D department of company Z and is under obligation of secrecy according to his work contract. However, P is informed that he/she will not be promoted and he/she decides to leave the company in February 2008 and harm it.

The following claims will be filed before the EPO on the day before priority expires:

- Claim 1: Product.
- Claim 2: Product of claim 1 comprising feature A and preferably feature B.
- Claim 3: Method of making the product.
- Claim 4: Method of claim 3 comprising step C.

The priority application contained only a description of the product and the product including A and preferably B. In view of general common knowledge the priority application was enabling for the product.

Company Z turns to you and requests a patentability search and analysis to be done. This occurs one month before filing before the EPO. Company Z tells you that P was involved in the development and that P left the company in February 2008.

After performing the searches, you discover the following documents:

- D1, a European patent application, filed in March 2007 and published in September 2008, disclosing the product and the method for making the product.
- D2, a sales document showing the product, distributed at an annual conference in April 2007.
- D3, a document published by P at an annual conference in March 2008, describing the product in which feature A was added and details of the method for making the product including the feature A and which method included the steps of claim 3.
- D4, patent application, published in September 2007, disclosing the usefulness of feature A for a class of products including but not mentioning the product of claim 1. It also described the effect of step C in the technical field of the method, showing embodiments different from the method of claim 3.

Argue for each claim, whether it is novel and/or inventive departing from each document that you discovered.

Case study 4 – Validity

In this paper, candidates should assume that a European patent has been delivered with the three (3) independent claims presented.

The following documents D1 – D7 Opponent Documents
D1: PCT document A
D2: PAJ Japanese Abstracts
D3: US document A
D4: EP document A
D5: Engineering journal article
D6: US document A
D7: US document A

Question 1
Please quote the different features described in the independent Claim 1 (similar features appears in independent claims M and N of the invention). You could either use a separate paper or use the table provided below.

Question 2
If possible, use the support of the document D1-D7 to find a way to invalidate the patent. For each argument please localize inside the document, using the line number, all the elements which support your opinion. The candidate should select the most suitable method to invalidate the claims of this patent in accordance with the EPO praxis. In order to justify his/her point of view she/he should select among the documents provided the most suitable elements for supporting his assertions and provide a detailed explanation of the invalidation process by employing standard X, Y & A categorization and associated arguments. However, no detailed attorney-like analysis is required.

If multiple alternatives for invalidation are identified, indication of all strategies that may support the invalidation based upon legal ground should be presented in order to achieve full marks.

Validity / Table

Feature ref.	Features description
a)	
b)	
c)	
d)	
e)	
f)	
g)	

Case study 4 - Validity / Abstract and Claims of the delivered Patent

Abstract

Preformed articles of an amorphous metal foil which are particularly adapted to be used in the manufacture of an assembly having brazed joints, especially a heat exchanger. Methods for the manufacture of a heat exchanger or other assembly having brazed joints, which method includes the process step of providing a preformed article formed of a brazing foil composition of an amorphous metal alloy in contact with one or more elements of said heat exchanger or other assembly.

Independent claims of the Patent (3)

Independent Claim 1: A preformed article formed of an amorphous metal brazing foil having an irreversibly deformed, non-planar, three dimensional configuration including a primary planar face with at least one perforation passing therethrough, said article being adapted for use in the manufacture of an assembly having brazed joints, said manufacture comprising the brazing of a plurality of tubes to at least one plate, and the brazing of said plate to a shell encasing said plurality of tubes and said at least one plate.

Independent Claim M: A method for the manufacture of a heat exchanger or other assembly having brazed. joints, which method includes the process steps of: providing a preformed article formed of an amorphous metal brazing foil in contact with one or more elements of said heat exchanger or other assembly, said brazing foil having an irreversibly deformed, non-planar, three dimensional configuration including a primary planar face with at least one perforation passing therethrough, said preformed article being in contact with said one or more elements of said heat exchanger or other assembly during the fabrication thereof; and subsequently subjecting the heat exchanger or other assembly to suitable conditions in order to effectuate at least partial melting of said preformed article in order to produce brazed joints between elements of said heat exchanger or other assembly.

Independent Claim N: A heat exchanger or other assembly having brazed joints manufactured by a method which includes the process step of providing a preformed article formed of an amorphous metal brazing foil in contact with one or more elements of said heat exchanger or other assembly, said brazing foil having an irreversibly deformed, non-planar, three dimensional configuration including a primary planar face with at least one perforation passing there through.

Case study 4 - Validity / Document D1

[ABSTRACT]
In a plate heat exchanger, having double-walled plate formed heat transfer elements (1, 2), adjacent such heat transfer elements are permanently brazed together by means of three different and spaced brazing joints. A first brazing joint surrounds an area, which covers the heat transfer portions (3, 4) of the heat transfer elements and first inlet openings and outlet openings (8, 9) communicating with a flow passage (6) that is formed between said heat transfer portions. A second joint and a third joint surround respective inlet openings and outlet openings (10, 11), which are closed from communication with said flow passage (6). Leakage areas (16-19; 39), which communicate with the surrounding of the plate heat exchanger, are formed between said first joint and each one of said other joints.

[DETAILS]
Plate heat exchanger The present invention relates to a plate heat exchanger for heat transfer between a first fluid and a second fluid, in which plate heat exchanger plate formed heat transfer elements are permanently joined together to a plate package and between themselves delimit in alternate interspaces first flow passages for said first fluid and second flow passages for said second fluid, respectively; each heat transfer element comprises two plates abutting against each other and having throughopenings aligned with each other; and said throughopenings in the plates of the heat transfer elements form a first inlet channel and a first outlet channel through the plate package, which channels communicate with said first flow passage and are closed from communication with said second flow passages, and a second inlet channel and a second outlet channel through the plate package, which channels communicate with said second flow passages and are closed from communication with said first flow passages.

Plate heat exchangers in which every plate formed heat transfer element consists of two plates abutting against each other are previously known. A conventional openable plate heat exchanger of this kind is shown for instance in US XXXXXXX. Owing to the fact that each heat transfer element comprises two plates it is achieved a safety against getting the two heat exchange fluids, flowing on respective sides of the heat transfer element, mixed with each other within the plate heat exchanger, if a hole would be formed through one of the plates. A leakage of one of the fluids through a hole of this kind makes the fluid in question flowing out into the space between the plates and further therethrough to and past the edges of the plates, where the leakage can be observed. So that the heat exchange fluids during normal operation of the plate heat exchanger shall not flow out into the spaces between the plates in the respective heat transfer elements the plates in each heat transfer element have to seal against each other around their said through- openings. Sealing of this kind can be obtained for instance through welding, brazing or gluing. Even plate heat exchangers having permanently joined heat transfer elements, each comprising two plates abutting against each other, are previously known. A drawback with these known brazed plate heat exchangers is that the double-walled heat transfer elements are brazed together with each other in a conventional manner, i.e. in the same manner as single-walled heat transfer elements in a brazed plate heat exchanger. The adjacent heat transfer elements are, thus, joined with each other by means of a single continuous brazing joint, and if this brazing joint is not close or does not keep tight, there is a risk that the heat exchange fluids

despite the double-wall arrangement are mixed with each other in the plate heat exchanger without this being noticed.

The object of the present invention is to provide a plate heat exchanger having permanently joined doublewalled heat transfer elements, which is safer than previously known plate heat exchangers of this kind against mixing of the heat exchange fluids in the plate heat exchanger without this being noticed.
This object is obtained according to the invention by the adjacent heat transfer elements being joined together in each of said interspaces by means of three different and spaced joints, a first joint of which surrounds an area covering the flow passage that is delimited in the interspace as well as the inlet channel and the outlet channel through the plate package, which channels communicate with the flow passage, whereas a second one and a third one of said joints surrounds the one of said inlet channels and the one of said outlet channels, respectively, which constitute by-pass channels and are closed from communication with the flow passage in the interspace, and by leakage areas in said interspace, which are situated between said first joint and the respective one of said second and third joints, communicating with the surrounding of the plate heat exchanger. The invention concerns plate heat exchangers in general, having permanently joined heat transferring elements. For the joining of the heat transfer elements it is possible to use for instance welding, brazing or gluing.

In practice, the heat transfer elements of a brazed plate heat exchanger are often rectangular and pressed in a way such that relatively large plane corner portions thereof are brazed together in pairs around each one of those inlet channels and outlet channels which extend through the plate package. A special embodiment of the invention therefore concerns a brazed plate heat exchanger, in which said adjacent heat transfer elements have plane surfaces in said interspace, which are facing each other and delimit between themselves said leakage areas as well as at least parts of said three joints, the joints being constituted by brazing joints or gluing joints and being formed by a connection or bonding material, and the leakage areas being free of bonding material. When a leakage area is to be delimited in this way by and between two plane portions of two heat transfer elements, facing and abutting against each other, which plane portions should simultaneously be partly brazed or glued together by means of a bonding material, at least one of the plane portions opposite to the leakage area may be covered on its surface with a substance preventing the surface from being wetted by said bonding material when the latter is in a liquid state. Brazing technique for making possible such partial brazing together of two plane surfaces facing each other is known from previous publication
In a plate heat exchanger according to the invention one of said leakage areas may extend between said first joint and one of said second and third joints from one part to another of the edge surrounding each one of the adjacent heat transfer elements. However, it is preferred that the leakage areas extend around the respective ones of said by-pass channels.

Within the scope of the invention a leakage area of the above said kind may be delimited by different parts of two adjacent heat transfer elements. One possibility is that it is delimited by and between the two plates of the heat transfer elements situated closest to each other. In this case the leakage area may communicate with the surrounding of the plate heat exchanger either in a way such that part of the leakage area extends out to the edges of the

heat transfer elements, or through a hole in at least one of said plates and, thus, through the space between this plate and the further plate of the same heat transfer element.

Another possibility is that the leakage area is delimited by and between the plates of the two heat transfer elements, situated most remote or farthest from each other. In this case these two plates have throughopenings which are smaller than the aligned openings of the two plates of the heat transfer elements, which are situated closest to each other. Furthermore, in this case the plates situated farthest from each other are sealingly connected directly or indirectly with each other around their said openings, the leakage area being formed and extending around the connection area. Even in this case the leakage area communicates with the surrounding of the plate heat exchanger through the space between the plates in at least one of the two heat transfer elements.

It shall be noticed that the above said space between the two Plates in each heat transfer element may be microscopically thin, i.e. it need not be larger than the interspace that is formed between two plane plates abutting closely against each other. The invention is described in the following with reference to the accompanying drawings, in which figure 1 shows a number of double-walled heat transfer elements arranged as in a plate heat exchanger according to the invention but spaced from each other, figure 2A and 2B show two plates, which are to be included in one and the same double-walled heat transfer element of the kind shown in figure 1, figure 2C shows a thin foil of a bonding or brazing material intended for joining of two heat transfer elements according to figure 1, figure 3 shows a special embodiment of a plate to be included in one heat transfer element, figure 4 shows a section through several heat transfer elements, some of which comprise a plate formed in accordance with figure 3, figures 5-10 show sections through parts of heat transfer elements formed in different ways in accordance with the invention, and figure 11 shows a section through a plate heat exchanger, comprising heat transfer elements in accordance with figure 10.

Figure 1 shows five rectangular double-walled heat transfer elements 1, 2 having corrugated heat transfer portions 3, 4 and a plane end plate 5. The latter is intended to form together with the heat transfer elements 1, 2 a part of a plate package to be included 4 in a permanently joined so called brazed plate heat exchanger. In the plate heat exchanger there are delimited between the heat transfer elements 1, 2 alternating first flow passages 6 and second flow passages 7 for the respective ones of two fluids, between which heat is to be transferred through the heat transfer elements. The flow passages 6 and 7 are formed owing to the corrugations of the heat transferring portions 3, 4 of the heat transfer elements 1, 2 forming ridges and valleys, the ridges of adjacent heat transfer elements crossing and abutting against each other.

For access of the fluids to the flow passages 6 and 7, respectively, the heat transfer elements 1, 2 have in their corner portions through- openings 8-11, which form inlet channels and outlet channels through the plate package. Even the end plate 5 has corresponding openings aligned with the openings 8-11. The openings 8 and 9 in the heat transfer elements 1, 2 form inlet channels and outlet channels, respectively, for one of said fluids. These inlet channels and outlet channels communicate with said first flow passages 6 but are closed from connection with said second flow passages 7. The openings 10 and 11 form inlet channels and outlet channels, respectively, for the second fluid, which inlet channels and outlet channels communicate instead with the flow passages 7 but are closed

from connection with the flow passages 6. The flow paths described here through the plate heat exchanger according to figure 1 are formed owing to the heat transfer elements 1, 2 being brazed together in the following manner. Two adjacent heat transfer elements 1, 2, which delimit between themselves a flow passage 6, are brazed together around their edge portions. Furthermore, they are brazed together around their respective openings 10 and 11, which are formed in the corner portions of the two heat transfer elements. These corner portions are situated in the same plane as the crests of the corrugation ridges of the two heat transfer elements, which cross and abut against each other in the flow passage 6.

In a corresponding way two adjacent heat transfer elements, which between themselves delimit a flow passage 7, are brazed together. In this case, however, the heat transfer elements are instead brazed together apart from along their edges -around their respective openings 8 and 9. Figures 2A and 2B show two plates 12 and 13, which abutting against other shall form a double-walled heat transfer element 1 of the kind shown in figure 1. As can be seen from the figures 2A and 2B the plates 12 and 13 have the same press pattern of ridges and valleys, so that when these plates come to abutment against each other there will be formed a surface contact between them. Preferably, the plates have been pressed simultaneously in contact with each other, so that surface contact comes up between them across the hole of their surfaces facing each other.

The plates 12 and 13 have aligned openings 8a-11a. In annular areas 8b- 11b around the openings 8a-11a the plates are intended to be brazed together, so that fluids flowing through channels in the plate heat exchanger formed by the openings 8a-11a, cannot flow out between the plates 12, 13. The plates 12 and 13 are not brazed together at other places than around the openings 8a-11a. In figure 2A the numerals 14 and 15 designate the corner portions of the plate 12, through which the plate 12 is intended to be brazed together with a plate in an adjacent heat transfer element. By dash-dot lines 16 and 17 there are illustrated in figure 2A two annular surfaces on the corner portions 14, 15, which extend around the openings 10a and lla, respectively, and through which the plate 12 shall not be brazed together with the just mentioned plate in an adjacent heat transfer element. Even along a further surface 18 of the plate 12, which extends from the surface 16 to the edge of the plate 12, the plate 12 is to be free from brazing connection with said adjacent heat transfer element. A similar further surface 19 exists in connection with the annular surface 17. The edge portions of the plates 12 and 13, which are bent in the same direction, are designated 20 and 21, respectively, in the figures 2A and 2B.

Figure 2C shows a thin foil 22 of a brazing material, which is formed and intended for brazing together of a heat transfer element consisting of the plates 12 and 13 with a further heat transfer element situated closest to the plate 13. It is thus the plate 13 which is to be brazed together with one of the plates in the further heat transfer element. Then, surfaces corresponding to the surfaces 16-19 are to be present in connection with the openings 8a and 9a of the plate 13, which is illustrated in figure 2C in a way such that brazing material is missing in small areas 23 and 24.

Before brazing together of the heat transfer elements 1, 2 there is applied onto said surfaces 16-19 in every second interspace, and onto the corresponding surfaces in the other interspaces - at least on one of the plates to be brazed together -a substance having the effect that the plates on these surfaces cannot be wetted by the brazing material used, when this is in a liquid state. Hereby, the plates will remain free of brazing material and,

thus, will not be brazed together with each other through these surfaces when the brazing material has solidified.
In a brazed plate heat exchanger of the kind now described with reference to the figures 1 and 2A-C adjacent heat transfer elements will be brazed together by means of three separate and spaced brazing joints.

Thus, in an interspace, in which a flow passage 6 is delimited, a first brazing joint will extend around the edges of the heat transfer elements. A second brazing joint will extend around the openings 10 and a third brazing joint around the openings 11. Between the heat transfer elements there will be left opposite to the surfaces 16-19 areas in which there will be no brazing material. These areas separate the first brazing joint from the second brazing joint as well as from the third brazing joint.
Thanks to this arrangement of brazing joints a fluid, which for some reason leaks through or past one of said brazing joints close to one of the openings 10 and 11, will flow furtheron through one of said areas, that is free from brazing material, to and past the edges of the heat transfer elements to the surrounding of the plate heat exchanger.

Figure 3 shows a part of a heat transfer element formed differently than according to the figures 2A and 2B. An annular surface 25 extends around and closest to an opening 8c, and therearound extends a further annular surface 26. Around the surface 26 there is a surface 27 covering the whole of the corner portion of the heat transfer element around the surface 26. The shown heat transfer element is intended to be brazed together with an adjacent heat transfer element through the surfaces 25 and 27, whereas the surface 26 is intended to be free of brazing material and, thus, delimit an annular area between the two heat transfer elements which are brazed together. This area is free of brazing material and can receive and conduct a flow of liquid which for some reason has leaked past one of the brazing joints opposite to the surfaces 25 and 27.

Instead of being conducted further to the edges of the heat transfer elements a liquid flow of this kind is conducted in this case through a hole 28 in one of the plates in the heat transfer element shown in figure 3. Since the two plates of the heat transfer element are not brazed together more than at a narrow annular surface around each opening, corresponding to the surface 25, liquid flowing through the hole 28 will be able to flow furtheron between the plates to and past their edges to the surrounding of the plate heat exchanger. Figure 4 shows a section through parts of six doublewalled heat transfer elements, of the kind shown in figure 3, which are brazed together in pairs around their openings 8c.

Figure 5 illustrates a further embodiment of the invention. A first heat transfer element comprising two plates 29, 30 is brazed together with a second heat transfer element comprising two plates 31, 32. The plate 29 has a through-opening 33 (corresponding to for instance the opening lla in the plate 12 in figure 2A) and the plate 31 has a corresponding opening 34 of the same size. Corresponding openings in the plates 30 and 32 are larger than the openings 33 and 34 and are designated in figure 5 by the numerals 35 and 36, respectively. The openings 33,.34 and 35, 36 have a common centre axis 37. The space hereby formed between the plates 29 and 31 is partly filled out, closest to the openings 33, 34, by a ring 38 that is brazed together around the openings 33, 34 with the plate 29 as well as the plate 31. The rest of said space forms a leakage area 39 between the adjacent heat transfer elements. The leakage area 39 extends around the ring 38 and is delimited by, apart

from the ring 38 and the plates 29, 31, the edges of the plates 30, 32. The plates 30, 32 are brazed together along these edges.

In the arrangement according to figure 5 the brazing joint between the plates 30 and 32 delimits a flow passage (not shown) for a first fluid between the heat transfer elements 29, 30 and 31, 32, whereas the plates 29 and 31, the ring 38 and the brazing joints between the ring 38 and the plates 29 and 31 delimit an inlet channel or an outlet channel through the plate heat exchanger for a second fluid. If one of said brazing joints would prove not to be tight, one of said fluids will flow through or past the leaking brazing joint out into the leakage area 39. From there, the fluid will flow furtheron between the plates 29, 30 and/or between the plates 31, 32 in spaces 40, 41 formed between these plates.
The fluid will flow furtheron in one or both of the spaces 40, 41 to the surrounding of the plate heat exchanger across the edges of the plates. Figure 6 shows an embodiment of the invention similar to the one shown in the figures 3 and 4. A groove is formed in one of the heat transfer elements, so that an annular leakage space 42 is formed, extending around the through-openings 43-46 in the four plates 47-50 included in the heat transfer elements. Figures 7 and 8 show embodiments of the invention, which are of principally the same kind as the embodiment according to figure 5. The same numerals as used in figure 5 have been used, therefore, in the figures 7 and 8 with the addition of the letters -a and 12, respectively, for details corresponding to each other in the different figures.

One difference is that the ring 38 according to figure 5 is missing in the figures 7 and 8 and that, instead, the two plates 29a, 31a and 29b, 31b, respectively, which are situated farthest from each other, are brazed together directly with each other around their openings 33a, 34a and 33b, 34b, respectively.
The embodiment according to figure 8 differs from the one in figure 7 in that the plates 29b and 31b have been provided with annular depressions 51 and 52, respectively, opposite to the leakage space 39b. The purpose of these depressions is that the leakage space 39b shall be able to receive some liquid brazing material without this causing blockage of the connections between the leakage space 39b and the spaces 40b, 41b between the plates 29b, 30b and the plates 31b, 32b, respectively.

As can be seen, the plates 30b, 32b around their openings 35b, 36b have edge portions extending a distance into the leakage area 39b. Figure 9 shows a further development of the embodiment according to figure 8. Thus, the plates 29b and 31b have been provided with protuberances 53 on their sides turned away from each other. The protuberances 53, which are several in each plate, are situated between the leakage area 39b and the openings 33b, 34b and are distributed with mutual interspaces around the openings 33b, 34b.
Protuberances 53 formed on adjacent heat transfer elements and facing each other are brazed together. Figure 10 shows another further development of the embodiment according to figure 8. As can be seen the annular depression 52a in the plate 31b has been made deeper than the depression 51a in the plate 29b, so that even more liquid brazing material could be collected in the leakage area 39b without risk for blocking of its connection with the spaces between the plates 29b, 30b and 31b, 32b, respectively. As illustrated at 54 the foil of brazing material has further been formed in a way such that the risk for an access of brazing material should be collected in the leakage area 39b has been reduced. Figure 11 shows a section through part of a brazed plate heat exchanger comprising double- walled heat transfer elements of the kind shown in figure 10.

The heat transfer elements are arranged between two end plates 55 and 56. The end plate 55 has an inlet pipe 57 for a first fluid and an outlet pipe 58 for a second fluid. These pipes are connected aligned with the respective through-openings of the heat transfer elements, which openings form an inlet channel and an outlet channel, respectively, through the plate heat exchanger. A reinforcing member 59 which is brazed together with both the end plate 56 and with the inlet pipe 57, extends through the inlet channel for said first fluid. A similar reinforcing member 60 extends through the outlet channel for said second fluid and is brazed together with the end plate 56 and the outlet pipe 58. The reinforcing members 59 and 60 are needed to keep together the package of heat transfer elements, since each one of the heat transfer elements comprises two plates which are joined with each other through brazing only in the areas around the heat exchange fluid inlet channels and outlet channels through the plate heat exchanger. The various heat transfer elements, however, are brazed together - in addition to around their edges - at a lot of places across their corrugated heat transfer portions.

[DRAWINGS]

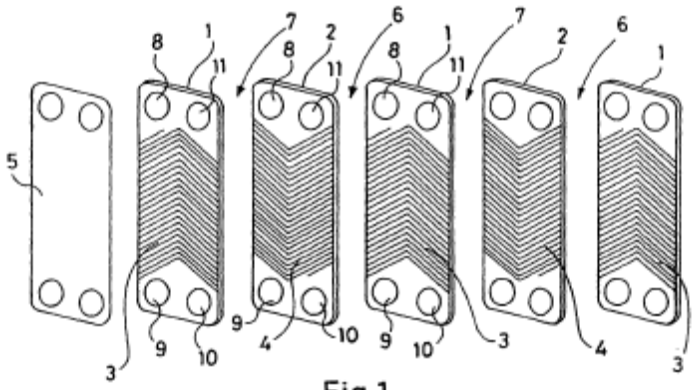


Fig.1

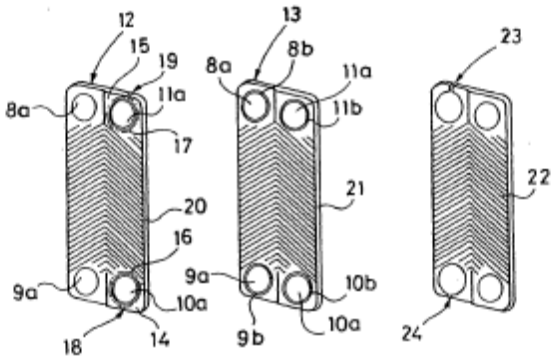


Fig.2A Fig.2B Fig.2C

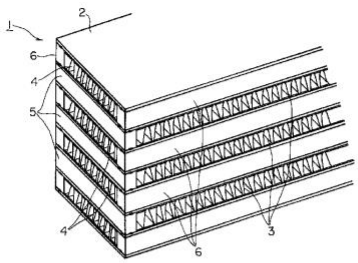
Case study 4 - Validity / Document D2

[ABSTRACT]
PURPOSE: To provide the production of a laminated heat exchanger having high productivity and no possibility of leakage.

CONSTITUTION: Each hollow cubic side walled material 5 is placed on left/right both end part 2a of a rectangular plate 2, a brazing filler metal sheet 7 of Ni base amorphous foil is placed on the upper surface of the plate 2 sandwiched by the hollow cubic side walled material 5, further, a corrugated fin 37 directed its groove parallel to the hollow cubic side walled material 5 is placed on thereon, the brazing filler metal sheet 7 is placed on the corrugated fin 3 and then placing other plate 2. And the corrugated fin and hollow cubic side walled material 5 as well as the corrugated fin 4 and hollow cubic side walled material 6 with changing its direction by right angle are placed on the second plate 2. These works are repeated at plural times and then welding is executed on the contact point between the end part of the hollow cubic side walled materoal6 and plate 2, the plate 2 to corrugate fins 3, 4, and the plate fin 2 to hollow cubic side walled materials 5, 6 are subjected to brazing.

[DRAWINGS]

【図2】



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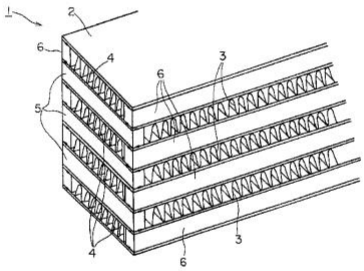
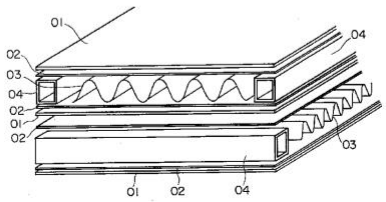


【図4】



Case study 4 - Validity / Document D3

[ABSTRACT]
Disclosed is an interlayer for brazing and diffusion bonding, having a portion as a continuous stratum with an amorphous structure. The amorphous stratum of the interlayer, being ductile, imparts structural integrity to the otherwise brittle alloy composition. Thus, forming and shaping of the interlayer to faying surfaces are improved. In the joining process, the interlayer melts, and on solidifying by cooling or interdiffusion of elements, is converted to a crystalline solid metallurgically bonded to the workpiece. Preferred are flat ribbons with a continuous amorphous surface stratum comprising at least 30 volume percent, and up to 100 percent, of the interlayer.

[DETAILS]
The field of the invention is joining of metals. More particularly, the invention is concerned with brazing and liquid phase diffusion bonding of metal workpieces using metal interlayers between the faying surfaces.
Brazing is a method of joining metals wherein a lower melting point material is interposed as a filler between two higher melting point metal surfaces. Through the application of heat, the brazing material is caused to melt and, by capilarly action, to fill the space between the metals. After melting occurs, the assembly is cooled. Usually, there is a slight degree of alloying at the braze-base metal interface.
Phase diffusion bonding (PDB) has been shown to be a useful method of joining superalloys. As in brazing, a thin alloy filler, or interlayer, is interposed between the surfaces to be joined. After heating to cause melting of the interlayers, the assembly is held above the melting temperature to promote interdiffusion between the base metal and filler. Among other phenomena, elements such as boron, which are typically used as melting point depressants in the interlayer, are caused by atomic diffussion to migrate into and throughout the base metal, thereby causing solidification of the joint. While the detail methods of brazing, PDB bonding and other analogous liquid phase joining processes differ with respect to the heating cycle and solidification phenomena, the filler alloys used for joining superalloys often have many similarities. Alloys of the desired composition for fillers are typically nickel-base and contain mostly chromium, cobalt, iron, silicon, and boron. To carry out the objects of the PDB bonding method, compositions are more precisely controlled and tailored to the types of superalloys being joined than when brazing is the object.
During mass production using brazing or PDB bonding, it is common practice to preplace the filler material. One way this is achieved is by forming the filler alloy into a suitable shape, called a preform, and inserting it between or adjacent to the surfaces to be joined before heating. It is desirable that the preform by formable to the nominal shape of the faying surface of the joint. Because if the preform cannot assume the necessary contour, the faying surfaces may be unduly kept apart; provision must either be made to move the surfaces together or to supply additional filler material to the joint during bonding to avoid an imperfect, unfilled joint. Both preventive actions are undesirable. Another problem arises if the preform does not have a surface area which substantially matches the area of the faying surfaces; an undesirable surplus or deficiency of filler material may result.
For many joint configurations, particularly those having contoured surfaces, it is desirable that the preform be supplied in a sheet or foil, 0.05 to 0.25 mm thick. One method of achieving this is to adhere particulate filler material to a thermoplastic carrier sheet which

volatilizes prior to melting of the alloy. Not only are there potential problems with the carrier residue, but the low effective density of filler engenders the previously mentioned problems attending poor preform configuration.
Most suitable are thin metal foil preforms, cut to the joint area and complying to the joint contour, either by stamping or in situ forming. However, a characteristic of many high temperature filler alloys of the types described above is that they tend to be very hard and brittle, due to the enrichment in melt depressants such as boron, and therefore are not readily rolled or formed into thin foils. One method of overcoming this problem is indicated in, U.S. Pat. No. X,XXX,XXX, wherein formable alloy in thin foil form is modified in composition by the surface addition of a melting point depressant element, such as boron. The interlayer so formed has a ductile interior and brittle exterior, allowing it to be die stamped to a complex shape. However, the interlayer formed in such a manner is costly to fabricate and is limited to certain core compositions. Further, the boron is not evenly distributed through the interlayer and the local melting point varies.

Another approach is to introduce the filler as a coating on one of the faying surfaces. However, this approach is limited in that the incorporation of a multiplicity of elements in the interlayer is not convenient, and usually at the most, three elements are included. Further, there can be adverse economics. Thus, interlayer foils currently appear most attractive. But there is a need for an improved superalloy bonding and brazing interlayer foil, having a desired multi-element homogeneous composition but capable of being economically produced and readily formed for complex joints.

Common braze and PDB foils, like most metals of common experience have a crystalline metal structure. Actually, little attention has been given to their microstructures heretofore, other than to obtain general homogeneity. It has been evident for sometime that certain metal alloys can exist in a metastable amorphous solid state. As such, they are characterized by an absence of the long-range atomic ordering characteristic of the more familiar crystalline state. Amorphous metals also called glassy metals, evidence substantially different properties from the same compositions in the crystalline state. Amorphous metals are formed by methods such as rapid quenching of liquid metals and physical or chemical deposition. While they have long been known to exist, in recent years more attention has been given to the development of useful amorphous materials. Various amorphous metal ribbons are currently obtainable commercially.

Compositions of, and methods for making amorphous metals are described in the technical literature, including a number of patents. A review of this literature shows a recent trend towards novel materials for specialized applications. For example, alloys for resisting radiation damage and corrosion, and alloys having low electrical resistivity; among uses suggested are reinforcing elastomers and plastics, forming electromagnets, and the like. Other more recent patents describe refractory element containing alloys for applications as diverse as razor blades and magnetostrictive devices. For a metal to be convertible to an amorphous solid it must have a particular composition and liquid state structure. It is said that the more readily formed amorphous alloys are mixtures of two transition metals or are transition or noble metals containing about 20 atomic percent metalloid, e.g., silicon, boron and phosphorous. Nonetheless, whether a particular composition can be made amorphous, and the conditions necessary to attain same, are largely a matter of experiment.

Generally amorphous metals are characterized by very high tensile strengths and hardnesses. It is these properties, coupled with the retention of a modicum of ductility, which make them most appealing for mechanical design concepts. Of course, any amorphous property advantages are lost as soon as a material is heated above the temperature at which the metastable phase converts to a crystalline structure. Typically, this transition temperature is approximately half the melting point. Thus, it has been an object of past development to devise new composition alloys with higher transition temperatures. And when an existing composition alloy is considered for use in its amorphous form, it has been obvious that the only suitable uses are those where it is maintained below its transition temperature. Therefore, since braze and PDB alloys are by their nature put into use by heating to high temperatures, and since amorphous metals are by nature not usable as such at high temperature, prior to the invention herein there was no obvious useful connection.

SUMMARY OF THE INVENTION

An object of the invention is to provide an improved method and interlayer foil for brazing and bonding. A further object is to provide ductile and formable interlayers suitable for joining complex alloys. The present invention embraces the concept that an interlayer foil with an amorphous metal structure produces an improved brazed or diffusion bonded structure, even though all trace of the amorphous structure is destroyed in making the final joined product. Hereafter, the designations MPV (Metastable Phase Variational) bonding and MPV interlayer are used when referring to processes and articles of the invention. As previously mentioned, there was no appreciation heretofore that an amorphous atomic structure would be of utility in a product or process wherein heating above the metastable phase transition temperature was inherent and amorphous properties were lost.

According to the invention, an improved MPV interlayer for joining metal workpieces is formable as a separate element with amorphous metal structure, is meltable at a temperature lower than the metals being joined, and is adapted to be solidified as a metallurgically bonded and crystalline solid between the faying surfaces of the workpieces. MPV interlayers in accord with the invention have at least 30 percent amorphous structure, thereby making them capable of being formed and shaped for joining purposes, even though they contain embrittling elements. As stated, MPV interlayers may be fully amorphous throughout. But MPV bonding desirably does not require interlayers of such character. Fully amorphous interlayers are more difficult to make when substantial thickness is required. When only a portion of the MPV interlayer is amorphous, the amorphous portion will be a continuous layer on at least one surface of the interlayer. Thus, such an interlayer will have a ductile amorphous stratum to which a crystalline stratum is integrally attached. Alternatively, amorphous strata may be on either side of the interlayer with a crystalline core.

In a preferred embodiment, an interlayer for joining superalloys has a nickel-base and a boron content. An alternate embodiment interlayer has substantially the composition of the superalloys for which it is usable, but lacks aluminum, titanium and carbon, while including a melting point depressant, such as boron. Preferred MPV interlayers typically have melting points about 60° C. less than the melting point of any workpiece on which they are used.

An advantage of the invention is that homogeneous interlayers can be formed from normally brittle materials, and the interlayers can be conveniently shaped and formed as by

stamping, punching, bending, and the like. In addition, the general handling of the interlayers is made easier. To practice the invention it is not necessary to be limited to particular alloy compositions and interlayer configurations which are entirely convertible to an amorphous state, but those which are only partially convertible are usable as well. The workpieces joined according to the invention will have stable high performance metallurgical structures. But with more formable amorphous structured interlayers, the ease for forming sound joints by brazing and bonding is improved, and the cost is lowered. The invention is particularly suited to the joining of high temperature nickel base superalloys but is adaptable to other metallurgical systems as well.

DESCRIPTION OF THE PREFERRED EMBODIMENT
The preferred embodiment is described in terms of joining nickel-base superalloys of the types which are used in gas turbine engines, although as will be apparent the invention will be equally applicable to other base alloys, and in any joining process where it is desirable to have an interlayer
alloys suitable for brazing and bonding cast nickel-base alloys could be found among:

- AMS (Aerospace Materials Specification) : mostly used as brazing alloys,
- UT (United Technologies) designations are more prevalently used for diffusion bonding.

It will be noted that generally the AMS alloys contain silicon and boron, will small quantities of phosphorous and carbon. The UT alloys mostly contain only boron as the melting point depressant, and have on the whole a lower metalloid content. As a result, the UT alloys will tend to have somewhat higher melting points than the AMS alloys. The alloys in Table 1, and other alloys for brazing and bonding, are commercially procurable or readily fabricated as ingots by conventional melting, pouring and casting techniques. ##TABLE1##
Based on the foregoing, a generalization of the properties required of MPVMPV interlayers can be made. These properties include a composition which is mechanically and chemically suited for use in conjunction with the workpieces being joined and a composition which produces a melting point which is less than that of the metals which are being joined. Typically, for joining iron and nickel base alloys, a desired interlayer will be a nickel alloy with a liquidus of 60° C. or more below the solidus of the workpieces. A narrower melting point difference might be acceptable in the case of some alloys, but generally it is necessary that the interlayer liquify sufficiently to flow and fill the joint at a temperature which does not adversely affect the base metals. In other circumstances, the interlayer melting point may have to be substantially less than that of the workpieces to avoid deleterious effects on the workpiece microstructure. Another characteristic required of the interlayer is that it be capable of forming a metallurgical bond with the workpieces upon the solidification from the melt. This is required because if there is no metallurgical bond, then the joint will have insufficient strength, whether it be a brazed or diffusion bonded joint.

The composition of a MPV interlayer must make it suited for conversion to an amorphous state. As stated previously, the characteristics of readily convertible alloys are not amenable to precise definition, and are largely a matter of experiment. Fortunately, known nickel brazing and bonding alloys have shown by experiment the desired characteristics. The invention will be usable with other base alloy systems and interlayers when experiment shows that interlayer alloys have all the necessary characteristics enumerated above.

As the previously referenced patents state, for diffusion bonding a preferred interlayer for superalloys contains up to 5% boron. A further preferred practice is that the interlayers

have a composition substantially similar to that of the superalloy but excluding or limiting aluminum, titanium and carbon, when boron is used as the melting point depressant. Although silicon is not commonly used as a melting point depressant for diffusion bonding it is quite common in AMS braze alloys. In specialized applications, silicon and phosphorous might be used in diffusion bonding interlayers as well. As should be evident from the general discussion herein, any alloy which is suitable for brazing or diffusion bonding is also suitable for MPV bonding if it can be made amorphous.

Interlayer Fabrication
As the summary indicates, a MPV interlayer in accord with the invention is in part comprised of at least a portion with an amorphous structure. This portion is present as a continuous, relatively ductile stratum which imparts integrity to the otherwise brittle interlayer. The following describes how such interlayers may be formed. The subsequent section describes more particularly the structure which must be present in a MPV interlayer. In this discussion, it is presumed that a desired interlayer foil has a particular thickness, length, and width. This is conceived as being most easily obtained by forming a random length ribbon of a particular cross section, and then shearing or stamping the ribbon to the exact foil size desired. However, it is also contemplated that the initial formation of a filament may be followed by further processing, as by machining or forming, to alter the cross section.
To convert an ingot of an interlayer alloy into a foil with amorphous structure, the metal may be melted and then resolidified with cooling of the melt at a high rate to form the desired solid shape. Several techniques are available for achieving this, and they mostly involve contacting the liquid metal with a smooth cool surface, such as copper maintained below 100° C. Most simply a small quantity of molten metal can be squeezed into a thin foil between two cool anvils. Alternatively, physically deposited particles may be accreted as a film. More desirably, continuous filament casting techniques revealed in various U.S. patents are usable, with suitable modification to resist molten super alloy attack and form the desired cross section. Of course, to obtain amorphous atomic structure in any portion of a filament formed from a liquid, the liquid must be cooled at a sufficiently rapid rate. For the nickel base interlayer alloys this is of the order of 10.sup.5 ° C. per second. Thus, only apparatus and processes adapted to achieve such conditions in filaments of the desired dimensions will be suitable for directly making MPV interlayers as they are further described below. While the invention is discussed in terms of ribbons, flat filaments and foils, in particular instances interlayers which have other lower aspect ratio cross sections, such as circular, are within contemplation.

The presence of the amorphous state in a filament or foil is typically determined by examination of the X-ray diffraction pattern. Optical and electron transmission microscopy can also be used to verify the absence of longrange crystallographic ordering which is characteristic of amorphous metals. For purposes of this specification, a portion of metal alloy characterized as amorphous may have within it isolated islands of crystalline metal structure material which are comprised of either impurities or elements of the metal alloy.

Further information regarding the techniques for rapidly quenching liquid metals in order to convert them into an amorphous atomic structure and details of the techniques for analyzing such material are obtainable by reference to literature. Our preferred mode of practicing the invention is to form the interlayer foil from the liquid with an amorphous stratum being created during the solidification process, The thickness and width of interlayers may vary considerably. Desired thicknesses may range from 0.02 to 0.25 mm

while widths may vary from 2 to 25 mm or more. The maximum thickness will be limited by the apparatus cooling rate capability and the necessary amorphous-crystalline structure balance described below. The width will be limited by the capability of the apparatus. Of course, multiple thin pieces may be used to build up a desired total interlayer thickness or width for a particular joint.

Interlayer Structure
A MPV interlayer of the invention must have at least a portion which has an amorphous structure. Inasmuch as the preferred manufacture of interlayers entails rapidly quenching liquid metals into ribbons, the portion of the foil which is in contact with the heat extraction surface or medium will be that which experiences the highest cooling rate and therefore, will most likely be amorphous. By way of example, if the interlayer is formed in an apparatus or method wherein heat is extracted from one side of the ribbon then that side will more easily be rendered amorphous.

The rate of heat extraction is of course dependent upon the particular method used to rapidly quench the interlayer alloy. The degree to which a particular interlayer alloy foil has an amorphous structure will be further influenced by its thermal and physical characteristics and thickness. The degree or ease of amorphous structure obtained will be enhanced by lowered thickness, specific heat, heat of fusion, and density and increased thermal conductivity. Generally, since the cooling rates required for forming an amorphous structure are exceedingly high, it is difficult to fully quench a relatively thick nickel alloy foil, e.g., one of the order of 0.2 mm. Thus, it is a desirable feature of the invention that MPV interlayers need not be fully amorphous, as disclosed below.

We have not run controlled experiments to determine the limiting structural configurations of interlayer foils, as they will be dependent on the cross section and the direction in which they are bent with respect to the crystalline-amorphous strata. And of course, the desired limits will be dependent on the end application of the interlayer foil with regard to the degree of formability which is required. But on the whole, our more significant conclusion is that an interlayer foil having at least a portion which is amorphous will exhibit an ability to be shaped and formed with greater resistance to the brittle fracture which is characteristic of interlayer with no amorphous structure whatsoever. Based on our observations, we believe that the amorphous portion of the interlayer should be at least about 30% of the thickness (or volume) of the foil when the foil is a nickel base boron containing alloy. A lower volume percent, e.g., 10, may be usable in special instances where the alloy has different properties or the application is less demanding than those we typically conceive for the manufacture of gas turbine components. Of course, it should be evident that foils which are in greater proportion amorphous, up to 100%, will be equally satisfactory as MPV interlayers.

Cross sectional structure of a foil wherein the amorphous atomic structure is present in two strata one on each principal surface, with a crystalline portion contained between. Such an interlayer would be produced by a method in which heat is extracted from both surfaces of the ribbon. Since there are two ductility lending strata, it would be anticipated that a lower thickness of each strata would be adequate to impart formability to the interlayer foil, Accordingly, our judgment is that the same total volume percent of amorphous structure, namely 30%, divided between the two strata will be most often adequate to achieve the objects of the invention in an interlayer The rectangular cross sections shown in the figures

are for exemplary purposes only and it should be apparent the foregoing descriptions are applicable to other cross sections as well.

MPV Joining Process

The following describes the practice of MPV bonding. An interlayer is provided having the following characteristics: a melting point less than the metals being joined; at least one continuous surface stratum with an amorphous metal structure which imparts formability to the interlayer; and an amorphous phase comprising 30 volume percent or more of the interlayer. The interlayer is then shaped as by stamping, shearing, machining, or otherwise, to the shape which conforms to the faying surfaces. The interlayer is then placed between the faying surfaces of the workpieces and the workpieces are positioned so that the faying surfaces are as close as feasible. (In particular instances, it may be desirable to supply surplus interlayer alloy to the joint; in such cases, the interlayer foil would have greater surface area than that of the faying surfaces of the workpieces.) If the faying surfaces are contoured, then as the workpieces are pressed together the interlayer foil will be bent accordingly if it has not been otherwise preformed to the contour.

The amorphous stratum in the interlayer will impart compliance to the interlayer to allow it to contour itself to the faying surfaces, beyond that which would be expectable for a purely crystalline interlayer where fracturing and possible mislocation might result. Next the assembly of workpieces and interlayer is heated, as by a furnace or induction heater, typically in a controlled atmosphere or vacuum. In other instances, fluxes and oxidizing heat sources might be used. The temperature is raised above the melting point of the interlayer, at a rate, and to a degree, sufficient to cause the interlayer to liquify within the joint. Usually the assembly is held at temperature for a period of time to obtain metallurgical interaction between the interlayer and the workpieces. Generally, this interaction entails dissolution of minor surface films on the workpiece and interlayer and a degree of alloying between the interlayer and the workpiece. Usually this occurs in a matter of minutes. In brazing, solidification of the interlayer is obtained by cooling the assembly. Typical cooling rates are 5° C. per second or less. As the joint often has relatively small exposed surface area compared to the workpieces, this may mean that heat extraction from the interlayer will be through the workpiece and epitaxial solidification from the workpiece surface will often take place. Of course, non-epitaxially solidified braze joints can be quite satisfactory as well.

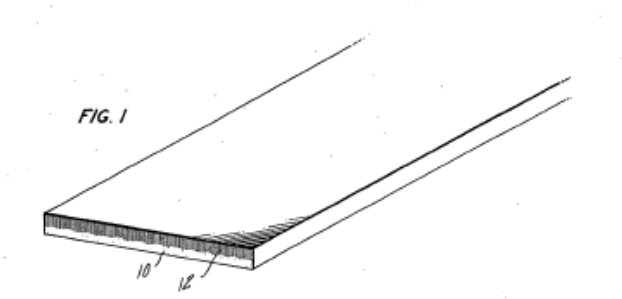
In transient liquid phase diffusion bonding, after the interlayer melts, the temperature is sustained usually constantly at a point above the interlayer melting point--as high as the workpiece materials will endure without adverse effect--for a period of time sufficient for interdiffusion of elements to take place between the interlayer and the workpiece. As is disclosed in the references, this interdiffusion leads to solidification of the interlayer due to its changing composition. The phenomena in the joint region are such that the interdiffused interlayer will solidify epitaxially from the faying surfaces of the workpieces, which of course typically have crystalline metal structures. Thus, a common feature of MPV joining is that a crystalline metal structure results in the joints, most usually one which is epitaxial with the work pieces.

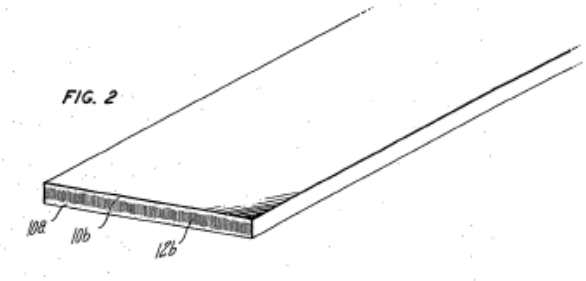
An interlayer must produce a sound metallurgical structure with good bonding to the workpieces. This is determinable by mechanical testing. Even more conveniently, metallographic inspection of a good workpiece joint will show it to be substantially free of voids, oxide films, and concentrated precipitates formed during joining. An interlayer must

also have a composition which produces a joint with the capability of resisting the thermal stresses associated with cooling of the assembly. Properties which affect its performance are its elevated temperature strength and ductility, thermal expansion, shrinkage on solidification, and solidusliquidus temperature differential.

A particularly useful application of MPV bonding is for the joining of cast single crystal superalloys. In such instances it is an object to have the single crystal structure extended across the joint region of a workpiece assembly. To achieve this, the crystal structures of the workpieces are essentially aligned to within a tolerance which experiment shows will avoid creation of a discontinuity after joining. The MPV interlayer is interposed and the diffusion bonding process is carried out as generally above, to ensure epitaxy. It will be found that a single crystal joined assembly will be the result from the epitaxial solidification.

[DRAWINGS]





Case study 4 - Validity / Document D4

[ABSTRACT]
A flexible multilayered brazing material is disclosed comprising at least one layer of ductile brazing foil defining a core body having two major surfaces and at least one minor surface, and at least one layer of ductile brazing foil substantially covering
said two major surfaces and at least one minor surface. In particular, the layer(s) and the covering foil are each at least about 50% amorphous, with the
covering foil being, most preferably, helically wrapped around the layers. The multilayered brazing materials enable brazing of large gaps and wide gaps formed by juxtaposed parts to be brazed. Processes for producing the flexible multilayered brazing material are also disclosed.

[DETAILS]
The present invention relates to brazing of metal parts and, in particular, to brazing filler metals useful for brazing gaps of thickness greater than about 100um and width of several inches or more. Brazing is a process for joining metal parts,
often of dissimilar composition, to each other. Typically, a filler metal that has a melting point lower than that of the metal parts to be joined is interposed
between the parts to form an assembly. The assembly is then heated to a temperature sufficient to melt the filler metal. Upon cooling, a strong, preferably corrosion resistance, joint is formed. Conventional brazing filler materials exist in a wide variety of forms which are characteristic of metallic materials, namely: powders, pastes formed from powders, foils, strips and rods. Among these forms, strips and foils of brazing filler metals offer the most promise in the formation of uniformly brazed joints because of the relative ease of placement of the brazing filler metals into the assembly to be brazed. Recently, a variety of alloys have been developed which can be cast into homogeneous, ductile, thin brazing foils by, for example, the casting process disclosed in U.S. XXXXXXX. This casting process, known as planar flow casting, involves solidification of molten metal into a thin foil by casting onto a rapidly moving quenching surface. Alloys suitable for casting into such foils are disclosed, for example, in U.S. XXXXXXX. However, homogeneous ductile brazing foil materials produced thus far do not exceed about 90' m (=.O35 in) in
thickness. In many applications, however, the brazing gap thickness is greater than about 100 um and/or wider than about 250 mm (4 0 in.) Accordingly, it has been necessary to individually place a plurality of the foils into the joint to be brazed, either in a stacked and/or side-by-side configuration. Unfortunately, problems are created in maintaining the layers in proper alignment with each other and, as a result, the use of a plurality of individual layers has not gained commercial acceptance. It is known to consolidate a number of layers of at least 50% amorphous ribbon by the process disclosed in U.S. XXXXXXX. Also, attempts have
been made to use adhesives to consolidate multiple layers of these materials. In the former instance, however, copper-phosphorus and nickelboron-silicon-base brazing foils become brittle on consolidation and, therefore, would have extremely
limited use in brazing joints of complex shape. In the latter instance, use of adhesives produces the
unacceptable result of unwanted residue or porosity in the brazed joint. As a result, non-uniform and, in many instances, unacceptably weak joints are produced.

There remains a need in the art for thick and/or exceptionally wide, flexible brazing foils which can accommodate brazing of large parts such as tail pipes of aircraft turbine engines.

SUMMARY OF THE INVENTION

In accordance with the invention, there is provided a flexible multilayered brazing material suitable for use in brazing joints having a gap thickness greater than about 100 km andior a width in excess of the width of a single foil. The flexible multilayered brazing material comprises, in combination, at least one layer of ductile
brazing foil defining a core body having two major surfaces and at least one minor surface, and at least one layer of ductile brazing foil substantially covering said two major surfaces and at least one minor surface of said core body. More particularly,
the core body and cover layer are each composed of metastable material which is at least about 50% amorphous.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 illustrates the simplest form of a product of the present invention, with the cover layer having been folded over the core body. Figure 2 illustrates the simplest form of the most preferred product of the present invention, with the cover layer helically wrapped around the core body. Figure 3 illustrates the production of exceptionally wide strip by arranging a plurality of layers in side-by-side relationship to define a core body which is then wrapped in the cover layer. Figure 4 is a side view of apparatus useful for producing multilayered product of the type illustrated
in Figure 1. Figure 5a is a sectional view taken across the line A-A in Figure 4 showing the general construction of the forming die near the inlet end thereof

Figure 5b is a sectional view 'taken across the line B-B of Figure 4 illustrating the general construction of the forming die near the outlet end thereof. Figure 6 is a top view of the forming die illustrated in Figure 4 showing the folding regimen of the cover layer as it travels through the forming die. Figure 7 is a top view of an apparatus useful for producing the product of the type illustrated in Figures 2 and 3. Figure 8 is a side view of the apparatus illustrated in Figure 7.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is illustrated, in its simplest form, in Figures 1 and 2. Figure 1 shows a multilayered brazing strip in accordance with the present invention consisting of a single layer of brazing material defining a core body 1 encased in a covering layer 2. In this embodiment, the cover layer 2 is formed by folding a single strip of brazing foil having a width equal to about 21 + 2d, where "I" is the width of the core body 1 and "d" is the thickness of core body 1, about the core body 1 such that the edges of the cover layer 2 contact to form a seam 3 along one surface of-the multilayered product. Figure 2 shows an alternate, more preferred embodiment of the present invention wherein the core layer 1' is helic,ally wrapped
along its length with a cover layer 2 . In the embodiment of Figure 2, the width of the cover layer need not be related to the width of the core body because the angle of wrapping will control ,the formation of a continuous cover and the seam 3 . In
either embodiment, it is very desirable to avoid any significant overlap of edges of the cover layer in order to maintain substantial uniformity of the thickness of the final product. In the present invention, the thickness of the multilayered product can be controlled by providing more than one layer to define the core body or, similarly, more than one cover layer.

However, regarding in the latter, one cover layer is most preferred. Another embodiment of the present invention is illustrated in Fig. 3. In this embodiment, a plurality of layers 1 ", 1 O" are arranged in side-by-side relation
to define the core body and thereafter wrapped in a cover layer 2" to produce wide, thick strip. With this embodiment, the width of the strip is, in a practical sense, limited only by the capabilities of the equipment available to properly wrap the core
layers. Although the present invention is conceptionally quite simple, it offers a number of advantages over prior art products.

First, alignment problems associated with individually stacked multiple layers in a gap are overcome. Second, elimination of problems associated with using adhesives to bond multiple layers together to form a preformed multilayered product is avoided. Third, brazing is uniform, i.e., non-uniformity in brazement thickness as ordinarily occurs with pastes, powders and rod feed are eliminated. Fourth, thick brazing material formed of at least 50% amorphous ductile foils can be produced which heretofore was unavailable for brazing large components. Fifth, flexible multilayered brazing materials formed from at least 50% amorphous ductile foils can be produced which are particularly useful in the production of uniformly brazed joints having complex shapes. The brazing foils employed to produce the multilayered products of the present invention must be ductile. That is, the core layer must consist of brazing foil having sufficient flexibility to enable it to be bent to a radius of about 10 times the thickness of the foil without breaking. In addition, the cover layer must be sufficiently flexible such that it can be bent to a, radius equal to or slightly less than the thickness of the core body without breaking.

Suitable foils useful for the core body material and cover layer are at least about 50% amorphous foils disclosed, for example, in U.S: Patent No XXXXXXX. As a result of the use of ductile foils in the core body and as the cover layer. The multilayered product will exhibit sufficient flexibility such that it can be bent to a radius equal to about the width of the multilayered product without breaking and without causing substantial displacement of the core body relative to the cover layer upon returns to the unbent condition. The products of the present invention can be produced by a variety of techniques employing a wide range of equipment. Figures 4-6 illustrate a preferred process for continuous manufacturing of multilayered flexible brazing strips from a plurality of ductile, brazing foils. Figures 7 and 8 illustrate the most preferred process for continuous manufacturing of multilayered flexible brazing strip from a plurality of ductile brazing foils. According to the process illustrated in Figure 4, a first ductile brazing foil 1 is continuously dispensed from a first guide roll 10 past a first grade roll 11 into a forming die 12. Simultaneously, a second ductile brazing foil 2 is continuously dispensed from a second feed roll 10a past a second guide roll Ila into forming die 12. As described heretofore, the second foil has a width equal to about 21 + 2d. In the process illustrated in Fig. 4, the second foil is fed beneath the first foil to produce a multilayered preform as illustrated in Fig. 5a. Forming die 12, illustrated in detail in Figures 5a, 5b and 6, consists of a generally flat bottom portion 120 and angular side walls 121,122. The angular side walls 121, 122 gradually change shape from the input end 12a of the forming die 12 to the output end 12b of the forming die 12, thereby causing the second foil to be deformed in such a manner as to gradually fold over the major and minor side surface(s) of the first strip. This gradual folding process is more clearly illustrated by reference to Figure 6, referring to lines 21, 22 which represent the edges of second foil 2. Referring again to Figure 4, the multilayered perform is then subjected to cold rolling, at

cold rolling mill 13, sufficient to cause permanent deformation of the second strip (cover layer) necessary to produce the final product illustrated in Figure. 1.

Ordinarily, the degree of permanent (plastic) deformation or cold rolling is about 1-2%, and should not exceed about 396. The cold rolled, flexible, multilayered brazing strip is then wound onto a take up roll 13. It should be readily apparent that the above described process includes only the basic steps necessary to produce products of the present invention of the type illustrated in Figure 1. Products of the type wherein the core body consists of multiple stacked layers or multiple layers in sideby-side relationship are readily producible by using the above described process, modified to provide additional feed rolls or feed rolls which supply multiple strips. It should also be readily apparent that the forming step can be accomplished by any of a wide variety of equipment other than the above described forming die such as, for example, rolling equipment arranged in the direction of travel of the strips which effects the folding regimen illustrated schematically in Fig. 6. Moreover, it should be apparent that additional apparatus features such as guiding and aligning rolls and drive mechanisms have been omitted from the illustration because they are not necessary for a complete understanding of the present invention and because it understood by those skilled in the art to include the same. The most preferred process for production of products of the present invention is illustrated by the apparatus shown in Figures 7 and 8.

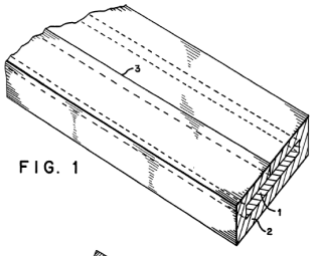
As is readily apparent, the embodiment illustrated therein is employed for the production of products of the type described heretofore with reference to Figures 2 and 3. According to Figure 7, the core body 1' is fed through the open center of closed loop 70 driven, for example, by a drive ear 71 attached to a motor 72. Associated with the loop 70 is a feed roll 73 mounted on a roll holder 74 arranged at an angle relative to the plane of rotation of the loop 70 to effect a helical wrapping of the core body 1' with the cover layer 2'. The helically wrapped preform then plses through guide rolls 75 and 76 (bottom rolls 75 and 76' illustrated in Figure 8) to a cold rolling mill 77 (employing cold rolling rolls 78 and 79 as shown in Figure 8) plastically deform the cover layer to produce the final form of the multilayered brazing strip illustrated in Figure 2. From the cold rolling mill, the flexible multilayered product is fed to a take-up roll 80. As described with respect to Figures 4-6, the apparatus illustrated in Figures 7 and 8 has been simplified so as to convey the basic features necessary to enable one skilled in the art to make and use the invention. It will be readily apparent that basic changes in the product construction can be effected, for example, by changing the angle of
offset between the plane of rotation of the loop 70 and the roll holder 74. (As the angle e approaches go', significant overlap of the cover layer can occur: alternatively, as the angle becomes more obtuse, gaps in the cover layer can be created.) Further, in order to produce products of the type illustrated in Figure 3, it is readily apparent that multiple strips forming the core body would be fed in side-by-side relation through the apparatus illustrated in Figures 7 and 8. The following examples are presented to illustrate the production of products within the scope of the present invention. They are not intended to limit the scope of the invention defined by the appended claims in any respect.

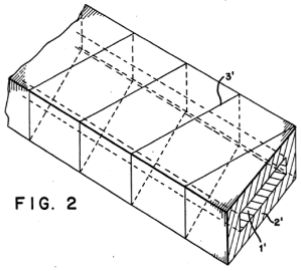
EXAMPLE -1
A multilayered, flexible brazing material having a width of about 25mm (= 1 inch), a thickness of about 150 um (= 6 mil) and a length of about 15 m (~ 4 5fe et) was produced using an amorphous alloy having nominal composition (in weight percent)

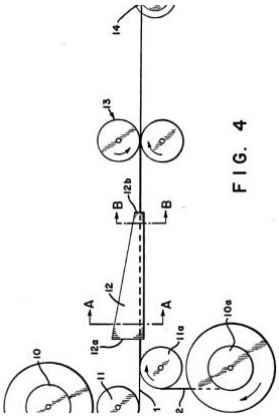
Cr7Fe3Si4.5C0.6B 3.2NibaIT.h e multilayered brazing product was produced by continuously drawing two foils, one 50mm (about 2 inch wide and about 50 um (2 mil) thick and one about 25mm (one inch) wide and about 50 um (2 mil) thick simultaneously using a specially designed die followed by cold rolling (schematically illustrated in Figures 4-6). During the drawings, the wide foil folds onto the narrow foil, effectively encasing the narrow foil. The multilayered foil was cold rolled at a 60mímin (=180'/min) production rate under a pressure of about 25 kPa to produce a rolled strip of about 150u m (= 6 mil) thick. Production rate was controlled by
regulating the rotation speed of the cold rolling mill and the take-up roll which is positioned after the cold rolling mill (shown in Figure 4).

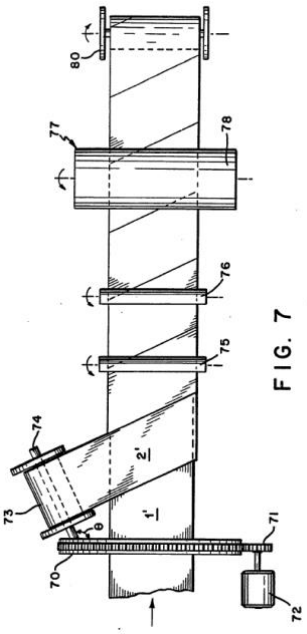
EXAMPLE 2
A 160mm wide and 150 um thick flexible multilayered brazing product is produced from amorphous foil having a nominal composition as recited in Example 1. The production technïque consists of laying up, in side-by-side fashion, three amorphous
foils of about 50 mm in width and about 50 Lm in thickness and thereafter helically wrapping a covering foil of about 50mm width and about 50 bm thickness to form a flat helicoid surrounding the three side-by-side foils forming the core body.
Afterwards, the wrapped foil is rolled through a two roll cold rolling mill. (As schematically illustrated in figures 7 and 8). As a result, a flat multilayered
product of substantially rectangle cross-section is produced. Having described the invention in full clear concise and exact terminology so as to enable one skilled in the art to make and use the same, the full scope of the invention is defined by the appended claims.

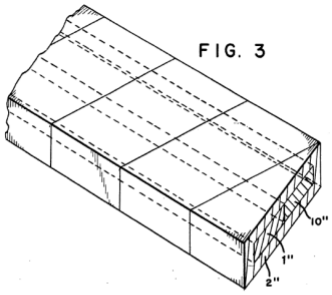
[DRAWINGS]

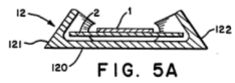


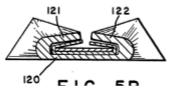


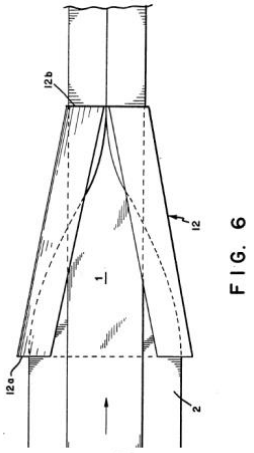


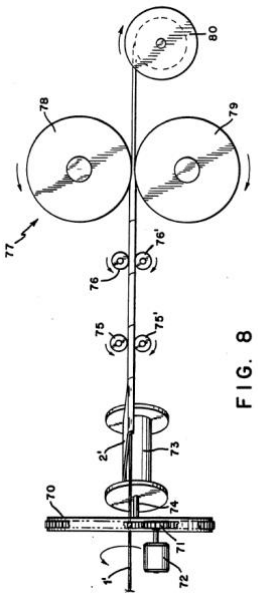












Case study 4 - Validity / Document D5

[ABSTRACT]
The potential of a photofabrication process involving photolithography and electrochemical milling has been established for the production of accurate holes in a range of sheet materials (10-500#m thick), including molybdenum, platinum, Pt- lORh, sterling silver, carat gold and silver- and palladium-based alloys. Based on scanning electron microscopy, the new technique shows its unique capability of producing high quality components in materials which were hitherto considered to be difficult or impossible to fabricate. Furthermore, the technique does not involve the use of any highly toxic or aggressive chemicals; a non-passivating neutral solution of sodium chloride is used as the electrolyte. Details of the type, concentration and application of the electrolyte are discussed. The technique appears to be potentially attractive to the manufacturers of fine apertures and similar intricate shapes of industrial components and jewellery items.

[DRAWINGS]

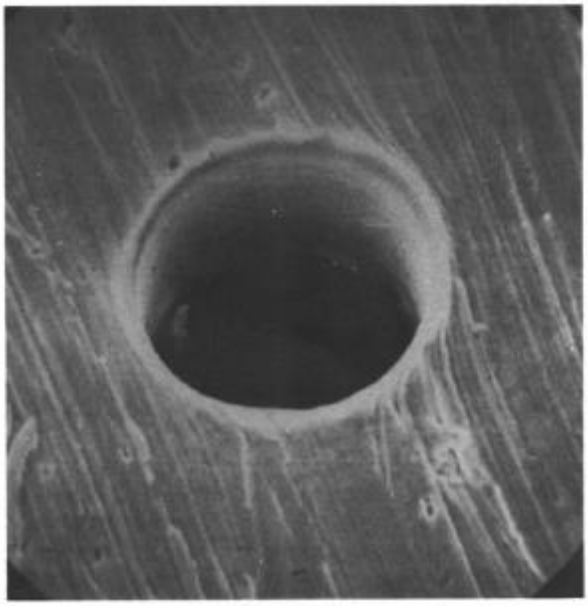


Fig 18 SEM picture (45° tilt) of aperture in platinum foil produced by present photoelectrochemical technique (670× magnification)

Case study 4 - Validity / Document D6

[ABSTRACT]
Brazing of metal parts employing a homogeneous, ductile, filler metal foil is disclosed. The brazing foil, useful for brazing cobalt based alloys, has a composition consisting essentially of 0 to about 4 atom percent iron, 0 to about 26 atom percent chromium, 0 to about 20 atom percent nickel, 0 to about 4 atom percent tungsten, 0 to about 4 atom percent molybdenum, 0 to about 20 atom percent boron, 0 to about 12 atom percent silicon, 0 to about 2 atom percent carbon and the balance essentially cobalt and incidental impurities. In addition to containing the foregoing elements within the above-noted composition ranges, the composition must be such that the total of iron, chromium, nickel, tungsten, molybdenum and cobalt ranges from about 75 to 85 atom percent and the total of boron, silicon and carbon ranges from about 15 to 25 atom percent. The ductile foil permits fabrication of preforms of complex shapes which do not require binders and/or fluxes necessary for brazing powders presently used to braze cobalt and nickel base alloys.

[DETAILS]
Brazing is a process for joining metal parts, often of dissimilar composition, to each other. Typically, a filler metal that has a melting point lower than that of the metal parts to be joined together is interposed between the metal parts to form an assembly. The assembly is then heated to a temperature sufficient to melt the filler metal. Upon cooling, a strong, corrosion resistant, leak-tight joint is formed.

Nickel and cobalt based alloys are conventionally joined by means of hydrogen, inert gas or vacuum brazing techniques. Such methods are employed to maintain low levels of contamination in the joint area. For high service temperature applications, nickel or cobalt based brazing filler alloys, having American Welding Society designation BNi or BCo compositions, per AWS A5.8, are used. These alloys produce brazed joints with high temperature strength and corrosion ad oxidation resistance.

The brazing alloys suitable for use with cobalt and nickel based alloys contain a substantial amount (about 3 to 11 weight percent) of metalloid elements such as boron, silicon and carbon. Consequently, such alloys are very brittle and are available only as powder, powder-binder pastes, powder-binder tapes and bulky cast preforms. Powders are generally unsuitable for many brazing operations, such as dip brazing, and do not easily permit brazing of complex shapes.
Although some powders are available as pastes employing organic binders, the binders form objectionable voids and residues during brazing.

Some brazing alloys are available in foil form. However, such materials are either fabricated only through a costly sequence of rolling and careful heat-treating steps or are prepared by powder metallurgical techniques.
Rolled foil is not sufficiently ductile to permit stamping of complex shapes therefrom. Powder metallurgical foil is not homogeneous and employs binders, which form objectionable voids and residues during brazing.

Ductile glassy metal alloys have been disclosed in U.S. Pat. No. XXXXXXX, issued Dec. 24, 1974 to H. S. Chen et al. These alloys include compositions having the formula Ma Yb Zc, where M is a metal selected from the group consisting of iron, nickel, cobalt, vanadium and

chromium, Y is an element selected from the group consisting of phosphorus, boron and carbon, and Z is an element selected from the group consisting of aluminum, silicon, tin, germanium, indium, atimony and beryllium, 'a' ranges from about 60 to 90 atom percent, 'b' ranges from about 10 to 30 atom percent and 'c' ranges from about 0.1 to 15 atom percent. Also disclosed are glassy wires having the formula Ti Xj, where T is at least one transition metal and X is an element selected from the group consisting of phosphorus, boron, carbon, aluminum, silicon, tin, germanium, indium, beryllium and antimony, 'i' ranges from about 70 to 87 atom percent and 'j' ranges from about 13 to 30 atom percent. Such materials are conveniently prepared by rapid quenching from the melt using processing techniques that are now well -known in the art.
No brazing composition are disclosed therein, however. There remains a need in the art for a homogeneous, cobalt based brazing material that is available in ductile foil form.

SUMMARY OF THE INVENTION
In accordance with the invention, there is provided a homogeneous, ductile brazing foil useful as a filler metal for a brazed metal article. The brazing foil is composed of metastable material having at least 50 percent glassy structure, and has a thickness ranging from about 20 MU m (0.0008 inch) to 90 MU m (0.0035 inch).
It has been found that use of a cobalt based brazing foil that is flexible, thin and homogeneous, as described above, improves braze joint strength, enhances joining precision and reduces process time.

More specifically, the brazing foil has a composition consisting essentially of 0 to about 4 atom percent iron, 0 to about 26 atom percent chromium, 0 to about 20 atom percent nickel, 0 to about 4 atom percent tungsten, 0 to about 4 atom percent molybdenum, 0 to about 20 atom percent boron, 0 to about 12 atom percent silicon, 0 to about 2 atom percent carbon and the balance essentially cobalt and incidental impurities. In addition to containing the foregoing elements within the above-noted composition ranges, the composition must be such that the total of iron, chromium, nickel, tungsten, molybdenum and cobalt ranges from about 75 to 85 atom percent and the total of boron, silicon and carbon constitutes the remainder, that is, about 15 to 25 atom percent.

The homogeneous brazing foil of the invention is fabricated by a process which comprises forming a melt of the composition and quenching the melt on a rotating quench wheel at a rate of at least about 105 (degree) C./sec.

The filler metal foil is easily fabricable as homogeneous, ductile ribbon, which is useful for brazing as cast. Advantageously, the metal foil can be stamped into complex shapes to provide braze performs. Further, the homogeneous, ductile brazing foil of the invention eliminates the need for binders and pastes that would otherwise form voids and contaminating residues. Also, the filler material provided by the invention enables alternative brazing processes of cobalt and nickel based alloys, e.g., dip brazing in molten salts, to be employed.

DETAILED DESCRIPTION OF THE INVENTION
In any brazing process, the brazing material must have a melting point that will be sufficiently high to provide strength to meet service requirements of the metal parts brazed together. However, the melting point must not be so high as to make difficult the brazing operation. Further, the filler material must be compatible, both chemically and

metallurgically, with the materials being brazed. The brazing material must be more noble than the metal being brazed to avoid corrosion. Ideally, the brazing material must be in ductile foil form so that complex shapes may be stamped thereform. Finally, the brazing foil should be homogeneous, that is, contain no binders or other materials that would otherwise form voids or contaminating residues during brazing.

In accordance with a preferred embodiment of the invention a homogeneous, ductile cobalt based brazing material in foil form is provide. The brazing foil has a composition consisting essentially of 0 to about 4 atom percent iron, 0 to about 26 atom percent chromium, 0 to about 20 atom percent nickel, 0 to about 4 atom percent tungsten, 0 to about 4 atom percent molybdenum, 0 to about 20 atom percent boron, 0 to about 12 atom percent silicon, 0 to about 2 atom percent carbon and the balance essentially cobalt and incidental impurities.
The composition is such that the total of iron, chromium, nickel, tungsten, molybdenum and cobalt ranges from about 75 to 85 atom percent and the total of boron, silicon and carbon comprises the balance, that is about 15 to 25 atom percent. These compositions are compatible with and more noble than cobalt based alloys and are suitable for brazing nickel as well as cobalt base alloys.

By homogeneous is meant that the foil, produced, is of substantially uniform composition in all dimensions. By ductile is meant that the foil can be bent to a round radius as small as ten times the foil thickness without fracture. Examples of brazing alloy compositions within the scope of the invention are set forth below.

The brazing temperature of the brazing alloys of the invention ranges from about 1,035 (degree) C. to 1,300 (degree) C. The brazing foils of the invention are prepared by cooling a melt of the desired composition at a rate of at least about 105 (degree) C./ sec, employing metal alloy quenching techniques well-known to the glassy metal alloy art; see, e.g., U.S. Pat. No. XXXXXXX, discussed earlier, the purity of all compositions is that found in normal commercial practice. A variety of techinques are available for fabricating continuous ribbon, wire, sheet, etc. Typically, a particular composition is selected, powders or granules of the requisite elements in the desired portions are melted and homogenized, and the molten alloy is rapidly quenched on a chill surface, such as a rapidly rotating metal cylinder.

Under these quenching conditions, a metastable, homogeneous, ductile material is obtained. The metastable material may be glassy, in which case there is no long range order. X-ray diffraction patterns of glassy metal alloys show only a diffuse halo, similar to that observed for inorganic oxide glasses. Such glassy alloys must be at least 50% glassy to be sufficiently ductile to permit subsequent handling, such as stamping complex shapes from ribbons of the alloys. Preferably, the glassy metal alloys must be at least 80% glassy, and most preferably substantialy (or totally) glassy, to attain superior ductility.

The metastable phase may also be a solid solution of the constituent elements.
In the case of the alloys of the invention, such metastable, solid solution phases are not ordinarily produced under conventional processing techniques employed in the art of fabricating crystalline alloys. X-ray diffraction patterns of the solid solution alloys show the sharp diffraction peaks characteristic of crystalline alloys, with some broadening of the peaks due to desired fine grained size of crystallites. Such metastable materials are also ductile when produced under the conditions described above.

The brazing material of the invention is advantageously produced in foil (or ribbon) form, and may be used in brazing applications as cast, whether the material is glassy or a solid solution. Alternatively, foils of glassy metal alloys may be heat treated to obtain a crystalline phase, preferably fine-grained, in order to promote longer die life when stamping of complex shapes is contemplated.
Foils as produced by the processing described above typically are about 20 to 90 MU m (0.0008 to 0.0035 inch) thick, which is also the desired spacing between bodies being brazed. Such spacing mximizes the strength of the braze joint.
Thinner foils stacked to form thickness greater than 90 MU m may also be mployed.
Further, no fluxes are required during brazing, and no binders are present in the foil.
Thus, formation of voids and contaminating residues is eliminated. Consequently, the ductile brazing ribbons of the invention provide both ease of brazing, by eliminating the need for spacers, and minimal post-brazing treatment.

The brazing foils of the invention are superior to various powder brazes of the same composition in providing good braze joints. This is probably due to the ability to apply the brazing foil where the braze is required, rather than depending on capillarity to transport braze filler from the edge of surfaces to be brazed.

EXAMPLE 1
Ribbons about 6.5 mm (0.25 inch) wide and about 40 to 60 MU m (about 0.0010 to 0.0035 inch) thick were formed by squirting a melt of the particular composition by overpressure of argon onto a rapidly rotating copper chill wheel (surface speed about 1,000 to 2000 m/min). Metastable, homogeneous ribbons of substantially glassy alloys having compositions listed in weight percent and atom percent were produced.

EXAMPLE 2
Tensile test specimens were cut from Haynes Alloy 188 ('Haynes' is a registered trademark of Cabot Corporation, Kokomo, Ind.), in strip form the composition of Haynes Alloy 188 is given.

The thickness was 0.16 cm (0.063 inch). A brazing alloy of the invention, a glassy, ductile ribbon of nominal composition of Sample No. 1 and having dimensions 46 MU m (0.0018 inch) thick by 6.3 mm (0.25 inch) wide, was used to braze the test specimens.

The tensile specimens were dimensioned and fabricated as lap shear specimens per AWS C3.2-63. The specimens were cut perpendicularly to the length direction.
Braze joints were of the lap type, with the lap dimension carefully controlled to 0.95 cm (3/8inch). Brazing specimens were degreased with warm benzene. Lap joints containing brazing ribbons of the invention were assembled with the ribbons side-by-side the length of the lap joint. In the case of these brazing alloys, the ribbons acted as the spacers. A single spot weld was used to hold the assembly together, as is common industrial practice.

Brazing was done in a vacuum furnace which was evacuated to a pressure of 1.33 * 10-2 Pa (10-4 Torr). The furnace was held at 1,300 (degree) C. for 15 minutes. Upon brazing, three shear specimens were subjected to tensile shear testing, with the following results:
-- _____
-- Shear Strength Tensile Strength

-- Area of
-- Sample GPa (psi) GPa (psi) Failure
-- _____
-- 1-A 0.113 (16,320) 0.338 (48,960)
-- Base metal
-- 1-B 0.112 (16,267) 0.336 (48,800)
-- Base metal
-- 1-C 0.120 (17,333) 0.359 (52,000)
-- Base metal
-- _____

All brazes were observed to fail in the base metal and not in the braze; therefore, the values reported are lower bounds.

EXAMPLE 3
Tensile test specimens of Haynes Alloy 188 were prepared for brazing as in Example 2. A brazing alloy of the invention, a glassy ductile ribbon of nominal composition of Sample No. 2 and having dimensions 46 MU m (0.0018 inch) thick by 6.3 mm (0.25 inch) wide was used to braze three test specimens.

Brazing was done in a vacuum furnace which was evacuated to a pressure of 1.33 * 10-2 Pa (10-4 Torr). The furnace was held at 1,300 (degree) C. for 15 minutes. The brazed joints evidenced the following joint strengths.

-- _____
-- Shear Strength Tensile Strength
-- Area of
-- Sample GPa (psi) GPa (psi) Failure
-- _____
-- 2-A 0.052 (7573) 0.313 (45440) Joint
-- 2-B 0.094 (13653) 0.565 (81920) Joint
-- 2-C 0.042 (6133) 0.254 (36800) Joint
-- _____

EXAMPLE 4
Tensile test specimens of Haynes Alloy 188 were pepared for brazing as in Example 2. A brazing alloy of the invention, a glassy ductile ribbon of nominal composition of Sample No. 3 and having dimensions 46 MU m (0.0018 inch) thick by 3.2 mm (0.125 inch) wide was used to braze one test specimen. Brazing was done in a vacuum furnace which was evacuated to a pressure of 1.33 * 10-2 Pa (10-4 Torr). The furnace was held at 1,300 (degree) C. for 15 minutes. The brazed joints evidenced the following joint strengths:

-- _____
-- Shear Strength Tensile Strength
-- Area of
-- Sample GPa (psi) GPa (psi) Failure
-- _____
-- 3-A 0.047 (6880) 0.285 (41280) Joint
-- _____

EXAMPLE 5
Tensile test specimens of Haynes Alloy 188 were prepared for brazing as in Example 2. A brazing alloy of the invention, a glassy ductile ribbon of nominal composition of Sample No. 4, and having the dimensions 41 MU m (0.0016 inch) thick and 6.3 mm (0.25 inch) wide was used to braze two test specimens.

Brazing was done in a vacuum furnace evacuated to 1.33 * 10-2 Pa)10-4 Torr).
The furnace was held at 1,200 (degree) C. for 15 minutes. The brazed joints evidenced the following joint strengths.

-- _____
-- Shear Strength Tensile Strength
-- Area of
-- Sample GPa (psi) GPa (psi) Failure
-- _____
-- 4-A 0.051 (7413) 0.301 (44,480)
-- Joint
-- 4-B 0.052 (7627) 0.316 (45,760)
-- Joint
-- _____

Case study 4 - Validity / Document D7

[ABSTRACT]
Nickel-Chromium-Silicon alloys of the nominal composition, Ni(45-78) Cr(16.34) Si(6.21)in the form of thin foil are made ductile by the presence of appreciable amounts of an amorphous phase and a metastable, solid solution, microcrystalline single phase and are especially suitable for preplacement as preforms in a joining operation such as brazing. Up to abour 40 atomic percent of the nickel is replaceable with palladium.

[DETAILS]
The nickel-chromium-silicon alloys in the nickel-rich corner of the Ni-Cr-Si ternary triangle such as the composition specified in Aeronautical Material Specification 4782, (Ni62.3 Cr18.9 Si18.8) have been used in the form of powders, pastes and less than 100 percent dense foil fabricated from powder, because of the brittle nature of these alloys when these alloys have a silicon content greater than 6 atomic percent.

The disadvantages of using powder and pastes is that the alloy when molten, has to flow into the joint and fill up the gap between the mating parts. The flow of the molten alloy is strongly sensitive to the brazing environment and under non-ideal conditions the alloy may not flow through the joint gap. Also the organic binders in the pastes leave a residual contamination which alter the properties of the brazed joint. The use of sintered foil which has a density of less than 100 percent will result in voids in the brazed joint.

U.S. Pat. No. XXXXXXX discloses a wire product where alloys are represented by the formula Ti Xj wherein T is a transition metal and X is Al, Sb, Be, B, Ge, C, In, P, Si or Sn. The transition metals include metals from Groups IB, IIIB, IVB, VB, VIB, VIIB and VIIIB of the periodic table. The patent also teaches that the alloys contain at least 50 percent amorphous phase. As is apparent from that description, about 280 binary alloys are disclosed and an infinite number of alloys when mixtures of metals are used for T and X. The only alloys specifically disclosed are Pd77.5 Cu6 Si16.5 and Ni40 Pd40 P20. The patent also discloses ternary alloys of the formula Ma Yb Zc in sheet, ribbon and powder form wherein M is Ni, Fe, Cr, Co or V, Y is P, C or B and Z is Al, Si, Sn, Sb, Ge, In or Be.

It is believed that a 100 percent dense foil of the Ni-Cr-Si alloys which are ductile in nature and is therefore suited for fabricating into brazing preforms of a required geometry, by conventional stamping or photo etching techniques, without cracking would be an advancement in the art.

The advantages of the present invention over the present techniques is the ability to make ductile foil which would be normally brittle if made by conventional techniques.
The process of making ductile foil also results in foil of uniform composition which is highly desirable for obtaining brazed joints with a high degree of reproductibility.
Such a ductile foil is especially suitable for fabricating into brazing preforms of required geometry.

SUMMARY OF THE INVENTION
In one aspect of this invention there is provided an alloy in the form of a brazing foil having a thickness of from about 0.0005 to about 0.005 inches and consisting essentially of from about 45 to about 78 atomic percent of nickel, from about 16 to about 34 atomic percent of

chromium and from about 6 to about 21 atomic percent of silicon. Optionally up to about 40 atomic percent of the nickel can be replaced with palladium.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS
For a better understanding of the present invention, together with the other and further objects, advantages and capabilities thereof, reference is made to the following disclosure and appended claims in connection with the above description of some of the aspects of the invention.

U.S. Pat. No. XXXXXXX claims that additions of silicon aid in the formation of the amorphous phase. However, the sole purpose of additions of silicon to the alloy of this invention is for its effect of depressing the melting range, as commonly used in nickel-base brazing alloys. Up to 40 atomic percent of the nickel is replaceable with palladium to depress the melting range further than that provided by silicon.

In the nickel-chromium-silicon system, alloys of a silicon content greater than about 6 atomic percent form nickel and chromium silicides which embrittle the alloy and do not allow for fabricating into thin foil by conventional casting and rolling techniques.
The formation of silicides is well documented in the description of the Ni-Cr-Si ternary system as described by Knotek, Lugscheider and Eschnauer in Hartlegierungen Zum Verschleiss--Schutz, P. 30, Verlag Stahleisen MBH, Dusseldorf, 1975.

It is known that rapid cooling of a molten metal will in some instances form amorphous materials instead of crystalline phases. Some techniques for rapid quenching are disclosed in U.S. Pat. Nos. XXXXXXX; XXXXXXX; XXXXXXX and XXXXXXX. In the practice of this invention it is preferred to use a metal stream from an orifice to impinge upon a rotating drum having its external surfaces cooled by an internal cooling medium such as water. The metal stream upon solidifying forms a sheet-like material that is projected from the drum by centrifugal force.

Depending on the cooling rate during the rapid quenching, the resulting structure consists of a combination of an amorphous phase, new phases not obtainable under equilibrium conditions and a solid solution with solubility limits extended beyond their equilibrium values as described by Pol Duwez, R. H. Willens in Transactions of the Metallurgical Society of AIME, Volume 227 p. 362, April 1963.
The amorphous phase is intrinsically ductile because the glassy structure allows for slip in all possible directions. Additional ductility results from the presence of a microcrystalline single phase metastable solid solution which has a large grain-boundary area.

A rapid cooling rate of about 105 (degree) C./sec to 106 (degree) C./sec would prevent the formation of these embrittling silicides and extend the solubility of silicon in the Nickel-Chromium binary system. At the same time such high rates of cooling would create an appreciable amount of amorphous phase which has a disordered glassy structure. Above about 10 percent amorphous phase is preferred.

The alloy of this invention can be fabricated into thin foil containing appreciable amounts of amorphous phase and a metastable, micro-crystalline, solid solution, single phase, by the available rapid quenching techniques such as, melt extraction, melt-spin, vapor deposition or sputtering with cooling rates of about 105 (degree) C./sec to 106 (degree) C./sec.

An alloy fabricated in such manner is ductile and allows for fabrication of performs of intricate geometry, for preplacement in a brazing operation. The ductile foils of this invention have a thickness of from about 0.0005 to about 0.005 inches with thicknesses of from about 0.0015 inches to about 0.004 inches being preferred.

While alloys having the composition, Ni(45-78) Cr(16-34) Si(6-21) can be prepared in accordance with this invention in the form of a ductile brazing foil, preferred materials are Ni(60-65) Cr(17-20) Si(18-20) with AMS 4782 alloy having the composition, Ni62.3 Cr18.9 Si18.8 being especially preferred.
If desired up to about 40 atomic percent of the nickel present in the alloys can be replaced with palladium.

While there has been shown and described what are at present considered the preferred embodiments of the invention, it will be obvious to those skilled in the art that various changes and modifications may be made therein without departing from the scope of the invention as defined by the appended claims.

Case study 1 – Novelty - Sample answer

General Mark deductions

Marks should be deducted from the final score only once from total score for Part 2 if the candidate uses such phrases in his/her answer as 'one or more of D1-D5 is novelty destroying' OR that 'one or more claims of the Sonnepan application is not novel in light of ….' OR 'one or more claims is anticipated by the disclosure in…' OR 'one or more claims is not patentable'. Five marks will be deducted only once at the fist instance such a phrase has been used. The reason behind the deductions is that a patent attorney and not a patent searcher would render such conclusions and patent searchers should always refrain from drawing any conclusions about the novelty of an invention.

Prior Art Analysis

Remarks for D1
Marks awarded if candidate notes that the publication date of cited JP application (D1) is after both the filing and priority dates of the application in question. This tests the candidates knowledge of using filing dates for assessing novelty/validity of patents rather than using the publication date as for non-patent literature.
Marks awarded for identifying that corresponding WO9952311, was published prior to the priority date of the Sonnepan application despite all the other corresponding family members, including D1 being published afterwards. The candidate should have stated that WO9952311 should be consulted (if published in English) as the machine translations of the claims for D1 are poor.
Marks awarded for stating that D1 should be categorized as relevant and provide three possible reasons on the basis of technical disclosure of D1. The candidate should draw a comparison between the technical features of at least independent claim 1 of the Sonnepan application and the relevant technical features of D1 in providing his or her answer.

Remarks for D2
Marks awarded if candidate states that the date of publication for this document needs to be further investigated as the identified date cannot be assumed to be the date of publication, but if 15 May 2000 is indeed the date on which the document was made publicly available, then state this assumption or alternatively state that perhaps P&G filed a patent application concerning the globules that pre-dates this announcement. However, no further mark can be awarded for commentary that is based on a hypothetical patent filing.
Marks awarded for stating D2 should be categorized as **irrelevant** for the following reasons: Assuming the date of publication for D2 is 15 May 2000, then this document became publicly available after the date on which the priority application was filed (22 Dec. 1999), but before the date on which the SonnePan application was filed (19 Dec. 2000). The candidate should explain that the priority date of claims 1-5 and 7-11 is 22 Dec 1999, as the subject matter claimed in claims 1-5, 6 (in part) and 7-11 is disclosed by the priority document. Therefore, D2 does not appear to be a relevant document in respect of claims 1-5, 6 (in part) or 7- 11. The priority date for claim 6 is also 22 Dec. 1999, with the exception of, when claim 6 is directed at probiotic microorganisms and/or prebiotic substances. Probiotic microorganisms and prebiotic substances were only disclosed as a possible biologically active substance at the date of filing of the Sonnepan patent application. D2 does not disclose either probiotic microorganisms or prebiotic substances as a biologically active substance that can be included in the milk globules. Therefore, D2 does not appear to be relevant to the claimed food component of claim 6 when the biologically active substance is a probiotic microorganism and/or a prebiotic substance. The candidate should draw a comparison between at least independent claim 1 of the Sonnepan application and the disclosure of D2 in providing his or her answer. (Although the candidate may note that neither phosphatidylinositol nor phosphatidylcholine may fall within “enzymes, nutrients, natural or synthetic secondary plant constituents or substances having antioxidant activity“ as claimed in claim 6, this a moot point and no marks should be awarded, as the priority date of claim 6 in respect of these classes of biologically active substances precludes D2 from being considered a relevant document.) (The candidate may also note that D2 does not disclose the subject matter of claims 7-11. But again, this is a moot point and no marks should be awarded, as the priority date of these claims precludes D2 from being considered a relevant document.)

Remarks for D3
Marks awarded if candidate states that US’414 published in 1996, a few years before the Sonnepan application or its corresponding priority application was filed.
US’414 appears to be a relevant document on a novelty basis for the following reasons. US’414 discloses a nutritional product that contain: a) a guar gum core (as the fibre),

b) a zein (protein) layer (**as the biologically active material**)-remember that the Sonnepan application is not limited to probiotic bacteria only, but rather the biologically active substance is defined in the application as a substance that "can intervene in physiological processes" and US '414 states that the zein protein can lower cholesterol; and (c) a zein coating (as the shell). The Sonnepan application discloses that the shell forming substance can be a protein and also discloses that the biologically active substance can be a nutrient such as a protein. There is no disclosure in the Sonnepan application that the biologically active substance and the coating cannot be one and the same. It is apparent from US '414 that zein is a shell forming substance, as it is disclosed as an outer coating of the particle (see Encapsulation Experiments 2-4).

The candidate should draw a comparison between at least independent claim 1 of the Sonnepan application and the disclosure of D3 in providing his or her answer.

Claim 1

Claim 1 of the Sonnepan application claims a *multifunctional*
…structure (US'414 particles are multifunctional as they provide both guar gum as dietary fibre and cholesterol lowering agent and zein as cholesterol lowering agent.)

Claim 1 of the Sonnepan application claims *a core comprising at least one dietary fibre, which core is surrounded by at least one biologically active substance* (US'414 particles are produced by spraying the zein protein on to the guar gum core see Encapsulation Experiments 2-4)

Claim 1 of the Sonnepan application claims a *core and biologically active substance(s) are encapsulated by one or more shell forming substances* (US'414 particles are coated with zein see for Encapsulation experiment #2 where the fibre is first surrounded with zein, sieved and then coated
once more with zein). Therefore, US '414 appears to be a relevant document in respect of claim 1.

Remarks for D4

Marks awarded if candidate states that journal article published in 1996, a few years before the Sonnepan application or its corresponding priority application was filed.

D4 does not appear to be a relevant document.

Although D4 discloses microcapsules that contain alginate which is a plant fibre (as it is derived from brown algae) that is coated with chitosan or DEAE dextran (a shell forming substance that is a polysaccharide), the document does not disclose a microcapsule that contains a biologically active substance, as a pigment is encapsulated for the purpose of a synthetic aqueous based resin such as a latex.

The candidate should draw a comparison between at least independent claim 1 of the Sonnepan application and the disclosure of D4 in providing his or her answer.

Remarks for D5
Although WO '501 was published on 24 December 2000, which was after the filing date of the Sonnepan patent application, the WO '501 claims an earlier priority date (7 June 1999) than the Sonnepan patent application (22 Dec. 1999). Thus, WO'501 may be citeable against the novelty of one or more claims of the Sonnepan patent application if (i) all of the subject matter in WO '501 was first disclosed in its priority document such that the priority date of WO '501 cannot be contested; (ii) both the WO'501 and the Sonnepan patent application are currently pending in one or more of the same jurisdictions; (iii) the patent law of the jurisdiction(s) include in the prior art base patent applications that are published after the filing date of the Sonnepan patent, but claim an earlier priority date; (iv) the priority date of WO'501 precedes the priority date of at least one of the claims of the Sonnepan patent application; and (v)WO'501 discloses all of the features of one or more claims of the Sonnepan application.
Assume that (i) -(v) are true The priority dates for claims 1-5, 6 (in part) and 7-11 is 22 Dec. 1999. When the food component claimed in claim 6 is a probiotic microroganisms and/or a prebiotic substance, the priority date is 19 Dec. 2000, because the priority document does not disclose probiotic microorganims or a prebiotic substance. As the priority date of WO'501 precedes both of these dates, the priority date of any of the claims will not be an issue. WO'501 appears to be a relevant document in respect of any one of claims 1-11 for the following technical reasons. WO'501 exemplifies particles that contain a) a psyllium core (as the fibre), b) a pectin or inulin layer (as the biologically active material-remember that the Sonnepan application is not limited to probiotic bacteria only, but rather the biologically active substance is defined in the application as a substance that "can intervene in physiological processes" and WO '501 states that the disclosed dietary fibres provide various gastrointestinal benefits including emptying time of the stomach; and (c) an inulin coating (as the shell). It is apparent from WO '501 that inulin is a shell forming substance, as it is disclosed as a outer coating of the particle that imparts a sweet taste. The candidate should draw a comparison between at least independent claim 1 of the Sonnepan application and the disclosure of D5 in providing his or her answer. Claim 1 Claim 1 of the Sonnepan application claims a *multifunctional* …structure (WO'501 particles are multifunctional as they provide both pysllium as dietary fibre surrounded by pectin which is another dietary fibre. As dietary fibres are disclosed as having multiple functions, the particles could be considered multifunctional. Claim 1 of the Sonnepan application claims *a core comprising at least one dietary fibre, which core is surrounded by at least one biologically active substance* (WO '501 particles are produced by spraying the pectin on to the psyllium core see for example Test 1.)

Claim 1 of the Sonnepan application claims a *core and biologically active substance(s) are encapsulated by one or more shell forming substances* (WO'501 particles are coated with inulin see for example Test 1). Therefore, WO'501 appears to be a relevant document in respect of claim 1.

Case study 2 – Infringement – Sample answer

General remarks

First of all, it should be considered that any remarks on the applicability of the documents because of the expiry dates should be awarded with an extra mark as shown in the marking guide. Also an explanation that for patent infringement/patent clearance searches both granted patents and patent applications may be considered relevant (as long as they are in force/pending), and that in the case of patent applications it is unknown whether the claims will be granted as published, should be awarded an extra mark as shown in the marking guide.

If a candidate only gives the correct relevancy of a document without discussion on what grounds, then only 1 mark per document will be awarded.

US 2008/233162 (Document 1)

This publication is a potentially relevant patent publication in the US, since it claims a scaffold as used in the client's production process (3- dimensional scaffold for tissue regeneration, comprising a polymer (such as PLA, PGA), formed by electrospinning. Potentially relevant claims are at least claims 1, 2, 5 and 14.

Candidate should mention that as the document is a patent application, it is unknown whether the claims will be granted as published.

US 5,192,312 (Document 2)

The filing date of this document is 5 March 1990, this will mean that the patent has expired on 9 March 2010. Assuming no patent term extension has been granted, it no longer provides any enforceable rights and for this reason, the patent does not appear relevant.

If the candidate does not assess the expiry of the patent, no marks will be awarded for any further discussion on the disclosure provided in US5192312 or the interpretation of its claims.

US 5,855,610 (Document 3)

The candidate should mention that this patent claims a heart valve comprising a biodegradable polymer, seeded with presumably homologous cells and configured to form a tissue structure (such as a valve, see claim 3). The difference, however, is that claim 1 requires that the structure is formed by a.o. implanting the matrix into a recipient human and then harvesting the matrix, i.e. remove it from the patient again. This is certainly not performed in the process of the client.

However, claim 1 is a product claim (and for the relevant part a product-by-process claim), and the protection of such a claim would encompass all methods of forming it. Claim 1 thus should not be considered to be limited to the process of implanting and harvesting.

Furthermore, claim 6 is also potentially relevant, because it claims a heart valve, wherein the cells form extracellular matrix following implantation into a human. Although in the client's process, as described, the cells will have already formed some extracellular matrix before implantation, the process of forming matrix will continue after implantation. Thus claim 6 could potentially be relevant. One mark should also be awarded for stating that the document is potentially relevant.

Candidate should mention that the patent term has yet to expire

EP 1 077 072 (Document 4)

The process claimed in claim 1 of the patent is identical to the process of the client except for the conditions of the flow rate and pressure in the bioreactor. Whereas the claim is limited to a continuous or discontinuous increasing of flow rate and pressure, the client's process is described as a steady state process. Thus, claim 1 and its dependent claims should be considered irrelevant. However, the argument that the client's process also has a step in which the flow rate and pressure are increased (starting from 0 to reach a steady state). If this argument is not made and claim 1 is still considered to be potentially relevant by the candidate, no marks should be awarded.

The potentially relevant claim of this document is independent claim 24. This claims a heart valve that can be produced by a method according to claim 1. From the description provided, it is possible that the heart valve produced by the client is a heart valve that can be produced by the method of claim 1. Thus, the document should be considered potentially relevant on the basis of claim 24.

Candidate should mention that the patent term has yet to expire

US 6,514,515 (Document 5)

This patent claims a biodegradable scaffold comprising poly(OH)alkanoate (which is meant for tissue engineering, especially for heart valves, see claims 27, 28 and 32). Such a scaffold is used in the client's process as described. Accordingly, the document should be considered potentially relevant provided that the client's scaffold has one or more of the claimed mechanical properties.

Candidate should mention that the patent term has yet to expire

Literature extract (Document 6)

Since this is a literature article and not a patent document, the article does not give rise to any enforceable rights. The document cannot pose a potential patent infringement risk and is therefore not relevant.

EP 1 339 356 (Document 7)

The difference between the product claimed in this patent and the client's product as described is that the scaffold of EP1339356 is seeded with (endothelial and) collagen cells. The candidates should note that the description of the client's process is silent on

application of collagen cells, which of course does not mean that these cells will not be used and/or comprised in the product of the client. Thus, this document should be considered potentially relevant.

Candidate should mention that the patent term has yet to expire

WO 2006/099334 (Document 8)

The process and product described in the claims of WO2006/099334 differs from the process/products of the client, because the order in which the muscle cells (fibroblasts) and the endothelial cells are deposited on the scaffold is reversed. Thus, the document is not potentially relevant if the same claims as the PCT are granted at national or regional phase. Alternatively, the one mark may also be awarded if the candidate states that as the full description of WO2006/099334 had not been provided, it is possible that the reverse order had been disclosed but not claimed in the published PCT application. It is therefore possible that at national or regional phase of this international application, that granted claims in which the same order of cell deposition is claimed can arise, in which case the document could be potentially relevant.

EP 1 878 451 (Document 9)

This document is a family member of (the potentially relevant document) US 6,514,515. However, the device claimed in this document is only mentioned as a meniscus repair ad regeneration device, an articular cartilage repair device, a tendon repair device, a ligament repair device or a bone graft scaffold. Thus, the document does not appear to be potentially relevant.

Case study 3 – Patentability – Sample answer

Identification of effectives dates of the EP patent application filed by Z

Claims 1 and 2:
Since the product and the product including the feature A and preferably the feature B were disclosed in the priority document in an enabling way, claims 1 and 2 have the same effective date of 27 November 2007.

Claims 3 and 4:
However, Claims 3 and 4 will have the latest effective date of 27 November 2008, which is the day before the priority expires, which is the filing date of the European patent application.

Claims analysis

CLAIM 1 (Independent, effective date 27 November 2007)

- D1 is a prior right that may be relevant to the novelty of claim 1, because it disclosed the product and because it was filed before the effective date of claim 1 and published after that date
- D2 may be relevant to the novelty of claim 1, since it was published before the effective date and because it disclosed the product

CLAIM 2 (dependent on claim 1, effective date 27 November 2007)

<u>Note on claim structure</u>

- The feature “preferably B” in claim 2 is non-limiting and therefore is disregarded. Expressions like “preferably”, “for example”, “such as” or “more particularly” are to be considered carefully to ensure that they do not introduce ambiguity. Expressions of this kind have no limiting effect on the scope of a claim; that is to say, the feature following any such expression is to be regarded as optional.
- D1 does not disclose the feature A.

<u>Detailed analysis</u>

- Since D1 is a prior right, it can only be cited on the basis of novelty. Thus a combination of D1 and D4 for an inventive step is not allowed. D1 does not appear to be relevant to the novelty of claim 2, because it does not disclose feature A.
- However, the combination of D2 and D4 may be used to argue that claim 2 lacks inventive step.

CLAIM 3 (Independent, effective date 27 November 2008)

- D1 may be relevant to the novelty of claim 3, since it was published before the effective date of claim 3 and it discloses the method of making the product
- The publication of D3 is an evident abuse, within the meaning of Art. 55(1)(a) EPC since it appears to be an intention to harm. For the calculation of the 6- month period referred to in Art 55(1)(a) EPC, the relevant date is the actual filing date of the European Patent Application. The date of priority is not taken into account in calculating the

period. D3 was published earlier than 6 months preceding the date of 27 November 2008 and therefore D3 may be relevant to the novelty of claim 1, as Art 55(1)(a) EPC does not apply.

CLAIM 4 (Dependent on claim 3, effective date 27 November 2008)

- Although it appears that none of the documents retrieved by the search disclose the subject matter of claim 4, an argument may be raised that claim 4 may lack inventive step in light of the combination of the disclosures of D1 and D4, since both D1 and D4 were published before the effective date of claim 4.
- The combination of the disclosures of D3 and D4 may also raise an inventive step argument in relation to claim 4, since both D3 and D4 were published before the effective date of claim 4

Case study 4 – Validity – Sample answer

Question 1
Seven [7] features described in the independent Claim 1:

Feature	Features description
a)	A preformed article
b)	formed of an amorphous metal
c)	brazing foil having an irreversibly deformed, non-planar, three dimensional configuration
d)	including a primary planar face with at least one perforation passing there through,
e)	said article being adapted for use in the manufacture of an assembly having brazed joints
f)	said manufacture comprising the brazing of a plurality of tubes to at least one plate, and
g)	the brazing of said plate to a shell encasing said plurality of tubes and said at least one plate

Question 2

Identification of main headings
The following headings are regarded as items that needed to be addressed to obtain marks for this question.

- Selecting the main document to be used for arguing lack of novelty for claim 1, M&N
- Extracting the correct relevant parts from selected document and map them correspondingly to the defined features in the claim chart for claim 1, M & N.
- Correct analysis and discussions on how to use and relate selected documents in relation to the novelty for claim 1, M & N.
- Selecting the right combination of two documents for discussions on the possible lack of inventive step of claim N.
- Extraction of relevant parts and reasoning based on a patentability discussion with regard to inventive step by combining the selected documents in relation to claim N
- Discussions on patentability featuring the combination of D1 & D3 in relation to claim N

Claim 1 – Novelty
Selected Document**: D3**-*X*

Feature analysis:

Means	***Invalidated features according to***
a)	Document D3 discloses a preformed article which is a ductile TMP (Transient Metastable Phase) interlayer foil for brazing (preformed article) which is formed of amorphous metal (see page 3, line 28 - page 4, line 12, especially page 4, lines 5-6).

b)	Document D3 discloses a preformed article which is a ductile TMP (Transient Metastable Phase) interlayer foil for brazing (preformed article) which is formed of amorphous metal (see page 3, line 28 - page 4, line 12, especially page 4, lines 5-6).
c)	In Document D3 it is explained that the interlayer foil is shaped e.g. by stamping, punching, bending. These shaping methods inevitably produce an irreversibly deformed, non-planar, three dimensional configuration. Punching produces perforations (see page 3, lines 16-18 and page 8, lines 5-9).
d)	In Document D3 it is explained that the interlayer foil is shaped e.g. by stamping, punching, bending. These shaping methods inevitably produce an irreversibly deformed, non-planar, three dimensional configuration. Punching produces perforations (see page 3, lines 16-18 and page 8, lines 5-9).
e)	This feature is also known from Document D3 because the interlayer foil of D3 is adapted for use in the manufacture of an assembly having brazed joints (see page 3, lines 30-35, also D1, page 4 relevant)
f)	Does not add novelty regarding manufacturing conditions of a heat exchanger without defining any relationship between the claimed preformed article and the plates, tubes and shell of the heat exchanger.
g)	*Does not add novelty regarding manufacturing conditions of a heat exchanger without defining any relationship between the claimed preformed article and the plates, tubes and shell of the heat exchanger.*

Claim M - Novelty
Selected Document**: D3** - *X*

Feature analysis:
The method of claim M concerns the manufacture of any assembly with brazed joints. It is not restricted to the manufacture of a particular heat exchanger. This kind of method is disclosed by D3 (page 1, lines 15-17), which known method includes the process steps of:

- providing an interlayer foil (preformed article having the features (a) to (d) of claim 1 which are known from D3, (as explained above) in contact with one or more elements of the assembly, (see page 8, lines 7-13) and
- partially melting said preformed article in order to produce brazed joints between elements of the assembly (see page 8, lines 18-22).

Claim N - Novelty
Selected Document: **D3** - X

Feature analysis:
Claim N is directed to a heat exchanger or other assembly having brazed joints. It is not restricted to a particular heat exchanger but embraces any assembly with brazed joints. The claimed assembly is only defined by a method which embraces or does not differ from the method as defined by claim M, which method is regarded as known from **D3** in the above paragraphs.

Claim N – Inventive Step
Selected Document: **D1** -Y, **D3**-Y

Feature analysis:
D1 describes a plate heat exchanger in which adjacent plates are brazed together by a thin foil (22) of brazing material illustrated in Figure 2C. The brazing foil has a non-planar, three-dimensional configuration to match the surfaces of the plates to be joined and is also provided with perforations at its corners to match those of the plates (see page 5, line 33-40 & page 6, lines 14-21).
When the heat exchange plates are made of stainless steel, it would be obvious to form the brazing foil from amorphous metal in view of **D3** (see page 3, line 28 - page 4, line 12, especially page 4, lines 5-6).

NOTE: this sample answer lacks some explanation on why D2, D4, D5, D6, and D7 are not selected.