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PHARMACEUTICAL AND OTHER DOSAGE FORMS

Background of the Invention

The present invention relates to methods for preparing products by removal of a solid frozen solvent from a frozen matrix mixture.

Freeze-drying, i.e., lyophilization, is a well known method of drying heat-sensitive materials in order to protect them from thermal damage. In the past, preparations containing active ingredients, such as pharmaceuticals, nutrients, diagnostics, fertilizers and insecticides, have been prepared by freeze-drying aqueous solutions or suspensions containing these bioactive ingredients. Conventional methods of freeze drying or lyophilization involve the freezing of a material at a very low temperature followed by a dehydration by sublimation under high vacuum.

One problem that has arisen, however, with the use of conventional freeze-drying processes is cracking of the freeze-dried preparations. Typically, cracking is caused by the stresses set up during ice crystallization. Though cracking is never desirable, it is especially undesirable where drop methods of freezing are employed. In such cases, cracking of the frozen droplets usually results in unusable and inelegant remnants of fractured droplets.

Another problem encountered by use of known freeze-drying methods is a phenomenon called meltback. Meltback occurs when the heat required during the drying process melts the frozen material. As such, meltback defeats the whole purpose of freeze-drying-the removal of water through sublimation as opposed to evaporation. To avoid meltback in conventional freeze-drying methods, only limited amounts of material of limited thickness can be dried at one time or, alternatively, very low temperatures have to be used, thereby considerably extending the time required for sublimation. Even with these limitations, conventional freeze-drying methods are not always sufficient to prevent meltback.

Yet another problem inherent in conventional freeze-drying methods is a lack of resistance to disintegration in freeze-dried materials, i.e., they have little strength.

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Freeze-drying methods generally yield products that merely crumble when handled. Various freeze-drying and packaging methods have been employed in attempts to circumvent this problem. For example, U.S. Patent No. 4,305,502 describes a method for forming a shaped article by a lyophilization process in a depression in a sheet of film material. However, such packaging techniques do not avoid the problems posed by conventional freeze-drying methods; the tablets are still susceptible to crumbling if transferred to other packaging.

In the area of pharmaceuticals, known freeze-dried dosage forms do not always exhibit fast dissolution rates when brought into contact with appropriate solvents, such as water, saliva or gastrointestinal fluids. Rapid dissolution of pharmaceutical dosage forms can be of critical importance in instances where it is desirable that the pharmaceutical enter the physiological system as soon as possible. For example, many individuals, particularly pediatric and geriatric patients, experience difficulty and discomfort in swallowing solid, slow dissolving tablets and capsules. Similar difficulties are encountered when administering pharmaceuticals orally to animals in the veterinary treatment of those animals.

Various methods for freeze-drying pharmaceutical dosage forms by lyophilization have been developed to provide fast dissolving dosage forms. U.S. Patents Nos. 2,166,074; 3,234,091; 4,371,516 and 4,302,502 and United Kingdom Patents No. 698,767 and 1,310,824 are all concerned with freeze-dried dosage forms that are able to dissolve rapidly. In addition, U.S. Patent No. 4,642,093 teaches a procedure for preparing a freeze-dried (lyophilized) foam dosage form using conventional lyophilization techniques that results in rapidly dissolving pharmaceutical dosage forms. Yet another problem intrinsic to conventional lyophilization methods is the lack of uniform porosity in the lyophilized product. Uniform porosity in a lyophilized product is critical for post-loading a dosage form with an active agent. Thus, there is a need for a method of producing a dosage form that will avoid cracking and meltback and having adequate strength porosity and exhibiting a fast speed of dissolution upon ingestion.

Description of the Invention

It is an object of the present invention to provide an improved solid dosage form of the type comprising a porous network of matrix material that disperses rapidly in water. The matrix material is made up from at least about 0.1% by weight of a matrix forming agent selected from the group consisting of gelatin, pectin, soy fiber protein and mixtures thereof, and one or more amino acids having from about 2 to 12 carbon atoms. The preferred amino acid is glycine, while the preferred matrix forming agent is gelatin

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and/or pectin. In a particularly preferred embodiment, the dosage form additionally comprises mannitol.

The dosage form is formed by subjecting a matrix material solution to lyophilization or solid-state dissolution. In a preferred embodiment of the present invention, the matrix material solution used to form the inventive dosage form contains from about 0.1% to about 15% matrix material by weight. Preferably, the matric material solution comprises from about 0.1% to about 3% of the matrix forming agent by weight, from about 0.5% to about 10% of the one or more amino acids by weight, and from about 0.5% to about 10% mannitol by weight.

Where lyophilization is used to form the inventive solid dosage form, any active or bioactive agent contained in the dosage form may be advantageously present in a coated form. In this embodiment, the active or bioactive agent is present in particulate form and the particles of the agent are coated with an appropriate coating agent(s) to protect the active or bioactive agent from process solvents, the aqueous environment of the oral or other mucosal cavity, or environmental conditions that would dissolve or deteriorate said active. These coating materials may be selected from natural or synthetic polymers that are either hydrophilic or hydrophobic in nature or other hydrophobic materials such a fatty acid, glycerides, triglycerides and mixtures thereof. In this way, the taste of the active or bioactive agent may be masked, while at the same time permitting the solid dosage form to dissolve rapidly upon contact with physiological solvents. Examples of active agents that may be coated in accordance with the present invention include acetaminophen, ibuprofen, chlorpheniramine maleate, pseudoephedrine and dectromethorphan.

The dosage forms of the present invention are quite robust in comparison to prior art dosage forms, especially those prepared by lyophilization. Also, the inventive dosage forms exhibit greatly reduced or no shrinkage under high temperature or humidity conditions when compared to prior art dosage forms, especially those prepared using lyophilisation. The dosage forms of the invention disperse rapidly in water, e.g. in less than 10 seconds.

The dosage forms according to the present invention can be prepared by a solid-state dissolution method of removing solid solvent from solidified samples. In this method, one or more delivery matrix forming agents (and optionally a sample to be delivered) are dissolved or dispersed in a first solvent, solidified and subsequently contacted with a second solvent at a temperature at or higher than the solidification point of the second

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solvent and at a temperature at or lower than the solidification point of the first solvent. The first solvent in the solidified state is substantially miscible with the second solvent, while the matrix forming agent(s) (and sample if present) are substantially insoluble in the second solvent. The first solvent is thereby substantially removed from the solidified matrix yielding a solid matrix (optionally containing the sample) substantially free of the first solvent.

Or, one or more matrix forming agents (and optionally a sample to be delivered) are dispersed or dissolved in a first solvent and a unit volume of the solution or dispersion is then solidified. The solidified unit volume is contacted with the second as described in the preceding paragraph. In one alternative, the processed dosage form may be contacted with a bioactive agent to yield a dosage form having a specific amount of the bioactive agent dispersed therethrough.

It is a further object of the present invention to provide a solid carrier system for chemicals that a user may add to a medium to instantaneously obtain a solution or dispersion of desired concentration. It is a further additional object of the present invention to provide dosage forms that include active ingredients, such as pharmaceuticals, nutrients, diagnostics, confectioneries, fertilizers and insecticides.

The dosage forms of the present invention are produced with minimal cracking or meltback of the processed sample. They exhibit rapid dissolution in appropriate solvents, having uniform porosity and adequate strength of handling, i.e. resistance to disintegration or crumbling under normal manufacturing and handling conditions.

The dosage forms of the present invention and in particular those containing glycine as one of the matrix components have the following advantages : quick dissolution and disintegration, pleasant taste and mouthfeel, nutritional value, low calorie content and noncariogenicity. In the realm of pharmaceutical use, the present dosage forms exhibit rapid dissolution upon contact with physiological solvents, such as water, saliva, or gastrointestinal fluids. Therefore, the present inventive pharmaceutical dosage forms provide a more rapid dispersion of the pharmaceutical within the body upon ingestion.

Pharmaceutical applications comprise dosage forms having mucoadhesive properties or designed deliver a drug at a controlled rate; dosing units designed to deliver drugs in the eye, in vaginal, rectal and other body orifices; solid dosage forms designed to replace liquid formulations; dry medicated preparations for topical application after resolvation (reconstitution); preparation of medicated units or sheets for topical application; preparation of more palatable dosage forms of drugs that exhibit disagreeable

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organoleptic properties: dosage forms for oral delivery of drugs to persons who have difficulty swallowing tablets or capsules.

Embodiments of the present invention can be used in various applications. Applications in the food industry comprise preparation of and presentation of dried products composed of food materials; to provide a method for the selective extraction of a material in the solid form during the drying process; preparation of confectionery products; preparation of dosing units for the purpose of modifying properties (e.g. taste, color etc.) or quality of drinking water. Veterinary applications comprise the preparation of dosing units for veterinary use; the preparation of aquarium care and feed products. As cosmetical applications there may be mentioned the preparation of dry systems for medical and cosmetic use after resolvation. Diagnostic applications comprise enzyme/cofactors and biochemical carrier systems. Sanitary applications are, for example, the preparation of dosing units for water purification or the preparation of fragrance carrier units for personal, household and industrial use. Other applications comprise reconstitutable carrier units for pigmented application for paint and other artistic uses; agriculture and horticulture products requiring release of active ingredients in the presence of water or rain; the preparation of easily removable mold or model material or the preparation of easily removable space maintenance and/or alignment aid for construction or manufacturing.

Though the following description focuses on the inclusion of pharmaceuticals as the active agents, it is to be understood that the desirable properties of the inventive methods and dosage forms may be advantageously used in connection with many different types of active agents.

The solid-state dissolution method for preparing delivery matrices and dosage forms begins with a mixture of at least one matrix forming agent in a first solvent. This mixture may be aqueous in nature and may contain various chemicals, drugs and adjuvants in a suitable first solvent. The resulting mixture is cooled at a controlled rate until completely solidified, and subsequently immersed into a suitable second solvent at a temperature below the melting point of the first solvent. The solidified first solvent substantially dissolves into the second solvent and produces a solid product essentially free of the first solvent as a matrix and any chemicals or drugs present in the original mixture. Residual second solvent may be evaporated subsequent to removing the matrices from the second solvent bath. Alternatively, residual second solvent may be removed by contacting the sample with one or more additional solvents having greater volatility than the second solvent.

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The various ingredients that may be incorporated into the initial mixture may include matrix forming agents and secondary components. Matrix forming agents suitable for use in the present invention include materials derived from animal or vegetable proteins, such as the gelatins, dextrins and soy, wheat and psyllium seed proteins; gums such as acacia, guar, agar, and xanthan; polysaccharides; alginates; carboxymethylcelluloses; carrageenans; dextrans; pectins; synthetic polymers such as polyvinylpyrrolidone; and polypeptide/protein or polysaccharide complexes such as gelatin-acacia complexes.

Other matrix forming agents suitable for use in the present invention include sugars such as mannitol, dextrose, lactose, and galactose; cyclic sugars such as cyclodextrin; inorganic salts such as sodium phosphate, sodium chloride and aluminum silicates; and amino acids having from 2 to 12 carbon atoms such a glycine, L-alanine, L-aspartic acid, L-glutamic acid, L-hydroxyproline, L-isoleucine, L-leucine and L-phenylalanine. Persons having skill in the art will recognize other acceptable matrix forming agents that may be employed in the present invention.

One or more matrix forming agents may be incorporated into the solution or suspension prior to solidification. The matrix forming agent may be present in addition to a surfactant or to the exclusion of a surfactant. In addition to forming the matrix, the matrix forming agent may aid in maintaining the dispersion of any active ingredient within the solution or suspension. This is especially helpful in the case of active agents that are not sufficiently soluble in water and must, therefore, be suspended rather than dissolved.

Secondary components such as preservatives, flavors, antioxidants, surfactants, sweeteners, viscosity enhancers, or colorings may also be incorporated in the formulation. Other secondary components include the active or bioactive agents to be dosed or delivered. These active agents may include pharmaceuticals, nutrients, vitamins, minerals, diagnostics, fertilizers and insecticides. Examples of pharmaceutical agents that may be incorporated in the initial mixture are chlorpheniramine maleate, pseudoephedrine, detromethorphan, meclizine dihydrochloride, haloperidol, albuterol sulfate, dimenhydrinate, and benzodiazepines such as diazepam, lorazepam and congeners thereof. However, virtually any pharmaceutical agent may be used in connection with the present invention, either by adding the pharmaceutical to the mixture to be solidified or by post loading the pharmaceutical onto a preformed placebo delivery matrix or dosage form.

The speed in which the sample prepared by the inventive method dissolves is dependent in large part on the choice of matrix forming agent(s) and their concentration. In particular, dosage forms of the size mentioned in the examples described hereinafter,

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will dissolve or disperse quite rapidly, for example, in less than about 10 seconds or even faster e.g. in less than about 5 seconds or even less, e.g. about 3 seconds. Compounds (either alone or in combination) that can be used as a matrix forming material for producing placebos or matrixes comprise hydroyethylcellulose, sodium carboxymethylcellulose, microcrystalline cellulose, corn syrup solids, maltrins (maltodextrins), polydextroses, pectins, carrageenan, agar, chitosan, locust bean gum, xanthan gum, tragacanth, guar gum, konjac flour, rice flour, wheat gluten, sodium starch glycolate, gelatin (pharmaceutical or food grade), soy fiber protein, potato protein, papain, horse radish peroxidase, glycine, mannitol, cyclodextrins (including Beta-cyclodextrin and hydroxypropyl beta-cyclodextrin), sucrose, xylitol, galactose, dextrose, polygalacturonic acid, magnesium aluminum silicate, magnesium trisilicate or natural clays.

Preferred matrix forming agents include pharmaceutical grade gelatins, pectins (nonhydrolyzed, partially hydrolyzed or hydrolyzed), glycine and mannitol, either alone or in combination.

In a further aspect of the present invention, there are provided improved solid dosage forms of the type comprising a porous network of matrix material that disperses rapidly in water, in particular in less than about ten seconds. The matrix material in these dosage forms is made up from at least about 0.1% by weight of a matrix forming agent selected from the group consisting of gelatin, pectin, soy fiber protein and mixtures thereof, and one or more amino acids having from about 2 to 12 carbon atoms. The latter amino acids comprise, for example, glycine, L-alanine, L-aspartic acid, L-glutamic acid, L-hydroxy-proline, L-isoleucine, L-leucine and L-phenylalanine.

A preferred combination of matrix forming agents is gelatin and one or more amino acids having from 2 to 12 carbon atoms, especially glycine. In these combinations, the amino acid(s) are present relative to the solvent used to form the matrix solution in a ratio of about 1:18 to about 1:180, in particular of about 1:30 to about 1:100, by weight on a wet basis. These matrix materials may further comprise sugars such as mannitol, dextrose, lactose, galactose, trehalose and cyclic sugars such as cyclodextrins or substituted cyclodextrins, in particular mannitol. A particularly preferred combination of matrix forming agent is gelatin, glycine and mannitol.

The solution or suspension of which the present dosage forms are made may further contain the secondary components mentioned before and also xanthan gum and polyacrylic acid polymers and salts thereof (also referred to as carbomers or carboxyvinyl polymers, e.g. carbopol™), which may be added e.g. to increase viscosity.

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The ratio between the materials in these combinations may vary within certain ranges. In particular the ratio of the quantity of gelatin, pectin or soy fiber protein to amino acid varies from about 10/1 to 1/5, in particular from 5/1 to 1/3 or more in particular from 3/1 to 1/1. A preferred ratio is 1.5/1. The ratio of the amount of mannitol to gelatin, pectin, soy fiber protein or mixtures thereof is in the range of 5/1 to 1/5, in particular from 2/1 to 1/2. A preferred ratio is 1.5/2.

The solution or dispersion of materials for preparing the matrix contains from 0.1 % to 15 % by weight of gelatin, pectin, soy fiber protein or mixtures thereof, in particular from 1 % to 3 % more in particular from 1.2 % to 2.5 %. It further contains from 0.1 % to 10 %, in particular from 1 % to 2.5 % by weight of amino acid and from 0.1 % to 10 %, in particular from 1 % to 3.0 % of mannitol, the remainder being solvent. The percentages mentioned in this paragraph all are by weight. Typically the weight ratio of the solvent or dispersion to the non-solvent components is in the range of about 5 to 50, in particular from about 10 to 30, for example about 20.

Various concentrations of matrix forming agents may be used in the present invention. Preferred concentrations of matrix forming agents in a suitable solvent are about 0.1 to 15% weight/weight (w/w). A more preferred concentration is about 0.5 to 4% (w/w). Optimum results are obtained from the present inventive method in pharmaceutical applications when an approximately 2% weight/weight aqueous solution of a given matrix forming agent is used.

The concentrations of secondary components incorporated in the initial mixture are limited primarily by the solubility of the secondary component(s) in the solvent used to dissolve the component. The concentration required is defined by the amount of agent to be incorporated in the dosage form. Therefore, concentrations of these components in the initial mixtures may range from about 0.0001 to 20%.

Various solvents may be employed in the present invention. A first solvent must be chosen that will dissolve and/or disperse the matrix forming agents, and other miscellaneous agents of the sample. Furthermore, the first solvent must be such that it has a solidification point higher than the solidification point of the second solvent. A preferred first solvent is water; other suitable first solvents include polyethyleneglycols, carboxypolymethylenes, tert-butyl alcohol, acetonitrile, acetamide and phenol. A first solvent may comprise a suitable combination of any of these solvents, such as, for example a water:tert-butyl alcohol solvent mixture.

The second solvent should desirably act as a solvent for the solidified first solvent. It is advantageous that the dissolution solvent also have a solidification point below the

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solidification point of the first solvent. When a substantially dry sample, placebo or dosage form is desired, it is advantageous that the second solvent have a relatively low boiling point or relatively high vapor pressure such that the second solvent evaporates quickly from the processed sample. Therefore, preferred second solvents will have boiling points or vapor pressures such that the solvent evaporates readily at atmospheric pressure or at reduced pressure. Preferred second solvents for use with water as the first solvent include materials which are water miscible. These materials may be used in the solid, liquid or gaseous state. However, those skilled in the art will appreciate that various solid sample formulations may be desired that are not dry but have substantial amounts of liquid dispersed throughout. Hence, a solvent having a relatively high boiling point such as, for example, dimethylformamide or ethylene glycol, could be employed as the second solvent.

It is advantageous that the dosage form components (matrix forming agents and secondary components) be substantially insoluble in the second solvent, i.e., the second solvent will not dissolve the sample components. Hence, depending on these components, acceptable second solvents include methanol, ethanol, acetone, water, isopropyl alcohol, methyl isobutyl ketone and liquid carbon dioxide. Various mixtures of these solvents may comprise the second solvent of the present invention. Various combinations of first solvent:second solvent may be employed in the present invention. A preferred first solvent:second solvent system for pharmaceutical purposes is water: absolute ethanol. Other systems may be chosen based on the sample components to be processed. Therefore, other suitable first solvent:second solvent systems include tert-butyl alcohol:water; acetamide: methanol; phenol:isobutyl ketone and polyethylene glycol: an alcohol, among others.

The mixtures to be solidified may be in a variety of forms. They may be solutions, suspensions, dispersions, emulsions, or foams. Persons having skill in the art will recognize acceptable methods for preparing each of these. A foam sample may be prepared by dispersing a gas in a liquid. A preferred method for preparing such a foam is described in U.S. Patent No. 4,642,903.

The mixture may be solidified by any conventional cooling process. For example, the mixture may be solidified by dispensing it into preformed molds and subsequently cooling such molds on refrigerated shelves or in refrigerated chambers. Alternatively, the molds containing the mixture may be passed through a stream of cold gas or vapor, such as liquid nitrogen in a freezing tunnel. A preferred method for solidifying the mixtures in the molds is to surround the molds in dry ice until the mixture has solidified.

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As an alternative to the use of molds, the mixtures may be solidified in dropwise fashion. For example, the mixture may be pumped or fed under gravity through an orifice in order to form drops, spheres or a spray of small particles. These drops can then be solidified by passage through a cold gas or liquid, for example, liquid nitrogen or liquid nitrogen vapor. Another possibility is that drops of the mixture may be solidified in a chilled liquid that is immiscible with the mixture. In such cases, the relative densities of the liquid and the mixture are controlled such that the drops can either pass through the chilled immiscible liquid as they solidify or, alternatively, the solidified droplets may float on the surface of the chilled immiscible liquid. This latter flotation feature facilitates the collection of the solidified droplets. An example of a liquid that may be chilled and that is immiscible with most primarily aqueous mixtures is trichloroethylene.

The resulting solidified mixture is contacted in the second solvent whereby the solidified first solvent dissolves into the second solvent. The contact time depends upon the amount of first solvent to be dissolved from the solidified mixture. This in turn is related to the size of the solidified mixture. The time required is further related to the temperature of the second solvent.

It is advantageous that the second solvent be at a temperature lower than the solidification point of the first solvent. For applications using a water:ethanol system the temperature of the second solvent may be about 0 to -100°C. A preferred temperature for this system is about -4 to -20°C.

In other systems, it is preferred that the second solvent be at a temperature of about 1 to 100°C below the solidification point of the first solvent. A more preferred temperature for the second solvent is about 4 to 20°C below the solidification point of the first solvent. At these temperatures, the amount of second solvent required to dissolve first solvent should be about 2 to 40 times the total weight of delivery matrices or dosage forms to be processed.

A preferred weight of second solvent for use at a temperature of about 10 to 20°C below the melting paint of the first solvent is about 4 to 6 times the total weight of the dosage form or matrix to be processed.

A preferred amount of ethanol for use at -4 to -20°C is about 20 times the weight of samples to be processed. For example, to process 40 1 ml matrices, about 800 g of ethanol would be used. When these preferred temperatures and weights of second

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solvent are employed, the contact times of matrix with second solvent are about 1 to 20 hours. A contact time of about 2 to 10 hours is preferred for a water:ethanol system. For large sizes, longer contact times are necessary. These preferred contact times and temperatures afford maximum strength and porosity of the processed formulation. Various methods exist for contacting the frozen dosage unit/matrix with the second solvent. These include immersing the formulation into a solvent bath and spraying the formulation with the solvent. A preferred method of contacting the solidified mixture with the second solvent is immersion.

Intimate contact of the second solvent with the dosage form can be assured by continuous or intermittent mixing of the second solvent with the sample or pumping of the second solvent through a vessel containing the sample with or without recirculation of the second solvent. Alternatively, microwave assistance may be used to facilitate dissolution of the first solvent.

Removal of the resulting processed sample or product from the second solvent yields a sample or dosage form having uniform porosity and high resistance to crumbling. The product or formulation may be immediately used, packaged, or stored.

Alternatively, any residual second solvent may be removed by placing the product in a vacuum chamber under reduced pressure, exposing a volatile second solvent to the atmosphere at normal or elevated temperatures, or passing a stream of air or nitrogen over the sample at normal or elevated temperatures with or without recirculation. Alternatively, microwave assisted drying may be used.

In another embodiment, the product may be contacted with a third solvent to remove any residual second solvent. It is advantageous that the third solvent is a solvent having greater volatility than the second solvent such that it will readily evaporate from the product. This third solvent advantageously will be substantially immiscible with the product constituents.

Formulations containing an agent such as a chemical or drug that is insoluble in the second or dissolution solvent may be prepared by directly adding the agent to the dispersion or solution to be solidified . However, active agents that are substantially soluble in the second solvent should desirably not be added to the initial mixture because some portion of this chemical or drug may be lost to the second solvent upon dissolution of the first solvent into the second solvent. Therefore, dosage forms or matrices having such chemicals or drugs may be advantageously prepared by first

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preparing a placebo or blank dosage form and subsequently contacting that dosage form with a specific amount of the active agent in a unit volume of a suitable solvent. These active agents may be loaded or dosed on the placebo as a solution, suspension, dispersion or emulsion of the agent in a carrier solvent immiscible with the placebo materials. Thus, the active agent will be substantially distributed throughout the placebo. The carrier solvent is then allowed to evaporate at normal pressure and normal or elevated temperatures, by passing a stream of air or nitrogen over the dosage form at normal or elevated temperatures, or by placing the dosage form in a vacuum chamber under reduced pressure and normal or elevated temperatures. Alternatively, microwave assisted drying may be used. Alternatively, the dosage form may be placed in a vacuum chamber to remove the residual carrier solvent.

The active agents that may be post loaded on the placebo or blank include the secondary components that may be added to the initial mixture to be processed. The concentration of these agents in the post loading solution is defined by the amount of agent desired in the final processed dosage forms. These concentrations are only limited by the solubility of the agent in the post loading solvent, although the use of serial post loading and/or suspensions can overcome most solubility limitations. Accordingly, the concentration of the active agent may range from about 0.0001% to 20% or more. The concentration of active agent in the final dosage form prepared by either method, i.e., post loading or conventional premixing, is related to the amount of active agent desired to be delivered in the processed dosage form. This concentration is limited by the solubility of the active agent in the solvent, although dosage forms may be serially processed with multiple post loadings in order to increase the concentration to a desirable level. In addition, suspensions of the agent(s) may be used to post load the placebo. Accordingly, the concentration of active agent in the final matrix or dosage form may range from less than 0.01% to more than 300% of the weight of the dosage form.

Dosage forms may be prepared in a wide variety of sizes through use of the present invention, ranging from about 0.25 ml or g to 30 ml or g and larger. Large dosage forms may be advantageously prepared by the solid state dissolution process without the long drying times required by lyophilization.

Where lyophilization is used, it is advantageous to freeze the matrix material solution in molds that are coated or lined for easy release of the frozen material. Preferred molds are made from talc filled polypyropylene with a layer of silicone/simethicone baked on the surface(s) in contact with the matrix material solution.

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The invention is illustrated further by the following examples, which are not to be construed as limiting the invention in scope or spirit to the specific procedures described in them.

Experimental part

EXAMPLE 1

Gelatin (pharmaceutical grade) (15 g), mannitol (20 g), aspartame (20 g), L-alanine (10 g) were dissolved in 935 g of water with constant stirring. The resulting solution was carefully transferred into 1 g size molds. The molds and its contents were cooled with dry ice for about one hour or frozen quickly in a cold gas freezing tunnel. The water in the ice state was removed by a suitable method (either solid state dissolution or lyophilization). This produced a sample, i.e., a network of carrier material, that disintegrated rapidly when taken orally. Each of the processed samples weighed 65 mg. This process can be repeated by replacing the alanine with L-aspartic acid, L-glutamic acid, L-hydroxyproline, L-isoleucine, L-leucine and L-phenylalanine, either alone or in combination.

EXAMPLE 2

Formula A : Pectin (20 g) was dissolved in water with heating and constant stirring. The resulting solution was autoclaved at 121°C for 15 minutes. The autoclaved solution was then allowed to attain room temperature. The autoclaved solution was then dried by a suitable method. The dry autoclaved pectin was then washed with ethanol. The ethanol washed pectin was filtered and dried by suitable method. The washed pectin powder was used in Formula B.

Formula B: The dry ethanol washed pectin (12g), pectin (5g), mannitol (20 g), aspartame (5 g) and L-alanine (20 g) were dissolved in 938 g of purified water with constant stirring. The resulting solution was processed as in Example 1. The processed sample weighed 62 mg and dissolved rapidly in water and the mouth.

EXAMPLE 3

Mannitol (20 g), L-glutamic acid (25 g), and aspartame (5 g) were dissolved in 942 g of purified water. Soy fiber protein (30 g) and xanthangum (0.5 g) were dispersed in solution. The resulting dispersion was processed as in Example 1. This produced a sample, i.e., a network of carrier material, that disintegrated rapidly in one to five seconds when taken orally. Each of the processed samples weighed 58 mg.

EXAMPLE 4

Gelatin (pharmaceutical grade) (15 g), glycine (10 g), mannitol (20 g), aspartame

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(13.3 g), glutamic acid (2 g), D&C yellow #10 (0.02 g), and FD&C red #40 (0.02 g) were dissolved in purified water (564.3 g) with heating and constant stirring. The resulting solution was then allowed to attain room temperature. To 624.6 g of this solution, 3 g of spray-dried orange, 1 g of natural and artificial prosweet, and 11 g of artificial raspberry flavors were added with constant stirring. The mixture was stirred until uniform dispersion was obtained.

The fine acetaminophen powder, consisting of the active ingredient encapsulated in a hydrophobic matrix such as fatty acid(s)/glycerides, was then suspended uniformly in the flavor mixture. The resulting suspension was transferred to 1.5 ml size molds. The molds and their contents were frozen in a cold gas freezing tunnel.

The water in the ice state was removed by lyophilization. This produced a sample, i.e., a network of carrier material that disintegrated rapidly when taken orally. Each of the processed units contained 250 mg of acetaminophen.

EXAMPLE 5

Gelatin (pharmaceutical grade) (15 g), glycine (10 g), mannitol (20 g), aspartame (13.3 g), glutamic acid (2 g), D&C yellow #10 (0.02 g), and D&C green #5 (0.02 g) were dissolved in purified water (597.9 g) with heating and constant stirring. The resulting solution was then allowed to attain room temperature. To 644.9 g of this solution, 7.5 g of honey-lemon-lyptus and 1 g of natural and artificial flavors were added with constant stirring. The mixture was stirred until uniform dispersion was obtained.

The fine ibuprofen powder, consisting of the active ingredient encapsulated in a hydrophobic matrix such as fatty acid(s)/glycerides, was then suspended uniformly in the flavor mixture. The resulting suspension was transferred to 1.5 ml size molds. The molds and their contents were frozen in a cold gas freezing tunnel.

The water in the ice state was removed by lyophilization. This produced a sample, i.e., a network of carrier material that disintegrated rapidly when taken orally. Each of the processed units contained 200 mg of ibuprofen.

EXAMPLE 6

Gelatin (pharmaceutical grade) (15 g), glycine (10 g), mannitol (20 g), aspartame (13.3 g), glutamic acid (2 g), FD&C green #3 (0.01 g), and FD&C red #40 (0.02 g) were dissolved in purified water (761.7 g) with heating and constant stirring. The resulting solution was then allowed to attain room temperature. To 822 g of this solution, 3 g of artificial grape and 1 g of natural and artificial prosweet flavors was added with constant stirring. The mixture was stirred until uniform dispersion was obtained.

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The fine phenylopropanolamine hydrochloride/chlorpheniramine maleate powder, consisting of the active ingredient encapsulated in a hydrophobic matrix such as fatty acid(s)/glycerides, was then suspended uniformly in the flavor mix.

The resulting suspension was transferred to 0.5 ml size molds. The molds and their contents were frozen in a cold gas freezing tunnel.

The water in the ice state was removed by lyophilization. This produced a sample, i.e., a network of carrier material that disintegrated rapidly when taken orally. Each of the processed units contained 25 mg of phenylpropanolamine hydrochloride and 4 mg of chlorpheniramine maleate.

EXAMPLE 7

Gelatin (pharmaceutical grade) (15 g), glycine (10 g), mannitol (20 g) aspartame (13.3 g) and glutamic acid (2 g), were dissolved in purified water (665.5 g) with heating and constant stirring. The resulting solution was then allowed to attain room temperature. To 725.8 g of this solution, 5 g of methollyptus flavor was added with constant stirring. The mixture was stirred until uniform dispersion was obtained.

The fine pseudoephedrine hydrochloride powder, consisting of the active ingredient encapsulated in a hydrophobic matrix such as fatty acid(s)/glycerides, was then suspended uniformly in the flavor mixture. The resulting suspension was transferred to 1.5 ml size molds. The molds and their contents were frozen in a cold gas freezing tunnel.

The water in the ice state was removed by lyophilization. This produced a sample, i.e., a network of carrier material that disintegrated rapidly when taken orally. Each of the processed units contained 60 mg of pseudoephedrine hydrochloride.

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CLAIMS

1. A solid dosage form comprising a porous network of matrix material that disperses rapidly in water, the matrix material comprising at least about 0.1% by weight of a matrix forming agent selected from the group consisting of gelatin, pectin, soy fiber protein and mixtures thereof and one or more amino acids having from about 2 to 12 carbon atoms.

2. A dosage form according to claim 1 wherein the amino acids are glycine, L-aspartic acid, L-glutamic acid, L-hydroxyproline, L-isoleucine, L-leucine and L-phenylalanine.

3. A dosage form according to claim 1 or 2 additionally containing a sugar selected from mannitol, dextrose, lactose, galactose, trehalose cyclodextrins, and substituted cyclodextrins.

4. A dosage form according to claim 1 comprising gelatin and wherein the amino acid is glycine and the sugar is mannitol.

5. A dosage form according to any of claims 1 to 4 wherein the dosage form is formed from a matrix material solution containing from about 0.1% to about 15% matrix material by weight of the solution.

6. A dosage form according to claim 5 wherein the matrix material solution comprises about 0.1% to about 3% of the matrix forming agent by weight.

7. A dosage form according to claim 5 wherein the matrix material solution comprises about 0.5% to about 10% of the one or more amino acids by weight and about 0.5% to about 10% mannitol by weight.

8. A dosage form according to any of claims 1 to 7 wherein the dosage form is formed by subjecting the matrix material solution to lyophilization.

9. A dosage form according to any of claims 1 to 8 wherein the dosage form is formed by subjecting the matrix material solution to solid state dissolution.

10. A dosage form according to any of claims 1 to 9 additionally comprising an active agent.

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11. A dosage form according to claim 10 wherein the dosage form without active ingredient is first prepared and subsequently loaded with a predetermined quantity of the active ingredient.

12. A dosage form according to any of claims 1 to 11 wherein the matrix material solution additionally comprises a gas dispersed therethrough to form a foam dosage form.

13. A dosage form according to any of claims 10 or 11 which additionally comprises an active agent in particulate form, particles of the active agent being coated with a coating agent.

14. A dosage form of claim 13 wherein the coating agent is a fatty acid, a glyceride, triglyceride, or a mixture thereof.

15. A dosage form according to any of claims 1 to 14 wherein the dosage form disperses in water in less than about 10 seconds.

16. A dosage form according to any of claims 1 to 15 additionally containing xanthan gum or polyacrylic acid polymers or salts thereof.

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PHARMACEUTICAL AND OTHER DOSAGE FORMS

Background of the Invention

The present invention relates to methods for preparing products by removal of a solid frozen solvent from a frozen matrix mixture.

Freeze-drying, i.e., lyophilization, is a well known method of drying heat-sensitive materials in order to protect them from thermal damage. In the past, preparations containing active ingredients, such as pharmaceuticals, nutrients, diagnostics, fertilizers and insecticides, have been prepared by freeze-drying aqueous solutions or suspensions containing these bioactive ingredients. Conventional methods of freeze drying or lyophilization involve the freezing of a material at a very low temperature followed by a dehydration by sublimation under high vacuum.

One problem that has arisen, however, with the use of conventional freeze-drying processes is cracking of the freeze-dried preparations. Typically, cracking is caused by the stresses set up during ice crystallization. Though cracking is never desirable, it is especially undesirable where drop methods of freezing are employed. In such cases, cracking of the frozen droplets usually results in unusable and inelegant remnants of fractured droplets.

Another problem encountered by use of known freeze-drying methods is a phenomenon called meltback. Meltback occurs when the heat required during the drying process melts the frozen material. As such, meltback defeats the whole purpose of freeze-drying-the removal of water through sublimation as opposed to evaporation. To avoid meltback in conventional freeze-drying methods, only limited amounts of material of limited thickness can be dried at one time or, alternatively, very low temperatures have to be used, thereby considerably extending the time required for sublimation. Even with these limitations, conventional freeze-drying methods are not always sufficient to prevent meltback.

Yet another problem inherent in conventional freeze-drying methods is a lack of resistance to disintegration in freeze-dried materials, i.e., they have little strength.

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Freeze-drying methods generally yield products that merely crumble when handled. Various freeze-drying and packaging methods have been employed in attempts to circumvent this problem. For example, U.S. Patent No. 4,305,502 describes a method for forming a shaped article by a lyophilization process in a depression in a sheet of film material. However, such packaging techniques do not avoid the problems posed by conventional freeze-drying methods; the tablets are still susceptible to crumbling if transferred to other packaging.

In the area of pharmaceuticals, known freeze-dried dosage forms do not always exhibit fast dissolution rates when brought into contact with appropriate solvents, such as water, saliva or gastrointestinal fluids. Rapid dissolution of pharmaceutical dosage forms can be of critical importance in instances where it is desirable that the pharmaceutical enter the physiological system as soon as possible. For example, many individuals, particularly pediatric and geriatric patients, experience difficulty and discomfort in swallowing solid, slow dissolving tablets and capsules. Similar difficulties are encountered when administering pharmaceuticals orally to animals in the veterinary treatment of those animals.

Various methods for freeze-drying pharmaceutical dosage forms by lyophilization have been developed to provide fast dissolving dosage forms. U.S. Patents Nos. 2,166,074; 3,234,091; 4,371,516 and 4,302,502 and United Kingdom Patents No. 698,767 and 1,310,824 are all concerned with freeze-dried dosage forms that are able to dissolve rapidly. In addition, U.S. Patent No. 4,642,093 teaches a procedure for preparing a freeze-dried (lyophilized) foam dosage form using conventional lyophilization techniques that results in rapidly dissolving pharmaceutical dosage forms. Yet another problem intrinsic to conventional lyophilization methods is the lack of uniform porosity in the lyophilized product. Uniform porosity in a lyophilized product is critical for post-loading a dosage form with an active agent. Thus, there is a need for a method of producing a dosage form that will avoid cracking and meltback and having adequate strength porosity and exhibiting a fast speed of dissolution upon ingestion.

Description of the Invention

It is an object of the present invention to provide an improved solid dosage form of the type comprising a porous network of matrix material that disperses rapidly in water. The matrix material is made up from at least about 0.1% by weight of a matrix forming agent selected from the group consisting of gelatin, pectin, soy fiber protein and mixtures thereof, and one or more amino acids having from about 2 to 12 carbon atoms. The preferred amino acid is glycine, while the preferred matrix forming agent is gelatin

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and/or pectin. In a particularly preferred embodiment, the dosage form additionally comprises mannitol.

The dosage form is formed by subjecting a matrix material solution to lyophilization or solid-state dissolution. In a preferred embodiment of the present invention, the matrix material solution used to form the inventive dosage form contains from about 0.1% to about 15% matrix material by weight. Preferably, the matric material solution comprises from about 0.1% to about 3% of the matrix forming agent by weight, from about 0.5% to about 10% of the one or more amino acids by weight, and from about 0.5% to about 10% mannitol by weight.

Where lyophilization is used to form the inventive solid dosage form, any active or bioactive agent contained in the dosage form may be advantageously present in a coated form. In this embodiment, the active or bioactive agent is present in particulate form and the particles of the agent are coated with an appropriate coating agent(s) to protect the active or bioactive agent from process solvents, the aqueous environment of the oral or other mucosal cavity, or environmental conditions that would dissolve or deteriorate said active. These coating materials may be selected from natural or synthetic polymers that are either hydrophilic or hydrophobic in nature or other hydrophobic materials such a fatty acid, glycerides, triglycerides and mixtures thereof. In this way, the taste of the active or bioactive agent may be masked, while at the same time permitting the solid dosage form to dissolve rapidly upon contact with physiological solvents. Examples of active agents that may be coated in accordance with the present invention include acetaminophen, ibuprofen, chlorpheniramine maleate, pseudoephedrine and dectromethorphan.

The dosage forms of the present invention are quite robust in comparison to prior art dosage forms, especially those prepared by lyophilization. Also, the inventive dosage forms exhibit greatly reduced or no shrinkage under high temperature or humidity conditions when compared to prior art dosage forms, especially those prepared using lyophilisation. The dosage forms of the invention disperse rapidly in water, e.g. in less than 10 seconds.

The dosage forms according to the present invention can be prepared by a solid-state dissolution method of removing solid solvent from solidified samples. In this method, one or more delivery matrix forming agents (and optionally a sample to be delivered) are dissolved or dispersed in a first solvent, solidified and subsequently contacted with a second solvent at a temperature at or higher than the solidification point of the second

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solvent and at a temperature at or lower than the solidification point of the first solvent. The first solvent in the solidified state is substantially miscible with the second solvent. while the matrix forming agent(s) (and sample if present) are substantially insoluble in the second solvent. The first solvent is thereby substantially removed from the solidified matrix yielding a solid matrix (optionally containing the sample) substantially free of the first solvent.

Or, one or more matrix forming agents (and optionally a sample to be delivered) are dispersed or dissolved in a first solvent and a unit volume of the solution or dispersion is then solidified. The solidified unit volume is contacted with the second as described in the preceding paragraph. In one alternative, the processed dosage form may be contacted with a bioactive agent to yield a dosage form having a specific amount of the bioactive agent dispersed therethrough.

It is a further object of the present invention to provide a solid carrier system for chemicals that a user may add to a medium to instantaneously obtain a solution or dispersion of desired concentration. It is a further additional object of the present invention to provide dosage forms that include active ingredients, such as pharmaceuticals, nutrients, diagnostics, confectioneries, fertilizers and insecticides.

The dosage forms of the present invention are produced with minimal cracking or meltback of the processed sample. They exhibit rapid dissolution in appropriate solvents, having uniform porosity and adequate strength of handling, i.e. resistance to disintegration or crumbling under normal manufacturing and handling conditions.

The dosage forms of the present invention and in particular those containing glycine as one of the matrix components have the following advantages : quick dissolution and disintegration, pleasant taste and mouthfeel, nutritional value, low calorie content and noncariogenicity. In the realm of pharmaceutical use, the present dosage forms exhibit rapid dissolution upon contact with physiological solvents, such as water, saliva, or gastrointestinal fluids. Therefore, the present inventive pharmaceutical dosage forms provide a more rapid dispersion of the pharmaceutical within the body upon ingestion.

Pharmaceutical applications comprise dosage forms having mucoadhesive properties or designed deliver a drug at a controlled rate; dosing units designed to deliver drugs in the eye, in vaginal, rectal and other body orifices; solid dosage forms designed to replace liquid formulations; dry medicated preparations for topical application after resolvation (reconstitution); preparation of medicated units or sheets for topical application; preparation of more palatable dosage forms of drugs that exhibit disagreeable

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organoleptic properties: dosage forms for oral delivery of drugs to persons who have difficulty swallowing tablets or capsules.

Embodiments of the present invention can be used in various applications. Applications in the food industry comprise preparation of and presentation of dried products composed of food materials; to provide a method for the selective extraction of a material in the solid form during the drying process; preparation of confectionery products; preparation of dosing units for the purpose of modifying properties (e.g. taste, color etc.) or quality of drinking water. Veterinary applications comprise the preparation of dosing units for veterinary use; the preparation of aquarium care and feed products. As cosmetical applications there may be mentioned the preparation of dry systems for medical and cosmetic use after resolvation. Diagnostic applications comprise enzyme/cofactors and biochemical carrier systems. Sanitary applications are, for example, the preparation of dosing units for water purification or the preparation of fragrance carrier units for personal, household and industrial use. Other applications comprise reconstitutable carrier units for pigmented application for paint and other artistic uses; agriculture and horticulture products requiring release of active ingredients in the presence of water or rain; the preparation of easily removable mold or model material or the preparation of easily removable space maintenance and/or alignment aid for construction or manufacturing.

Though the following description focuses on the inclusion of pharmaceuticals as the active agents, it is to be understood that the desirable properties of the inventive methods and dosage forms may be advantageously used in connection with many different types of active agents.

The solid-state dissolution method for preparing delivery matrices and dosage forms begins with a mixture of at least one matrix forming agent in a first solvent. This mixture may be aqueous in nature and may contain various chemicals, drugs and adjuvants in a suitable first solvent. The resulting mixture is cooled at a controlled rate until completely solidified, and subsequently immersed into a suitable second solvent at a temperature below the melting point of the first solvent. The solidified first solvent substantially dissolves into the second solvent and produces a solid product essentially free of the first solvent as a matrix and any chemicals or drugs present in the original mixture. Residual second solvent may be evaporated subsequent to removing the matrices from the second solvent bath. Alternatively, residual second solvent may be removed by contacting the sample with one or more additional solvents having greater volatility than the second solvent.

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The various ingredients that may be incorporated into the initial mixture may include matrix forming agents and secondary components. Matrix forming agents suitable for use in the present invention include materials derived from animal or vegetable proteins, such as the gelatins, dextrins and soy, wheat and psyllium seed proteins; gums such as acacia, guar, agar, and xanthan; polysaccharides; alginates; carboxymethylcelluloses; carrageenans; dextrans; pectins; synthetic polymers such as polyvinylpyrrolidone; and polypeptide/protein or polysaccharide complexes such as gelatin-acacia complexes.

Other matrix forming agents suitable for use in the present invention include sugars such as mannitol, dextrose, lactose, and galactose; cyclic sugars such as cyclodextrin; inorganic salts such as sodium phosphate, sodium chloride and aluminum silicates; and amino acids having from 2 to 12 carbon atoms such a glycine, L-alanine, L-aspartic acid, L-glutamic acid, L-hydroxyproline, L-isoleucine, L-leucine and L-phenylalanine. Persons having skill in the art will recognize other acceptable matrix forming agents that may be employed in the present invention.

One or more matrix forming agents may be incorporated into the solution or suspension prior to solidification. The matrix forming agent may be present in addition to a surfactant or to the exclusion of a surfactant. In addition to forming the matrix, the matrix forming agent may aid in maintaining the dispersion of any active ingredient within the solution or suspension. This is especially helpful in the case of active agents that are not sufficiently soluble in water and must, therefore, be suspended rather than dissolved.

Secondary components such as preservatives, flavors, antioxidants, surfactants, sweeteners, viscosity enhancers, or colorings may also be incorporated in the formulation. Other secondary components include the active or bioactive agents to be dosed or delivered. These active agents may include pharmaceuticals, nutrients, vitamins, minerals, diagnostics, fertilizers and insecticides. Examples of pharmaceutical agents that may be incorporated in the initial mixture are chlorpheniramine maleate, pseudoephedrine, detromethorphan, meclizine dihydrochloride, haloperidol, albuterol sulfate, dimenhydrinate, and benzodiazepines such as diazepam, lorazepam and congeners thereof. However, virtually any pharmaceutical agent may be used in connection with the present invention, either by adding the pharmaceutical to the mixture to be solidified or by post loading the pharmaceutical onto a preformed placebo delivery matrix or dosage form.

The speed in which the sample prepared by the inventive method dissolves is dependent in large part on the choice of matrix forming agent(s) and their concentration. In particular, dosage forms of the size mentioned in the examples described hereinafter,

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will dissolve or disperse quite rapidly, for example, in less than about 10 seconds or even faster e.g. in less than about 5 seconds or even less, e.g. about 3 seconds. Compounds (either alone or in combination) that can be used as a matrix forming material for producing placebos or matrixes comprise hydroyethylcellulose, sodium carboxymethylcellulose, microcrystalline cellulose, corn syrup solids, maltrins (maltodextrins), polydextroses, pectins, carrageenan, agar, chitosan, locust bean gum, xanthan gum, tragacanth, guar gum, konjac flour, rice flour, wheat gluten, sodium starch glycolate, gelatin (pharmaceutical or food grade), soy fiber protein, potato protein, papain, horse radish peroxidase, glycine, mannitol, cyclodextrins (including Beta-cyclodextrin and hydroxypropyl beta-cyclodextrin), sucrose, xylitol, galactose, dextrose, polygalacturonic acid, magnesium aluminum silicate, magnesium trisilicate or natural clays.

Preferred matrix forming agents include pharmaceutical grade gelatins, pectins (nonhydrolyzed, partially hydrolyzed or hydrolyzed), glycine and mannitol, either alone or in combination.

In a further aspect of the present invention, there are provided improved solid dosage forms of the type comprising a porous network of matrix material that disperses rapidly in water, in particular in less than about ten seconds. The matrix material in these dosage forms is made up from at least about 0.1% by weight of a matrix forming agent selected from the group consisting of gelatin, pectin, soy fiber protein and mixtures thereof, and one or more amino acids having from about 2 to 12 carbon atoms. The latter amino acids comprise, for example, glycine, L-alanine, L-aspartic acid, L-glutamic acid, L-hydroxy-proline, L-isoleucine, L-leucine and L-phenylalanine.

A preferred combination of matrix forming agents is gelatin and one or more amino acids having from 2 to 12 carbon atoms, especially glycine. In these combinations, the amino acid(s) are present relative to the solvent used to form the matrix solution in a ratio of about 1:18 to about 1:180, in particular of about 1:30 to about 1:100, by weight on a wet basis. These matrix materials may further comprise sugars such as mannitol, dextrose, lactose, galactose, trehalose and cyclic sugars such as cyclodextrins or substituted cyclodextrins, in particular mannitol. A particularly preferred combination of matrix forming agent is gelatin, glycine and mannitol.

The solution or suspension of which the present dosage forms are made may further contain the secondary components mentioned before and also xanthan gum and polyacrylic acid polymers and salts thereof (also referred to as carbomers or carboxyvinyl polymers, e.g. carbopol™), which may be added e.g. to increase viscosity.

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The ratio between the materials in these combinations may vary within certain ranges. In particular the ratio of the quantity of gelatin, pectin or soy fiber protein to amino acid varies from about 10/1 to 1/5, in particular from 5/1 to 1/3 or more in particular from 3/1 to 1/1. A preferred ratio is 1.5/1. The ratio of the amount of mannitol to gelatin, pectin, soy fiber protein or mixtures thereof is in the range of 5/1 to 1/5, in particular from 2/1 to 1/2. A preferred ratio is 1.5/2.

The solution or dispersion of materials for preparing the matrix contains from 0.1 % to 15 % by weight of gelatin, pectin, soy fiber protein or mixtures thereof, in particular from 1 % to 3 % more in particular from 1.2 % to 2.5 %. It further contains from 0.1 % to 10 %, in particular from 1 % to 2.5 % by weight of amino acid and from 0.1 % to 10 %, in particular from 1 % to 3.0 % of mannitol, the remainder being solvent. The percentages mentioned in this paragraph all are by weight. Typically the weight ratio of the solvent or dispersion to the non-solvent components is in the range of about 5 to 50, in particular from about 10 to 30, for example about 20.

Various concentrations of matrix forming agents may be used in the present invention. Preferred concentrations of matrix forming agents in a suitable solvent are about 0.1 to 15% weight/weight (w/w). A more preferred concentration is about 0.5 to 4% (w/w). Optimum results are obtained from the present inventive method in pharmaceutical applications when an approximately 2% weight/weight aqueous solution of a given matrix forming agent is used.

The concentrations of secondary components incorporated in the initial mixture are limited primarily by the solubility of the secondary component(s) in the solvent used to dissolve the component. The concentration required is defined by the amount of agent to be incorporated in the dosage form. Therefore, concentrations of these components in the initial mixtures may range from about 0.0001 to 20%.

Various solvents may be employed in the present invention. A first solvent must be chosen that will dissolve and/or disperse the matrix forming agents, and other miscellaneous agents of the sample. Furthermore, the first solvent must be such that it has a solidification point higher than the solidification point of the second solvent. A preferred first solvent is water; other suitable first solvents include polyethyleneglycols, carboxypolymethylenes, tert-butyl alcohol, acetonitrile, acetamide and phenol. A first solvent may comprise a suitable combination of any of these solvents, such as, for example a water:tert-butyl alcohol solvent mixture.

The second solvent should desirably act as a solvent for the solidified first solvent. It is advantageous that the dissolution solvent also have a solidification point below the

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solidification point of the first solvent. When a substantially dry sample, placebo or dosage form is desired, it is advantageous that the second solvent have a relatively low boiling point or relatively high vapor pressure such that the second solvent evaporates quickly from the processed sample. Therefore, preferred second solvents will have boiling points or vapor pressures such that the solvent evaporates readily at atmospheric pressure or at reduced pressure. Preferred second solvents for use with water as the first solvent include materials which are water miscible. These materials may be used in the solid, liquid or gaseous state. However, those skilled in the art will appreciate that various solid sample formulations may be desired that are not dry but have substantial amounts of liquid dispersed throughout. Hence, a solvent having a relatively high boiling point such as, for example, dimethylformamide or ethylene glycol, could be employed as the second solvent.

It is advantageous that the dosage form components (matrix forming agents and secondary components) be substantially insoluble in the second solvent, i.e., the second solvent will not dissolve the sample components. Hence, depending on these components, acceptable second solvents include methanol, ethanol, acetone, water, isopropyl alcohol, methyl isobutyl ketone and liquid carbon dioxide. Various mixtures of these solvents may comprise the second solvent of the present invention. Various combinations of first solvent:second solvent may be employed in the present invention. A preferred first solvent:second solvent system for pharmaceutical purposes is water: absolute ethanol. Other systems may be chosen based on the sample components to be processed. Therefore, other suitable first solvent:second solvent systems include tert-butyl alcohol:water; acetamide: methanol; phenol:isobutyl ketone and polyethylene glycol: an alcohol, among others.

The mixtures to be solidified may be in a variety of forms. They may be solutions, suspensions, dispersions, emulsions, or foams. Persons having skill in the art will recognize acceptable methods for preparing each of these. A foam sample may be prepared by dispersing a gas in a liquid. A preferred method for preparing such a foam is described in U.S. Patent No. 4,642,903.

The mixture may be solidified by any conventional cooling process. For example, the mixture may be solidified by dispensing it into preformed molds and subsequently cooling such molds on refrigerated shelves or in refrigerated chambers. Alternatively, the molds containing the mixture may be passed through a stream of cold gas or vapor, such as liquid nitrogen in a freezing tunnel. A preferred method for solidifying the mixtures in the molds is to surround the molds in dry ice until the mixture has solidified.

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As an alternative to the use of molds, the mixtures may be solidified in dropwise fashion. For example, the mixture may be pumped or fed under gravity through an orifice in order to form drops, spheres or a spray of small particles. These drops can then be solidified by passage through a cold gas or liquid, for example, liquid nitrogen or liquid nitrogen vapor. Another possibility is that drops of the mixture may be solidified in a chilled liquid that is immiscible with the mixture. In such cases, the relative densities of the liquid and the mixture are controlled such that the drops can either pass through the chilled immiscible liquid as they solidify or, alternatively, the solidified droplets may float on the surface of the chilled immiscible liquid. This latter flotation feature facilitates the collection of the solidified droplets. An example of a liquid that may be chilled and that is immiscible with most primarily aqueous mixtures is trichloroethylene.

The resulting solidified mixture is contacted in the second solvent whereby the solidified first solvent dissolves into the second solvent. The contact time depends upon the amount of first solvent to be dissolved from the solidified mixture. This in turn is related to the size of the solidified mixture. The time required is further related to the temperature of the second solvent.

It is advantageous that the second solvent be at a temperature lower than the solidification point of the first solvent. For applications using a water:ethanol system the temperature of the second solvent may be about 0 to -100°C. A preferred temperature for this system is about -4 to -20°C.

In other systems, it is preferred that the second solvent be at a temperature of about 1 to 100°C below the solidification point of the first solvent. A more preferred temperature for the second solvent is about 4 to 20°C below the solidification point of the first solvent. At these temperatures, the amount of second solvent required to dissolve first solvent should be about 2 to 40 times the total weight of delivery matrices or dosage forms to be processed.

A preferred weight of second solvent for use at a temperature of about 10 to 20°C below the melting paint of the first solvent is about 4 to 6 times the total weight of the dosage form or matrix to be processed.

A preferred amount of ethanol for use at -4 to -20°C is about 20 times the weight of samples to be processed. For example, to process 40 1 ml matrices, about 800 g of ethanol would be used. When these preferred temperatures and weights of second

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solvent are employed, the contact times of matrix with second solvent are about 1 to 20 hours. A contact time of about 2 to 10 hours is preferred for a water:ethanol system. For large sizes, longer contact times are necessary. These preferred contact times and temperatures afford maximum strength and porosity of the processed formulation. Various methods exist for contacting the frozen dosage unit/matrix with the second solvent. These include immersing the formulation into a solvent bath and spraying the formulation with the solvent. A preferred method of contacting the solidified mixture with the second solvent is immersion.

Intimate contact of the second solvent with the dosage form can be assured by continuous or intermittent mixing of the second solvent with the sample or pumping of the second solvent through a vessel containing the sample with or without recirculation of the second solvent. Alternatively, microwave assistance may be used to facilitate dissolution of the first solvent.

Removal of the resulting processed sample or product from the second solvent yields a sample or dosage form having uniform porosity and high resistance to crumbling. The product or formulation may be immediately used, packaged, or stored.

Alternatively, any residual second solvent may be removed by placing the product in a vacuum chamber under reduced pressure, exposing a volatile second solvent to the atmosphere at normal or elevated temperatures, or passing a stream of air or nitrogen over the sample at normal or elevated temperatures with or without recirculation. Alternatively, microwave assisted drying may be used.

In another embodiment, the product may be contacted with a third solvent to remove any residual second solvent. It is advantageous that the third solvent is a solvent having greater volatility than the second solvent such that it will readily evaporate from the product. This third solvent advantageously will be substantially immiscible with the product constituents.

Formulations containing an agent such as a chemical or drug that is insoluble in the second or dissolution solvent may be prepared by directly adding the agent to the dispersion or solution to be solidified . However, active agents that are substantially soluble in the second solvent should desirably not be added to the initial mixture because some portion of this chemical or drug may be lost to the second solvent upon dissolution of the first solvent into the second solvent. Therefore, dosage forms or matrices having such chemicals or drugs may be advantageously prepared by first

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preparing a placebo or blank dosage form and subsequently contacting that dosage form with a specific amount of the active agent in a unit volume of a suitable solvent. These active agents may be loaded or dosed on the placebo as a solution, suspension, dispersion or emulsion of the agent in a carrier solvent immiscible with the placebo materials. Thus, the active agent will be substantially distributed throughout the placebo. The carrier solvent is then allowed to evaporate at normal pressure and normal or elevated temperatures, by passing a stream of air or nitrogen over the dosage form at normal or elevated temperatures, or by placing the dosage form in a vacuum chamber under reduced pressure and normal or elevated temperatures. Alternatively, microwave assisted drying may be used. Alternatively, the dosage form may be placed in a vacuum chamber to remove the residual carrier solvent.

The active agents that may be post loaded on the placebo or blank include the secondary components that may be added to the initial mixture to be processed. The concentration of these agents in the post loading solution is defined by the amount of agent desired in the final processed dosage forms. These concentrations are only limited by the solubility of the agent in the post loading solvent, although the use of serial post loading and/or suspensions can overcome most solubility limitations. Accordingly, the concentration of the active agent may range from about 0.0001% to 20% or more. The concentration of active agent in the final dosage form prepared by either method, i.e., post loading or conventional premixing, is related to the amount of active agent desired to be delivered in the processed dosage form. This concentration is limited by the solubility of the active agent in the solvent, although dosage forms may be serially processed with multiple post loadings in order to increase the concentration to a desirable level. In addition, suspensions of the agent(s) may be used to post load the placebo. Accordingly, the concentration of active agent in the final matrix or dosage form may range from less than 0.01% to more than 300% of the weight of the dosage form.

Dosage forms may be prepared in a wide variety of sizes through use of the present invention, ranging from about 0.25 ml or g to 30 ml or g and larger. Large dosage forms may be advantageously prepared by the solid state dissolution process without the long drying times required by lyophilization.

Where lyophilization is used, it is advantageous to freeze the matrix material solution in molds that are coated or lined for easy release of the frozen material. Preferred molds are made from talc filled polypyropylene with a layer of silicone/simethicone baked on the surface(s) in contact with the matrix material solution.

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The invention is illustrated further by the following examples, which are not to be construed as limiting the invention in scope or spirit to the specific procedures described in them.

Experimental part

EXAMPLE 1

Gelatin (pharmaceutical grade) (15 g), mannitol (20 g), aspartame (20 g), L-alanine (10 g) were dissolved in 935 g of water with constant stirring. The resulting solution was carefully transferred into 1 g size molds. The molds and its contents were cooled with dry ice for about one hour or frozen quickly in a cold gas freezing tunnel. The water in the ice state was removed by a suitable method (either solid state dissolution or lyophilization). This produced a sample, i.e., a network of carrier material, that disintegrated rapidly when taken orally. Each of the processed samples weighed 65 mg. This process can be repeated by replacing the alanine with L-aspartic acid, L-glutamic acid, L-hydroxyproline, L-isoleucine, L-leucine and L-phenylalanine, either alone or in combination.

EXAMPLE 2

Formula A : Pectin (20 g) was dissolved in water with heating and constant stirring. The resulting solution was autoclaved at 121°C for 15 minutes. The autoclaved solution was then allowed to attain room temperature. The autoclaved solution was then dried by a suitable method. The dry autoclaved pectin was then washed with ethanol. The ethanol washed pectin was filtered and dried by suitable method. The washed pectin powder was used in Formula B.

Formula B: The dry ethanol washed pectin (12g), pectin (5g), mannitol (20 g), aspartame (5 g) and L-alanine (20 g) were dissolved in 938 g of purified water with constant stirring. The resulting solution was processed as in Example 1. The processed sample weighed 62 mg and dissolved rapidly in water and the mouth.

EXAMPLE 3

Mannitol (20 g), L-glutamic acid (25 g), and aspartame (5 g) were dissolved in 942 g of purified water. Soy fiber protein (30 g) and xanthangum (0.5 g) were dispersed in solution. The resulting dispersion was processed as in Example 1. This produced a sample, i.e., a network of carrier material, that disintegrated rapidly in one to five seconds when taken orally. Each of the processed samples weighed 58 mg.

EXAMPLE 4

Gelatin (pharmaceutical grade) (15 g), glycine (10 g), mannitol (20 g), aspartame

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(13.3 g), glutamic acid (2 g), D&C yellow #10 (0.02 g), and FD&C red #40 (0.02 g) were dissolved in purified water (564.3 g) with heating and constant stirring. The resulting solution was then allowed to attain room temperature. To 624.6 g of this solution. 3 g of spray-dried orange, 1 g of natural and artificial prosweet. and 11 g of artificial raspberry flavors were added with constant stirring. The mixture was stirred until uniform dispersion was obtained.

The fine acetaminophen powder, consisting of the active ingredient encapsulated in a hydrophobic matrix such as fatty acid(s)/glycerides. was then suspended uniformly in the flavor mixture. The resulting suspension was transferred to 1.5 ml size molds. The molds and their contents were frozen in a cold gas freezing tunnel.

The water in the ice state was removed by lyophilization. This produced a sample. i.e.. a network of carrier material that disintegrated rapidly when taken orally. Each of the processed units contained 250 mg of acetaminophen.

EXAMPLE 5

Gelatin (pharmaceutical grade) (15 g), glycine (10 g), mannitol (20 g), aspartame (13.3 g), glutamic acid (2 g), D&C yellow #10 (0.02 g), and D&C green #5 (0.02 g) were dissolved in purified water (597.9 g) with heating and constant stirring. The resulting solution was then allowed to attain room temperature. To 644.9 g of this solution. 7.5 g of honey-lemon-lyptus and 1 g of natural and artificial flavors were added with constant stirring. The mixture was stirred until uniform dispersion was obtained.

The fine ibuprofen powder, consisting of the active ingredient encapsulated in a hydrophobic matrix such as fatty acid(s)/glycerides, was then suspended uniformly in the flavor mixture. The resulting suspension was transferred to 1.5 ml size molds. The molds and their contents were frozen in a cold gas freezing tunnel.

The water in the ice state was removed by lyophilization. This produced a sample. i.e.. a network of carrier material that disintegrated rapidly when taken orally. Each of the processed units contained 200 mg of ibuprofen.

EXAMPLE 6

Gelatin (pharmaceutical grade) (15 g), glycine (10 g), mannitol (20 g), aspartame (13.3 g), glutamic acid (2 g), FD&C green #3 (0.01 g), and FD&C red #40 (0.02 g) were dissolved in purified water (761.7 g) with heating and constant stirring. The resulting solution was then allowed to attain room temperature. To 822 g of this solution, 3 g of artificial grape and 1 g of natural and artificial prosweet flavors was added with constant stirring. The mixture was stirred until uniform dispersion was obtained.

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The fine phenylopropanolamine hydrochloride/chlorpheniramine maleate powder, consisting of the active ingredient encapsulated in a hydrophobic matrix such as fatty acid(s)/glycerides, was then suspended uniformly in the flavor mix.
The resulting suspension was transferred to 0.5 ml size molds. The molds and their contents were frozen in a cold gas freezing tunnel.
The water in the ice state was removed by lyophilization. This produced a sample, i.e., a network of carrier material that disintegrated rapidly when taken orally. Each of the processed units contained 25 mg of phenylpropanolamine hydrochloride and 4 mg of chlorpheniramine maleate.

EXAMPLE 7

Gelatin (pharmaceutical grade) (15 g), glycine (10 g), mannitol (20 g) aspartame (13.3 g) and glutamic acid (2 g), were dissolved in purified water (665.5 g) with heating and constant stirring. The resulting solution was then allowed to attain room temperature. To 725.8 g of this solution, 5 g of methollyptus flavor was added with constant stirring. The mixture was stirred until uniform dispersion was obtained.
The fine pseudoephedrine hydrochloride powder, consisting of the active ingredient encapsulated in a hydrophobic matrix such as fatty acid(s)/glycerides, was then suspended uniformly in the flavor mixture. The resulting suspension was transferred to 1.5 ml size molds. The molds and their contents were frozen in a cold gas freezing tunnel.
The water in the ice state was removed by lyophilization. This produced a sample, i.e., a network of carrier material that disintegrated rapidly when taken orally. Each of the processed units contained 60 mg of pseudoephedrine hydrochloride.

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CLAIMS

1. A solid dosage form comprising a porous network of matrix material that disperses rapidly in water, the matrix material comprising at least about 0.1% by weight of a matrix forming agent selected from the group consisting of gelatin, pectin, soy fiber protein and mixtures thereof and one or more amino acids having from about 2 to 12 carbon atoms.

2. A dosage form according to claim 1 wherein the amino acids are glycine, L-aspartic acid, L-glutamic acid, L-hydroxyproline, L-isoleucine, L-leucine and L-phenylalanine.

3. A dosage form according to claim 1 or 2 additionally containing a sugar selected from mannitol, dextrose, lactose, galactose, trehalose cyclodextrins, and substituted cyclodextrins.

4. A dosage form according to claim 1 comprising gelatin and wherein the amino acid is glycine and the sugar is mannitol.

5. A dosage form according to any of claims 1 to 4 wherein the dosage form is formed from a matrix material solution containing from about 0.1% to about 15% matrix material by weight of the solution.

6. A dosage form according to claim 5 wherein the matrix material solution comprises about 0.1% to about 3% of the matrix forming agent by weight.

7. A dosage form according to claim 5 wherein the matrix material solution comprises about 0.5% to about 10% of the one or more amino acids by weight and about 0.5% to about 10% mannitol by weight.

8. A dosage form according to any of claims 1 to 7 wherein the dosage form is formed by subjecting the matrix material solution to lyophilization.

9. A dosage form according to any of claims 1 to 8 wherein the dosage form is formed by subjecting the matrix material solution to solid state dissolution.

10. A dosage form according to any of claims 1 to 9 additionally comprising an active agent.

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11. A dosage form according to claim 10 wherein the dosage form without active ingredient is first prepared and subsequently loaded with a predetermined quantity of the active ingredient.

12. A dosage form according to any of claims 1 to 11 wherein the matrix material solution additionally comprises a gas dispersed therethrough to form a foam dosage form.

13. A dosage form according to any of claims 10 or 11 which additionally comprises an active agent in particulate form, particles of the active agent being coated with a coating agent.

14. A dosage form of claim 13 wherein the coating agent is a fatty acid, a glyceride, triglyceride, or a mixture thereof.

15. A dosage form according to any of claims 1 to 14 wherein the dosage form disperses in water in less than about 10 seconds.

16. A dosage form according to any of claims 1 to 15 additionally containing xanthan gum or polyacrylic acid polymers or salts thereof.

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ABSTRACT

PHARMACEUTICAL AND OTHER DOSAGE FORMS

A fast dissolving, solid dosage form defined by a matrix containing gelatin, pectin and/or soy fiber protein and one or more amino acids having from about 2 to 12 carbon atoms.

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CLAIMS

1. A solid lyophilised dosage form comprising a porous network of matrix material that disperses rapidly in water, the matrix material comprising at least about 0.1% by weight of a matrix forming agent selected from the group consisting of gelatin, pectin, soy fiber protein and mixtures thereof and one or more amino acids having from about 2 to 12 carbon atoms, said matrix forming agent and said one or more amino acids being present in said dosage form in a weight ratio of from 10:1 to 1:5.

2. A dosage form according to claim 1 wherein the amino acids are selected from glycine, L-aspartic acid, L-glutamic acid, L-hydroxyproline, L-isoleucine, L-leucine and L-phenylalanine.

3. A dosage form according to either of claims 1 and 2 additionally containing a sugar selected from mannitol, dextrose, lactose, galactose, trehalose, cyclodextrins, and substituted cyclodextrins.

4. A dosage form according to claim 3 comprising gelatin and wherein the amino acid is glycine and the sugar is mannitol.

5. A dosage form according to any of claims 1 to 4 additionally comprising an active agent.

6. A dosage form according to claim 5 which additionally comprises an active agent in particulate form, particles of the active agent being coated with a coating agent.

7. A dosage form according to claim 6 wherein the coating agent is a fatty acid, a glyceride, triglyceride or a mixture thereof.

8. A dosage form according to any claims 1 to 7 wherein the dosage form disperses in water in less than about 10 seconds.

9. A dosage form according to any of claims 1 to 8 additionally containing xanthan gum or polyacrylic acid polymers or salts thereof.

10. A method of producing a solid lyophilised dosage form comprising a porous network of matrix material that disperses

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rapidly in water, which method comprises obtaining a matrix material solution containing a matrix forming material, and subjecting said solution to lyophilisation, said matrix material comprising at least about 0.1% by weight of a matrix forming agent selected from the group consisting of gelatin, pectin, soy fiber protein and mixtures thereof and one or more amino acids having from about 2 to 12 carbon atoms, and said matrix forming agent and said one or more amino acids being present in said matrix material solution in a weight ratio of from 10:1 to 1:5.

11. A method as claimed in claim **10** wherein said matrix material solution comprises about 0.1% to about 15% matrix material relative to the weight of the solution.

12. A method as claimed in claim **11** wherein said matrix material solution comprises about 0.1% to about 3% of said matrix forming agent by weight.

13. A method as claimed in claim **11** wherein said matrix material solution comprises about 0.5% to about 10% of said one or more amino acids by weight and about 0.5% to about 10% mannitol by weight.

14 A method according to any of claims **10** to **13** wherein the dosage form without active ingredient is first prepared and subsequently loaded with a predetermined quantity of the active ingredient.

15. A method according to any of claims **10** to **14** wherein the matrix material solution additionally comprises a gas dispersed therethrough to form a foam dosage form.

16. The dosage form or method according to any preceding claim wherein said weight ratio of matrix forming agent to said one or more amino acids is from 3:1 to 1:1.

17. The dosage form or method according to claim **16** wherein said weight ratio is from 1.5:1 to 1:1.

18. The dosage form or method according to any one of claims **1** to **15** wherein said weight ratio of matrix forming agent to said one or more amino acids is from 1.5:1 to 1:5.

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