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(57) Abstract

A method of making a soluble solid delivery system form comprising the steps of: (a) combining, in substantially dry form, components comprising a diluent, an amount of binder sufficient to increse the hardness of the components and/or the dosage form to an acceptable level; an amount of an active agent such that the dosage form contains an effective amount of active agent, and an amount of volatile salt effective to decrease the weight and increase the surface area of the dosage form formed when removed; (b) processing the product of step (a) to form a substantially homogeneous mixture; (c) forming a delivery system from the powder of step (b); and (d) volatilizing the volatile salt or a component thereof from the delivery system.

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PROCESS TO PREPARE SOLUBLE DELIVERY SYSTEMS USING VOLATILE SALTS

This invention relates to soluble delivery systems including dosage forms and other formulations particularly but not exclusively of active agents such as pharmaceuticals, veterinary products and agrochemicals. Delivery systems in accordance with this invention may comprise tablets, capsules, lozenges, granules, matrices, microspheres and the like. This invention also relates to methods of making these delivery systems.

Drugs and other active agents are most frequently administered orally by means of solid dosage forms. Large scale production methods used in their preparation usually require that these dosage forms contain other additives in addition to the active ingredients. These additives, generally known as excipients, may be included in the formulations to facilitate handling, to enhance the physical appearance, improve the stability and enhance the release or availability for absorption of the active agent or agents. The additives, ie excipients may include diluents, disintegrants, binders and lubricants.

Tablets are solid dosage forms which contain drugs or other active substances with or without suitable diluents. Soluble tablets which dissolve or disperse rapidly are preferred.

Tablets are usually prepared by compression, extrusion, freeze drying or molding. Tablets provide advantages both to the manufacturer (e.g., simplicity and economy of preparation, stability and convenience in packaging, shipping and dispensing) and the patient (e.g., accuracy of dosage, compactness, portability, blandness of taste and ease of administration). Tablets are one of the most common form of solid dose drug delivery. For review see, Pogany et al. (1988) Acta Pharm. Hung. 58:49- 58:49-55; Doelker et al. (1988) Boll. Chim. Farm. 127:37-49; Hiestand et al. (1977) J. Pharm. Sci. 66:510-519; and Cooper et al. (1972) J. Pharm. Sci. 61:1511-1555.

Compressed tablets are usually prepared by large-scale production methods, while molded tablets generally involve smaller scale operations. Compressed tablets usually contain no special coating and are made from a small number of powdered, crystalline or excipients made by a granulation procedure alone or in combination with disintegrants, controlled-release polymers, waxes, lubricants, diluents and, in many cases, colorants.

Compressed tablets may be coated with a variety of substances for a variety of purposes including the alteration of their physical characteristics and modification of the rate and extent of release of active ingredients. A sugar coating may be applied. Such coatings are beneficial in masking drugs possessing objectionable tastes or odours and in protecting materials sensitive to humidity, light or oxidation. Tablets may also be covered with a thin layer or film of water soluble or insoluble material. Enteric coated tablets are coated with substances that resist dissolution in gastric fluid but disintegrate in the intestine. Polymeric and other coating materials may be used to modify release. Multiple compressed tablets are made by more than one compression cycle. These include inlay tablets, layered tablets and press-coated tablets. Compressed tablets can be formulated into controlled-release tablets which release drug over a prolonged period of time. Typically, these tablets to provide pulsatile or sustained release.

Compressed tablets can also be formed into dosage forms for purposes other than direct oral delivery. These include, but are not limited to, disintegration into solution, effervescent, chewable or dispersible tablets, compressed suppositories, pessaries or inserts, and buccal and sublingual tablets.

A number of diluents are used in tableting to increase the bulk of the tablet to a practical size for compression. Diluents commonly used include dicalcium phosphate dihydrate, tricalcium phosphate, calcium sulfate, lactose, spray-dried lactose, pregelatinized starch, microcrystalline cellulose,

cellulose, kaolin, mannitol, sodium chloride, dry starch and powdered sugar. Certain diluents, particularly mannitol, trehalose, lactose, sorbitol, sucrose and inositol, are used to make chewable tablets. Microcrystalline cellulose is a nonfibrous form of cellulose obtained by spray-drying washed, acid-treated cellulose and is available in several grades that range in average particle size from 20-100μm.

Certain drawbacks are inherent in the use of any diluent and they must be chosen based on the intended use and reactivity with the drug. Lactose is widely used. However the combination of amine bases or amine salts with lactose in the presence of an alkaline lubricant results in losses in the bioavailability of the active agent and tablets that discolour on aging.

Hydrous lactose does not have properties that permit it to flow and use is limited to tablet formulations prepared by the wet granulation method. Both anhydrous lactose and spray-dried lactose have good flow properties eg flowability and compressibility and can be used in direct compression provided a suitable disintegrant and lubricant are present in the tablet. Similarly trehalose is available in amorphous and crystalline forms of both the dihydrate and anhydrous states which gives great flexibility for tailoring formulations for various uses.

Binders and granulators are used to impart cohesive qualities to the powdered material. Binders and granulators impart cohesiveness to the formulation which insures the tablet remaining intact after compression, as well as improving the free-flowing qualities by affording granules of a desired hardness and size.

The selection of a particular formulation of components is determined by a variety of parameters including the physical characteristics required of the finished delivery system. The exact formulation will contain a number of components, each chosen to impart a specific function and together to effect the specific desired properties. These are usually determined empirically.

The physical characteristics of tablets are measured in terms of strength, friability uniformity of dimensions, weight and disintegration and dissolution times.

Tablet strength, also termed hardness or tensile strength, is a measure of the cohesiveness of a tablet.

Hardness is defined as the resistance of the tablet to chipping, abrasion or breakage under conditions of storage, transportation and handling. There are a number of machines manufactured for measuring hardness, such as the Hebelein, distributed by Vector. If a tablet is too hard it may not disintegrate in the required period of time or meet the dissolution specification; if it is too soft it will not withstand the handling during subsequent processing, packaging, film coating, transport etc.

Friability is the ability of a tablet to resist chipping and abrasion. Friability is measured by tumbling tablets and determining the weight loss. Tumbling can be performed manually or mechanically, for instance by a Roche friabilator.

The thickness, weight, disintegration time and content uniformity of a tablet must be relatively invariant from run to run. Tablets may be subject to further processing such as coating prior to packaging. A wide variety of coatings are known in the art.

The request for rapidly soluble tablets has given rise to the development of effervescent tablets and the use of intragranular and extragranula disintegrants in tablets but these incur limitations due to difficulty of preparation and use.

According to a first aspect of the present invention a method of making a soluble delivery system form comprises the steps of:

a) combining, in substantially dry form, components comprising a diluent, an amount of binder sufficient to increase the hardness of the compounds and/or the dosage forms to acceptable levels; an amount of an active agent such that each dosage form contains an effective amount of active agent, and an amount of volatile salt effective to decrease the weight

and increase the surface area of the delivery system formed when removed;

b) processing the product of step a) to form a substantially homogeneous mixture;

c) forming a delivery system from the powder of step b); and

d) volatilizing the volatile salt or a component thereof from the delivery system.

The volatile salt may be adapted to vaporise entirely from the formulation. Alternatively the volatile salt may be adapted to decompose to form a volatile component, for example a gas and a non-volatile residue.

Preferred volatile salts may be selected from: ammonium carbonate, ammonium bicarbonate, ammonium acetate and mixtures thereof.

Preferred salts which decompose to form a volatile component are pharmaceutically acceptable bicarbonates, preferably sodium bicarbonate.

The invention encompasses methods of producing soluble tablets and other formulations from different physical forms of powdered trehalose and combinations thereof. The forms of trehalose include, trehalose dihydrate (TD), which is crystalline, amorphous trehalose (AT) which is vitreous, and the anhydrous forms of trehalose, anhydrous amorphous trehalose (AAT) and anhydrous crystalline trehalose (ACT). The anhydrous trehalose powders (AAT and ACT) may contain amorphous anhydrous trehalose, and/or crystalline anhydrous trehalose.

Use of trehalose in solid dosage forms is disclosed in our copending PCT/GB97/00367 claiming priority from US 08/599277 and US 08/599273 the subject matter of which is incorporated into this specification by reference.

As used herein, "trehalose" refers to any physical form of trehalose including anhydrous, partially hydrated, fully hydrated and mixtures and solutions thereof.

"Anhydrous trehalose" refers to any physical form of trehalose containing less than about 2 percent water. The anhydrous forms of trehalose may contain from about 0-2% water

and still retain beneficial properties in tableting. Amorphous trehalose (AT) contains about 2-9% water and TD contains about 9-10% water.

The invention encompasses dosage forms or other delivery systems formed with or without a disintegrant. Delivery systems including disintegrants may dissolve rapidly and release the active ingredient into the aqueous medium.

Preferred embodiments of this invention include dosage forms such as tablets composed of AAT and/or ACT with or without TD and/or AT optionally including other excipients. Formulations having different proportions or amounts of these components result in dosage forms with a wide variety of properties suitable for use with a number of active agents with different physicochemical and physiological properties. Use of trehalose, especially anhydrous forms thereof may stabilise the fill of capsules against migration of water from the shell.

In preferred embodiments of this invention the dosage forms incorporating the volatile salt are exposed to a vacuum or heat for a time and under conditions sufficient to remove the volatile salt or a constituent thereof. The dosage forms thus obtained have increased available surface area, decreased weight and increased dissolution rate compared to solid tablets of like dimensions. The dosage forms thus formed are also encompassed by the invention.

Preferred dosage forms or other delivery systems in accordance with this invention may comprise tablets, capsules or microcapsules. Alternative embodiments may comprise lozenges, granules, matrices and microspheres. Use of capsules, microcapsules and microspheres is especially preferred as these do not require compression, facilitating removal of the volatile salt and affording an optimum surface area for contact with an aqueous medium including dissolution.

Capsules are a solid preparation with a hard or soft shell which may take one of several shapes. They may be used as an oral dosage form with the advantage of an elegant appearance, easy to swallow and its capability to mask unpleasant tastes. Hard shell capsules have a shell and

contents. The shell has a water content of approx 12 - 16% and is often composed of gelatin. the shell is usually presented as two halves. The body (or one half) is filled with the formulation particulates and the capsule is then sealed by fixing the cap onto the body. A seal may or may not be used. Dyes and pacifiers may be used in the shell.

Capsule fillings may be on a small scale where particularly good powder flow properties are required to ensure constant uniformity.

On a large scale the powder/formulation is transferred to the body by a dosator or tamping device.

The powder used would not need to be free flowing if the dosator procedure was used as a cohesive plug would not form.

Capsule filing machines are available eg Zanasi etc, (see Ridgeway K, (editor) Hand Capsules: Development and Technology London, Pharmaceutical Press 1987).

Materials commonly used as binders include starch, gelatin and sugars such as sucrose, glucose, dextrose, molasses and lactose. Natural and synthetic gums that are also used may include acacia, sodium, alginate, extracts of Irish moss, panwar gum, ghatti gum, mucilage of isapol husks, carboxymethylcellulose etc. Any other suitable binders known in the art may be added including, but not limited to, polyvinyl pyrolidone (PVP) for example Ludipress, Kollidon (trade marks) and HES. Kollidon VA64 (BASF) is a preferred polyvinyl pyrolidone based binder. Ludipress (BASF) is a commercial tableting mixture of lactose and PVP. Byco A (Croda) is degraded gelatin of 2500-4000 M. Wt. range. HES (NPBI) is hydroxyethyl starch. As discussed below, under certain conditions, additional binders are necessary to achieve an appropriate degree of hardness in the dosage forms.

Lubricants are used for a number of purposes, including preventing adhesion of the blended materials to the surface of the die and punch, reducing interparticle friction, facilitating the ejection of the tablets from the die cavity and improving the flow of the tablet granulation.

In the examples presented herein, magnesium stearate was

routinely used as a lubricant, and is the preferred lubricant. Any other suitable lubricant known in the art may be used including, but not limited to, talc, calcium stearate, sodium stearyl fumarate, stearic acid, hydrogenated vegetable oil, lutrol and polyethylene glycol (PEG). Disintegrants are added to facilitate breakup or disintegration of the tablet before or after administration. Colouring agents make the dosage form more aesthetic in appearance and may serve as identification. Flavouring agents are usually added to provide sweetness to chewable or dissolvable tablets. The invention encompasses tablets formed from trehalose with or without any excipient or any suitable combinations of excipients.

The active agent is typically a pharmaceutical agent, biological modifier, or diagnostic component. Pharmaceutical agents include, but are not limited to, antipyretic and antiinflammatory drugs, analgesics, antiarthritic drugs, antispasmodics, antidepressants, antipsychotics, tranquilizers, antianxiety drugs, narcotic antagonists, antiparkinsonism agents, cholinergic agonists, chemotherapeutic drugs, immunosuppressive agents, antiviral agents, antibiotic agents, parasiticides, appetite suppressants, antiemetics, anticholinergics, antihistaminics, antimigraine agents, coronary, cerebral or peripheral vasodilators, hormonal agents, contraceptives, antithrombotic agents, diuretics, antihypertensive agents, cardiovascular drugs, opioids and vitamins. Detailed parameters and discussions of such active agents can be found, for instance in the Physician's Desk Reference (1995) 49th ed., Medical Economics Data Production Co. New Jersey. An amount of active agent is used such that there is an "effective amount" in each tablet formed. An effective amount is thus a single unit dosage which may vary depending on whether the tablets are obtained over the counter or via prescription. For instance, Sudafed® brand nasal decongestant contains 30 mg pseudo-ephedrine hydrochloride per unit dose when obtained over the counter and 60 mg per unit dose when obtained via prescription.

The chemical structures of such active agents, include,

but are not limited to, lipids, organics, proteins, synthetic peptides, natural peptides, peptide mimetics, peptide hormones, steroid hormones, D amino acid polymers, L amino acid polymers, oligosaccharides, polysaccharides, nucleotides, oligonucleotides, nucleic acids, protein-nucleic acid hybrids, antigens and small molecules. Suitable proteins include, but are not limited to, enzymes, biopharmaceuticals, growth hormones, growth factors, insulin, monoclonal antibodies, interferons, interleukins, collagen and cytokines. Suitable organics include, but are not limited to, vitamins, neurotransmitters, antimicrobials, antihistamines, analgesics and immunosuppressants. Suitable steroid hormones include, but are not limited to, corticosteroids, oestrogen, progesterone, testosterone and physiologically active analogs thereof. Suitable nucleic acids include, but are not limited to DNA, RNA and physiologically active analogs thereof.

Active agents commonly used in diagnostics include, but are not limited to, dyes, antibodies, enzymes, hormones and antibiotics.

The methods of making the delivery systems includes the steps of thoroughly mixing, in powder form, a binder, preferably, trehalose, active agent volatile salt, any other excipients and a sufficient amount of an additional binder to produce a dosage form of suitable hardness. After formation of the formulation, the salt is volatilized by exposure to reduce atmospheric pressure for a time and under conditions sufficient to substantially completely remove the salt or volatile component thereof. For instance, in the case of ammonium bicarbonate, vacuum drying at 1.5 Torr at 60°C for two hours was sufficient to remove the salt from a 3 mm thick tablet (see Example 1). Although the optimal conditions must be determined empirically, it is well within the skill of one in the art, given the instructions herein, to make this determination. The resulting RS tablet has a decreased weight (up to 50%) compared to other tablets of similar size.

Unlike effervescent tablets the claimed delivery systems can be exposed to humidity without dissolving. Thus, the

production, handling and packaging can be performed under ambient conditions, which is not possible with effervescent tablets, while retaining he light weight and rapid solubility inherent in effervescent tablets. Also, unlike effervescent tablets, these porous dosage forms may not release carbon dioxide in the presence of water and are thus suitable for chewable tablets or lozenges. Due to the increased surface area of the porous dosage forms, they are not as hard as the solid tablets. In order to decrease friability of these tablets, an effective amount of an additional binder is added during processing. Any suitable binder may be used provided it is compatible with the active agent. The effective amount of binder can be determined empirically given the instructions herein. For instance 2 - 5% Ludipress or Kollidon (trade marks) was found to be effective.

The use of trehalose produces dosage forms eg tablets with advantageous properties. Unlike amorphous lactose, tablets made from AT do not suffer from excess hardness and readily dissolve under the appropriate conditions. In addition, trehalose, as a non-reducing sugar, does not react with amino groups, and its surprising resistance to hydrolysis to yield reducing sugars enables its use where the active agent or any excipients contain labile amino groups.

The formulations may further comprise AT as a diluent. As used herein, AT is non-crystalline or "vitreous" trehalose containing water in an amount greater than 2% (anhydrous) but less than 10% (fully hydrated). At imparts stability on active agents dried therein and thus dry solid trehalose formulations containing active agents can readily be tableted with any other form of trehalose as a totally compatible tableting excipient. If the AT formulation produced is dried sufficiently to yield at least a mixture of anhydrous trehalose and AT, the dry solid formulation containing the active agent can be used directly in tableting without the use of additional anhydrous trehalose as a tableting excipient. Although this would be more energy consuming, it would yield the advantage of a monogeneously distributed active agent at a molecular level

within the tablet which may be desirable under certain circumstances.

Any excipients, known in the art can be included in the formulations. Excipients other than diluents include, but are not limited to, binders, lubricants, disintegrates, colouring agents and flavouring agents.

Any other dosage forms or formulations and method of manufacture known in the art can also be used. For instance, the invention encompasses coated tablets, chewable tablets, effervescent tablets, molded tablets or tablet triturates, encapsulated tablets, microencapsulated tablets, sustained release tablets, capsules and microcapsules. The dosage forms produced are suitable for use in any animal including humans. Although the tablets described herein are for human use, suitable veterinary and agrochemical delivery systems are readily fashioned given the skill of one in the art and the Examples and description presented herein.

The following examples are provided to illustrate, but not limit, the claimed invention. Powders used in solid dosage form preparation must have excellent flow properties and consistent particle size. For the purposes of these trials, particle size was not stringently controlled, but powders were formulated to have flow characteristics suitable for tablet production. The flow characteristics obtained were found to enable loading the tablet die without difficulty. A sieving procedure can be incorporated to ensure a more even particle size. This is essential in larger batches to guarantee thorough mixing of the components and it is well within the skill of one in the art to devise a suitable sieving procedure.

EXAMPLE 1

RS Tablet Formulations

300 µl aliquots of a solution of 43.4 mg/ml trehalose containing 66 mg/ml of an antimicrobial peptide was dried in 10 ml polypropylene tubes (10 mm diameter) in the FTS drier. Samples, at 25°C, were loaded onto a shelf in the drier that

had been preheated to 35°C. The vacuum pressure in the chamber was progressively reduced to 20 Torr over 10 minutes. This pressure was held for a further 30 minutes before the pressure was further reduced to 30 mTorr. After 17 hours, the shelf temperature was increased to 50°C. This shelf temperature was maintained for 3 hours after which the cycle was stopped. The amorphous trehalose (AT) matrix produced contained the active in solid solution in a foamed trehalose glass (FTG) and had an open plug-like structure similar to freeze-dried materials. Moisture content was typically 1.1 to 2% (w/w). The DSC trace of a typical sample with water content of 1.59% shows a glass transition of 83 - 84°C characteristic of the amorphous form of trehalose (Figure 1).

The FTGs formed were ground to a fine powder in a Waring blender in a controlled environment of 15% relative humidity (RH), before being used in the tableting formulations.

All the tableting components were then thoroughly mixed in a 20 ml glass vial and aliquots of 0.5 g of powder were weight out into a 0.5 inc Manesty type die. The tablet was formed by hammering onto the upper punch with a single light positioning blow, followed by a stronger single blow. The tablets were of a convex oval shape and at least 3 mm thick. On release from the die, the tablets were stored in sealed vials or, in the case of formulations containing ammonium bicarbonate, subjected to vacuum drying at 1.5 Torr and 60°C for two hours for removal of the volatile salt. Duplicate sets of the tablets containing ammonium bicarbonate were made, one set was subject to vacuum to remove the volatile salt and the other set was not treated further. Disintegration and dissolution of the tablets was studied in aqueous solution with gentle agitation and not stirred. The compositions and results obtained for tableting are presented in Table 1. Table 2 depicts the effect of volatile salt removal on various physical characteristics of the tablets. These results are presented as disintegration time in minutes (Distgn), and dissolution time in minutes (Dissln), of the tablets containing volatile salts. Disintegration is defined as total dissolution and "no dis"

indicates no disintegration. In Table 1, sample 1 is an example of tablets produced using AAT produced by spray drying. All other examples use AAT produced as FTG. In Table 1 amm. bicarb. stands for ammonium bicarbonate, L stands for Ludipress and Mg Stearate is present as a binder. As Ludipress is a mixture of 93% lactose monohydrate and 6% Kollidon. Thus in some formulations, such as blend 1, lactose was the major tableting excipient in the RS tablets produced and no difference in the quality or properties of the tablets were observed with the use of different excipients for the formulation of RS tablets.

TABLE 1

	SAMPLE	COMPOSITION (Wt%)			
	Trehalose glass	Binder	Amm. bicarb	Mg Stearate	Comments
1	30	L 39.5	30	0.5	Good tablets formed
2	56	L 13.5	30	0.5	Good tablets formed
3	80	L 19.5	-	0.5	Good tablets formed
4	42.5	L 40	16.5	1.0	Good tablets formed
5	39.2	L 30.8	29.5	0.5	Good tablets formed
6	44	L 26	29.5	0.5	Good tablets formed
7	38.8	HES 30.7	30	0.5	Good tablets formed

8	51.2	HES 18.3	30	0.5	Good tablets formed

TABLE 2

SAMPLE	BEFORE VAC DRYING		AFTER VAC DRYING		COMMENTS
	Distgn	Dissln	Distgn	Dissln	
1	no dis	12	2.5	6	Gradual surface dissolution. Disintegrates after vacuum
2	n/d	n/d	0.5	5	Good porous tablet
3	n/d	n/d	n/d	n/d	
4	3	11 - 12	1	4	
5	no dis	9	1.5	7	
6	3.5	4.5	1.26	2	
7	2	6.5	0.2	1.5	Rapid disintegration
8	no dis	9 - 10	0.2	2	Rapid dissolution

The results summarised in Tables 1 and 2 indicate that AAT produced from either FTGs or spray dried formulations, formed good tablets. Tablets formed using formulations containing volatile salt showed enhanced dissolution rates after removal of the volatile salt from the tablets under vacuum. Up to 50% (w/w) of the volatile salt can be incorporated into the tablet with the use of suitable binders. Generally, the FTGs gave better tablets than the spray dried formulations but this was dependent on the exact tableting mix used. These results also indicate that various binders are

suitable for use in the RS tablets. Though the results for only magnesium stearate are included other lubricants such as sodium benzoate and sodium stearyl fumarate have also been shown to be suitable for use. Thus, any lubricant is also suitable for use in the tablets formed using AAT.

EXAMPLE 2

Use of AAT and ACT in tablet production

The following example utilizes the amorphous and crystalline forms of anhydrous trehalose, for the production of tablets. The anhydrous trehalose was manufactured by heating crystalline TD at 60°C, at atmospheric pressures to obtain ACT or under vacuum with heat to obtain the AAT. Crystalline TD was incubated in open trays at temperatures of 55°C, 70°C and 80°C in a standard laboratory oven for 24 - 72 hours. Samples were assayed for water content by Karl Fischer analysis and selected samples were also analysed by DSC. Surprisingly, the samples all showed water contents ranging from 0.1 - 2%, event those heated at just 55°C. The EDSC trace of a sample heated at 70°C for 48 hours showed a crystalline melt at approximately 210 - 216°C characteristic of the melting temperature of ACT. The water content of the sample was 0.33%. This endotherm is distinct from the melt endotherm at the lower temperature of 96 - 101°C characteristic of TD seen in the DSC analysis of crystalline dihydrate.

Crystalline TD was incubated in open trays for 16 - 24 hours in either a Heraus vacuum oven with a reduced pressure of 1.5 Torr, or in a FTS freeze drier with a reduced pressure of 30 mTorr, and the shelf temperature set at 60°C. Samples were again assayed for water content by Karl Fischer analysis and selected samples were also analyzed by DSC. Samples typically showed water contents lower than those described above, ranging from 0.1 - 1.5%. The DSC trace of a sample heated at 60°C for 24 hours in a vacuum oven at 1.5 Torr no longer showed a crystalline melt at approximately 215°C, but instead showed a glass transition at 116 - 117°C characteristic of the amorphous form of trehalose demonstrating the formation of AAT. The

water content of the sample was below 0.1%.

The blends used in the tableting of anhydrous trehalose contained either single forms of anhydrous trehalose or mixtures thereof, and also optionally contained a number of commercially used binders such as Kollidon VA64, Ludipress, BycoA and HES and lubricants such as magnesium stearate, sodium lauryl sulfate and Lutrol.

The production of rapidly dissolving tablets was again achieved by the addition of a volatile salt to the tableting blend followed by the removal of the salt under vacuum to obtain a porous tablet that showed increased dissolution rates compared to tablets of the same blends without the volatile salt incorporated. Aliquots of 0.5 g of powder were weighed out into a 0.5 inch Manesty type die. The tablet was formed by hammering onto the upper punch (a single light positioning blow, followed by a stronger single blow). The tablets were of a convex oval shape and at least 3 mm thick. On release from the die, the tablets were stored in sealed vials. In tablets formed from blends containing ammonium bicarbonate, the volatile salt was removed under a vacuum of 1.5 Torr at 60°C for six hours to yield porous, rapidly dissolving tablets which were again stored in sealed vials prior to analysis. Disintegration and dissolution of the tablets was studied in distilled water at 28°C with gentle agitation.

The results obtained on tableting the various blends of anhydrous trehalose and disintegration and dissolution are presented in Tables 3 and 4 respectively. In Table 3, * stands for anhydrous trehalose, K stands for Kollidon and B stands for BycoA. Table 4 shows the effect of increased porosity on rate of disintegration/dissolution of selected tablets. Similar results were obtained for the formation of tablets from these formulations using the automated Manesty F3 tableting press.

TABLE 3

SAMPLE	COMPOSITION (Wt%)				COMMENTS
	Trehalose form	Tab.aid	Amm. bicarb.	Mg stearate	
1	99.5 ATT	-	-	0.5	Good
2	69.5 AAT	-	30	0.5	Good
3	59.5*	-	40	0.5	Some lamination
4	49.5*	-	50	0.5	Occasional lamination
5	64.97 ACT	HES 4.8	29.6	0.53	Excellent
6	39.5*	B 10	50	0.5	Mostly good
7	44.5*	B 5	50	0.5	Good. Few laminate after storage
8	69.5*	-	30	0.5	Excellent
9	67.5	B 2	30	0.5	Good
10	50*	-	50	-	Excellent
11	55*	K 5	40	-	Excellent
12	54.5*	K 5	40	0.5	Excellent

TABLE 4

SAMPLE	DISINT	DISSOL	COMMENTS
5	-	7.5 mins	no disintegration
6	-	1 min	-

7	15 secs	45 secs	most dissolves in 30 secs
8	-	4 mins	no disintegration
9	-	2 mins	no disintegration
10	10 secs	45 secs	-
11	15 secs	1 min	-
12	10 secs	1 min	-

The results presented in table 4 indicate that removal of volatile salt to give porous tablets significantly increased the disintegration and dissolution rates of the tablets produced. Complete removal of the volatile salt was assessed by difference in tablet weight before and after vacuum treatment. AT compresses better than FTG, and volatile salt can be incorporated in up to at least 50 weight %. This leads to a highly porous matrix after the volatile salt has been removed. AT alone remains a good binder, though some loss in intrinsic strength is seen in tablets of blends incorporating ammonium bicarbonate and especially once the volatile salt has been removed. Without a binder of some kind, these porous tablets are very fragile and a balance is therefore essential between a high proportion of volatile and inclusion of a small percentage of binder. Any binder known in the art may be employed. These porous tablets dissolve rapidly when compared to tablets formed from trehalose alone; the time for full dissolution is generally reduced from 10 - 15 minutes down to less than 1 minute.

CLAIMS

1. A method of making a soluble solid delivery system form comprising the steps of:

a) combining, in substantially dry form, components comprising a diluent, an amount of binder sufficient to increase the hardness of the components and/or the dosage form to an acceptable level; an amount of an active agent such that the dosage form contains an effective amount of active agent, and an amount of volatile salt effective to decrease the weight and increase the surface area of the dosage form formed when removed;

b) processing the product of step a) to form a substantially homogeneous mixture;

c) forming a delivery system from the powder of step b); and

d) volatilizing the volatile salt or a component thereof from the delivery system.

2. A method as claimed in claim 1, wherein the volatile salt is adapted to vaporise entirely from the delivery system.

3. A method as claimed in claim 2, wherein the volatile salt is selected from: ammonium carbonate, ammonium bicarbonate, ammonium acetate and mixtures thereof.

4. A method as claimed in claim 1, wherein the volatile salt is adapted to decompose to form a volatile component and a non-volatile residue.

5. A method as claimed in claim 4, wherein the volatile salt is a pharmaceutically acceptable bicarbonate.

6. A method as claimed in claim 5, wherein the volatile salt is sodium bicarbonate.

7. A method as claimed in any preceding claim, wherein the delivery system is selected from: tablets, lozenges, granules, matrices, capsules, microcapsules and microspheres.

8. A method according to any preceding claim, wherein the diluent is selected from: trehalose, dicalcium phosphate, dihydrate, calcium, tricalcium, phosphate, sulfate, lactose, spray-dried lactose, pregelatinized starch, microcrystalline cellulose, cellulose, kaolin, mannitol, sodium chloride, dry starch or powdered sugar and mixtures thereof.

9. A method as claimed in claim 8, wherein the trehalose is selected from: trehalose dihydrate, amorphous trehalose, anhydrous amorphous trehalose, anhydrous crystalline trehalose and mixtures thereof.

10. The method as claimed in any preceding claim, wherein the components of step a) further comprise at least one excipient selected from: diluents, lubricants, disintegrants, colouring agents and flavouring agents.

11. A method as claimed in claim 10, wherein the lubricant is selected from: talc, calcium stearate, sodium stearyl fumarate, stearic acid, hydrogenated vegetable oil, lutrol, polyethylene glycol and magnesium stearate.

12. A method as claimed in any preceding claim, wherein the binder is selected from: starch, gelatin, sugars, natural and synthetic gums, polyvinyl pyrolidone, hydroxyethyl starch and mixtures thereof.

13. A method as claimed in any preceding claim, wherein step d) includes the step of exposing the formulation to reduced pressure for a time sufficient to volatilize the volatile salt.

14. A method as claimed in claim 13, wherein the

pressure is 0.5- 30,000 mTorr for 0.5 - 6 hr.

15. A dosage form formulated according to the method of any preceding claim.

16. A tablet formulated according to the method of any of claims 1 to 14.

17. A capsule or microcapsule formulated according to the method of any of claims 1 to 14.

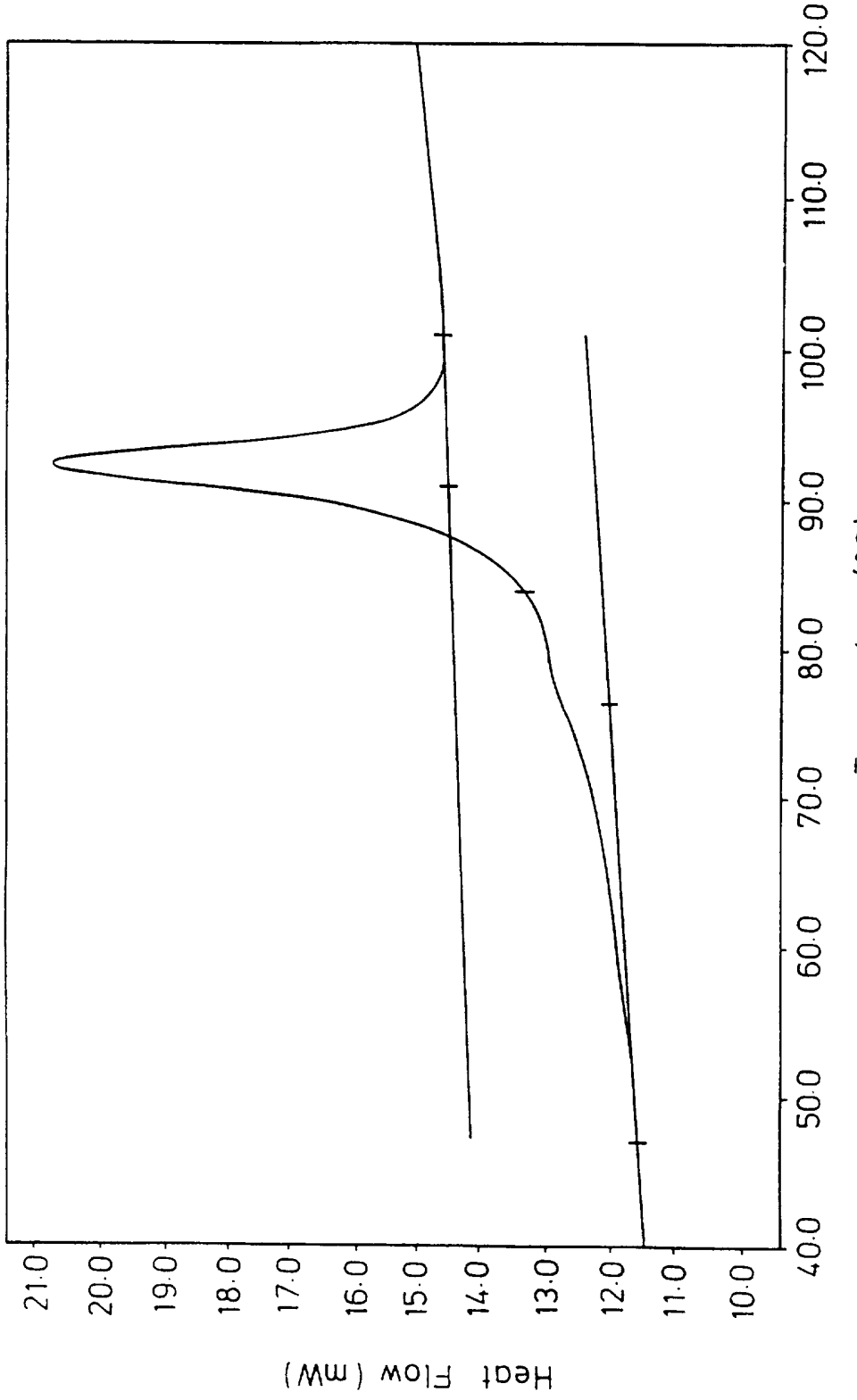
Heat Flow (mW)
21.0
20.0
19.0
18.0
17.0
16.0
15.0
14.0
13.0
12.0
11.0
10.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0
110.0
120.0
Temperature (°C)

FIG. 1

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/GB 97/00368

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FR 2 199 973 A (BOEHRINGER MANNHEIM AG) 19 April 1974 see the whole document -----	1-3,7, 10,13-17

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 June 1997	12.06.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Scarponi, U

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter al Application No
PCT/GB 97/00368

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