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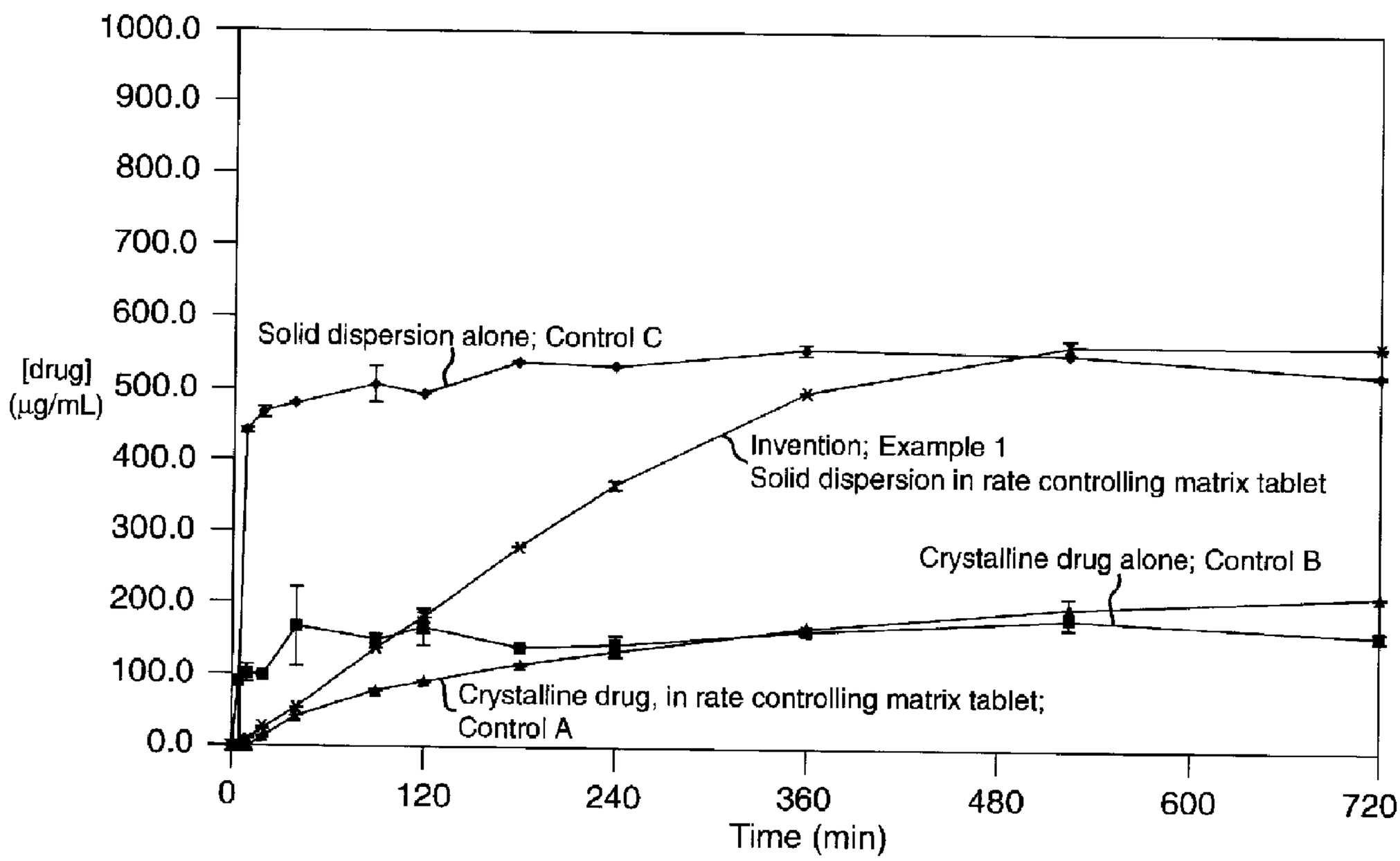

(57) Abrégé/Abstract:
There is disclosed a controlled release dosage form for a low solubility drug that is a spray-dried or spray-coated amorphous solid dispersion of the drug in an ionizable cellulosic polymer matrix that is in turn incorporated into a secondary erodible polymeric matrix and a method of treating a disease or disorder comprising administering such a dosage form.

MATRIX CONTROLLED RELEASE DEVICE

ABSTRACT OF THE DISCLOSURE

There is disclosed a controlled release dosage form for a low solubility drug that is a spray-dried or spray-coated amorphous solid dispersion of the drug in an ionizable cellulosic polymer matrix that is in turn incorporated into a secondary erodible polymeric matrix and a method of treating a disease or disorder comprising administering such a dosage form.

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MATRIX CONTROLLED RELEASE DEVICE

BACKGROUND OF THE INVENTION

The bioavailability of sparingly water-soluble drugs is well-known to be limited and to be profoundly affected by such factors as the fed state of the patient, the rate of metabolism in relation to the rate of absorption in the gastrointestinal (GI) tract, and the dosage form. Many attempts have been made to improve the form of dosage for such low solubility drugs, generally with a view to attaining an increase in drug concentration, thereby improving the absorption or bioavailability of the drug. Although many of these attempts have been somewhat successful they generally provide an immediate and often temporary increase in absorption in the sense that drug levels in the blood reach an undesirably high level very rapidly. It would be more desirable to simultaneously couple in a single dosage form high bioavailability for sparingly soluble drugs with controlled and sustained release of the drugs. Only a few attempts to accomplish this objective have been reported as methods to improve bioavailability and methods to attain controlled drug release are generally regarded not to be compatible, the conventional wisdom being that use of controlled release techniques would tend to diminish bioavailability.

Exemplary sustained release dosage forms have included crystalline drug particles dispersed in a swellable hydrogel matrix core that releases the drug by diffusion into the environment of use, as described in U.S. Patent No. 4,624,848; a hydrogel reservoir containing a multiplicity of tiny pills wherein each tiny pill consists of a wall surrounding a crystalline drug core, as described in U.S. Patent No. 4,851,232; and a

two-layered tablet wherein one layer is crystalline drug mixed with a hydrogel and the other layer is a hydrogel, as described in U.S. Patent No. 5,516,527.

One sustained release dosage form consists of a coated tablet with a core of a solid dispersion of drug in extremely hydrophilic polyoxamer hydrogels that releases the drug by diffusion from the swollen tablet mass and by erosion of the tablet surface. This is in keeping with the widely held view that water-soluble polymers are most suitable for forming solid amorphous dispersions of drugs in polymers. See Ford, 61 *Pharm. Acta. Helv.* 3 (1986).

U.S. Patents Nos. 4,343,789, 4,404,183 and 4,673,564 all have the same disclosure of a sustained release composition of the vasodilator nicardipine comprising a solid amorphous dispersion of the drug in microcrystalline cellulose, polyethylene oxide, polyvinyl pyrrolidone and the cellulosic polymers hydroxypropylcellulose, hydroxypropylmethylcellulose and hydroxypropylmethylcellulose phthalate. However, the preferred method of forming the dispersion is by extensive and time-consuming ball-milling, and there is no recognition of the concentration-enhancing and amorphous state-stabilizing properties of ionizable cellulosics for forming the drug dispersion.

Solid dispersion dosage forms may be formed by solvent evaporation, by spray drying, by spray coating, by spraying drug solution onto the carrier in a fluidized bed granulator, by twin screw extrusion, by melt fusion, by mechanical admixture such as by ball milling and by mechanical admixture at an elevated but non-melting temperature. See, for example, European Patent Application No. 0 552 708; U.S. Patent No. 5,456,923; Chowdary et al., 32 *Indian Drugs* 477 (1995); Dangprasirt et al., 21 *Drug Development & Ind. Pharm.* 2323 (1995); and Goracinova et al., 22 Drug *Development & Ind. Pharm.* 255 (1996).

Most solid dispersion drug delivery systems have been directed to the delivery of poorly water-soluble drugs as they generally tend to be immediate release forms; as a result, for drugs with short elimination half-lives, they have those forms' inherent drawbacks of high peak drug concentrations in the blood, short times following administration when drug concentrations in the blood reach a maximum (t_{max}), and relatively short duration of effective levels of concentration in the blood. In addition, although improved bioavailability relative to that for crystalline drug is reported, bioavailability for such dosage forms is nevertheless often low in an absolute sense. Specifically, such drug delivery systems often exhibit little overall improvement in the concentration of drug in a patient's blood over a given time period (commonly referred to as "AUC" in reference to the calculation of the area under a curve comprising a plot of concentration of drug in a patient's blood against time).

In the case of the solid polyoxamer dispersion mentioned above, the dosage form suffers from slow and incomplete release in cases where drug is released by diffusion through a membrane coating due to the inherent low solubility of the drug; conversely, in cases where drug is released by erosion of the drug/polyoxamer dispersion, drug release is typically non-zero order and variable, being dependent on the patient's fed state and gastric retention time. In addition, since the polyoxamer dispersion polymers disclosed are highly hydrophilic and generally require aqueous solvents for dissolution, these polymers cannot be used to form dispersions with hydrophobic drugs via solvent processing as it is difficult or impossible to dissolve the drug and polymer in a common solvent.

There is therefore still a need in the art for a controlled release dosage form for delivery of a low solubility drug with a short elimination half-life that

provides improved drug bioavailability. These needs and others which will become apparent to one skilled in the art are met by the present invention, which is summarized and described in detail below.

BRIEF SUMMARY OF THE INVENTION

In one aspect, the invention provides a controlled release dosage composition comprising: (a) a solid dispersion comprising a low solubility drug dispersed in a cellulosic polymer, a major portion of said drug being amorphous; and (b) an aqueous-soluble cellulosic erodible polymeric matrix having said dispersion incorporated therein.

In a further aspect, the invention provides a controlled release dosage composition comprising: (a) a solid dispersion comprising a low solubility drug substantially homogeneously dispersed in an ionizable cellulosic polymer, said drug being amorphous; and (b) an erodible polymeric matrix having said dispersion incorporated therein.

In a still further aspect, the invention provides a controlled release dosage composition comprising: (a) a solid dispersion comprising a low solubility drug dispersed in an ionizable cellulosic polymer having an alkylate substituent and an ester-linked carboxylic acid substituent, a major portion of said drug being amorphous; and (b) an erodible polymeric matrix having said dispersion incorporated therein.

The present invention in its simplest form is a controlled release dosage composition that comprises a solid amorphous substantially homogeneous dispersion of a low solubility drug in a concentration-enhancing dispersion polymer wherein the dispersion in turn is incorporated into an erodible polymeric (or hydrophilic) matrix. The dispersion polymer is an ionizable cellulosic, preferably containing alkylate and ester-linked carboxylic acid substituents. At least a major portion of the drug, i. e., at least about 60%, is amorphous (as opposed to crystalline). More preferably, substantially all of the drug, i. e., at least about 75%, is amorphous. Most preferably, essentially all of the drug, i. e., at least about 90%, is amorphous. The drug delivery mechanism is by erosion or diffusion to cause gradual drug release to the environment of use.

The present invention further comprises the use of a controlled release dosage composition for the treatment of a disease or disorder in an animal, preferably a mammal, more preferably a human.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGS. 1-4 are graphs comprising plots of release rates of drugs delivered by the controlled release composition of the present invention and of comparative release rates for controls.

DETAILED DESCRIPTION OF THE INVENTION

According to the present invention, there is provided a dosage form specifically designed to provide controlled release by an erosion or diffusion mechanism of a "low solubility" drug (defined below) that utilizes the drug in the form of an amorphous solid dispersion wherein a majority (>60%) of the drug is in an amorphous, as opposed to a crystalline form; the dispersion in turn

being incorporated into an erodible or hydrophilic polymeric matrix. The term "drug" is conventional, denoting a compound having beneficial, prophylactic, and/or therapeutic properties when administered to an animal, especially to a human. By an "erodible" matrix is meant water-erodible or water-swellable or water-soluble in the sense of being either erodible or swellable or dissolvable in pure water or requiring the presence of an acid or base to ionize the polymeric matrix sufficiently to cause erosion or dissolution. The form of the device may be any known conventional form, including a tablet, a capsule, a caplet, a bead, a multiparticulate, a powder or combinations thereof, and is generally useful in mammals and particularly useful for therapeutic uses in humans.

The drug may be delivered either in the form of gel or a suspension of solids in water or primarily as a solution of the drug, to the extent dissolution has taken place prior to erosion. While not wishing to be bound by any particular theory of delivery mechanism, the delivery is believed to take place by any one or more of the following mechanisms: (1) dissolution of the amorphous drug dispersion in the dosage form prior to erosion, coupled with diffusion from the dosage form, either directly or through a coating; (2) dissolution of the dispersion as the matrix erodes, with delivery primarily as a solution; or (3) delivery as a solid suspension as the matrix erodes, followed by dissolution in the GI tract.

Both the amorphous solid dispersion component and the erodible matrix component may contain osmagens, osmopolymers, solubility-enhancing agents and excipients. In addition, delayed or sustained release features may be added by coating the dosage form with controlled release coating formulations known in the art.

The dosage form of the present invention generally provides controlled delivery of the drug to an environment of use such that (1) the concentration of

drug in the in vitro or in vivo environment is enhanced and in turn the bioavailability of the drug is enhanced relative to a comparable dosage form where the drug is present in its undispersed state, *i.e.*, not incorporated into a solid dispersion before formulation; and (2) the time at which a maximum drug concentration (C_{max}) in an in vitro or in vivo environment of use is attained is delayed by from 30 minutes to 24 hours.

More specifically, the dosage forms of the invention provide one or more of the following features: (1) they provide a C_{max} in an aqueous environment *in vitro* test, which is at least 1.5-fold that achieved by an identical controlled release dosage composition containing the same quantity of drug in an undispersed state; (2) they provide a C_{max} in an aqueous environment in vitro test, at a time (t_{max}) which is at least 30 minutes longer but not more than 24 hours longer than the t_{max} observed when the solid dispersion is tested without incorporation into a sustained release polymeric matrix; (3) they provide an AUC in drug concentration in an aqueous use environment that is at least 1.25-fold that achieved by an identical controlled release dosage composition containing the same quantity of drug in an undispersed state; (4) when orally dosed to a human or other animal they provide a blood C_{max} (plasma or serum) that is achieved at a time t_{max} which is at least 30 minutes longer than observed when a control composition is dosed, the control composition comprising the drug dispersion alone, *i.e.*, not formulated in a sustained release polymeric matrix; (5) when orally dosed to a human or other animal they provide a blood C_{max} (plasma or serum) that is at least 1.25-fold that observed when a control composition is dosed, the control composition being identical to the test composition with the exception that the drug is formulated in the undispersed state; and (6) when orally dosed to a human or other animal they provide an AUC in drug concentration in the

blood that is at least 1.25-fold that observed when a control composition is dosed, the control composition being the same as that described in (5).

THE DRUG

Prior to formation of the dispersion, the drug in its pure state may be crystalline or amorphous, but when dispersed in the solid dispersion polymer, a major portion of the drug is in an amorphous or non-crystalline state such that its non-crystalline nature is demonstrable by powder X-ray diffraction analysis or by differential scanning calorimetry or by any other standard quantitative measurement. Preferably, the drug is substantially amorphous, and more preferably essentially completely amorphous. As used herein, the term "a major portion" of the drug means that at least 60% of the drug in the dispersion is in the amorphous form, rather than the crystalline form. Preferably, the drug in the dispersion is substantially amorphous. As used herein, "substantially amorphous" means that the amount of the drug in crystalline form does not exceed 25%. More preferably, the drug in the dispersion is essentially completely amorphous, meaning that the amount of drug in crystalline form does not exceed 10% as measured by any of the means noted above. By an "amorphous" state is meant that the drug may be present in (a) discrete drug-rich amorphous domains, (b) homogeneously distributed throughout the dispersion polymer (*e.g.*, a solid solution), or (c) any state or combination of states between the extremes of (a) and (b).

The solid dispersion is preferably substantially homogeneous so that the drug is dispersed as homogeneously as possible throughout the polymer. As used herein, “substantially homogeneous” means that the drug present in relatively pure amorphous domains within the solid dispersion is relatively small, on the order of

less than 20%, and preferably less than 10%. While the dispersion may have some drug-rich domains, it is preferred that the dispersion itself have a single glass transition temperature (T_g) which demonstrates that the dispersion is substantially homogenous. This contrasts with a physical mixture of pure amorphous drug particles and pure amorphous polymer particles which generally display two distinct T_gs, one that of the drug and one that of the polymer.

Since the solubility of a given drug is often pH-dependent, the device of the present invention is appropriate for delivery of any drug the solubility of which, over any portion of the physiologically relevant pH range, falls into the solubility ranges noted herein. In general, the class of drugs may be characterized by having a solubility sufficiently low that it is desirable to increase the drug's solubility either (a) within the dosage form to improve its delivery characteristics or (b) outside the dosage form to improve the rate or extent of drug absorption.

The drug is a "low-solubility drug," meaning that the drug has a minimum aqueous solubility at a physiologically relevant pH (*e.g.*, pH 1-8) of about 40 mg/ml or less. Thus, the drug may be either "substantially water-insoluble," that is having a minimum aqueous solubility at a physiologically relevant pH of less than 0.01 mg/mL, or "sparingly water-soluble," that is, having a water solubility up to about 1 to 2 mg/mL, or even moderate solubility where the solubility is as high as 20 to 40 mg/mL. In general, it may be said that the drug has a dose-to-aqueous solubility ratio greater than 5 mL, where the drug solubility is the minimum value observed in any physiologically relevant aqueous solution including USP simulated gastric and intestinal buffers.

In some cases, it is also desirable to enhance the solubility of the drug within the dosage form to increase the rate of diffusion or release from the dosage form or to improve the absorption of drug in the colon. In such cases, the invention may be applied to drugs with a minimum aqueous solubility as high as 20 to 40 mg/mL. This is particularly true when it is desired to deliver a solution of the drug. In such cases, the dose-to-aqueous solubility ratio may be as low as 1 mL.

Virtually any beneficial therapeutic agent that meets the solubility criteria may be used as the drug in the present invention. In addition, the drug may be employed in the form of its pharmaceutically acceptable salts as well as in anhydrous and hydrated forms and prodrugs. Preferred classes of drugs include, but are not limited to, antihypertensives, antidepressants, antianxiety agents, anti-atherosclerotic agents, anticlotting agents, anticonvulsants, blood glucose-lowering agents, decongestants, antihistamines, antitussives, anti-inflammatories, antipsychotic agents, cognitive enhancers, cholesterol-reducing agents, antiobesity agents, autoimmune disorders agents, anti-impotence agents, antibacterial and antifungal agents, hypnotic agents, anti-Parkinsonism agents, antibiotics, antiviral agents, anti-impotence agents, anti-neoplastics, barbituates, sedatives, nutritional agents, beta blockers, emetics, anti-emetics, diuretics, anticoagulants, cardiotonics, androgens, corticoids, anabolic agents, anti-depression agents, anti-infective agents, coronary vasodilators, carbonic anhydrase inhibitors, antiprotozoals, gastrointestinal agents, serotonin antagonists, anesthetics, hypoglycemic agents, dopaminergic agents, anti-Alzheimer's Disease agents, anti-ulcer agents, platelet inhibitors, and glycogen phosphorylase inhibitors.

Specific examples of the above and other classes of drugs and therapeutic agents deliverable by the invention are set forth below, by way of example

only. Specific examples of antihypertensives include prazosin, nifedipine, trimazosin and doxazosin mesylate; a specific example of an antianxiety agent is hydroxyzine; a specific example of a blood glucose-lowering agent is glipizide; a specific example of an anti-impotence agent is sildenafil citrate; specific examples of anti-neoplastics include chlorambucil, lomustine and echinomycin; specific examples of anti-inflammatory agents include betamethasone, prednisolone, aspirin, flurbiprofen and (+)-N-{4-[3-(4-fluorophenoxy)phenoxy]-2-cyclopenten-1-yl}-N-hyroxyurea; a specific example of a barbiturate is phenobarbital; specific examples of antivirals include acyclovir and virazole; specific examples of vitamins/nutritional agents include retinol and vitamin E; specific examples of a β-blocker include timolol and nadolol; a specific example of an emetic is apomorphine; specific examples of a diuretic include chlorthalidone and spironolactone; a specific example of an anticoagulant is dicumarol; specific examples of cardiotonic include digoxin and digitoxin; specific examples of an androgen include 17-methyltestosterone and testosterone; a specific example of a mineral corticoid is desoxycorticosterone; a specific example of a steroidal hypnotic/anesthetic is alfaxalone; specific examples of an anabolic agent include fluoxymesterone and methanstenolone; specific examples of antidepression agents include fluoxetine, paroxitine, venlafaxine, sertraline, sulpiride, [3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-(1-ethylpropyl)-amine and 3,5-dimethyl-4-(3'-pentoxy)-2-(2',4',6'-trimethylphenoxy)pyridine; specific examples of an antibiotic include ampicillin and penicillin G; specific examples of an anti-infective include benzalkonium chloride and chlorhexidine; specific examples of a coronary vasodilator include nitroglycerin and mioflazine; a specific example of a hypnotic is etomidate; specific examples of a carbonic anhydrase inhibitor include acetazolamide and chlorzolamide;

specific examples of an antifungal include econazole, terconazole and griseofulvin; a specific example of an antiprotozoal is metronidazole; a specific example of an imidazole-type anti-neoplastic is tubulazole; specific examples of an anthelmintic agent include thiabendazole and oxfendazole; specific examples of an antihistaminic include astemizole, levocabastine and cinnarizine; specific examples of antipsychotics include fluspirilene, penfluridole and ziprasidone; specific examples of a gastrointestinal agent include loperamide and cisapride; specific examples of a serotonin antagonist include ketanserin and mianserin; a specific example of an anesthetic is lidocaine; a specific example of a hypoglycemic agent is acetohexamide; a specific example of an anti-emetic is dimenhydrinate; a specific example of an antibacterial is cotrimoxazole; a specific example of a dopaminergic agent is L-DOPA; specific examples of anti-Alzheimer agents are THA and donepezil; a specific example of an anti-ulcer agent/H2 antagonist is famotidine; specific examples of a sedative/hypnotic include chlordiazepoxide and triazolam; a specific example of a vasodilator is alprostadil; a specific example of a platelet inhibitor is prostacyclin; specific examples of an ACE inhibitor/antihypertensive include enalaprilic acid and lisinopril; specific examples of a tetracycline antibiotic include oxytetracycline and minocycline; specific examples of a macrolide antibiotic include azithromycin, clarithromycin, erythromycin and spriamycin; specific examples of glycogen phosphorylase inhibitors include [R-(R*S*)]-5-Chloro-N-[2-hydroxy-3-[methoxymethylamino}-3-oxo-1-(phenylmethyl)-propyl]propyl]-1H-indole-2-carboxamide and 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-3((3R,4S)-dihydroxypyrrolidin-1-yl-)-(2R)-hydroxy-3-oxypropyl]amide.

Further examples of drugs deliverable by the invention are the glucose-lowering drug chlorpropamide,

the anti-fungal fluconazole, the anti-hypercholesterodemic atorvastatin calcium, the antipsychotic thiothixene hydrochloride, the anxiolytics hydroxyzine hydrochloride and doxepin hydrochloride, the anti-hypertensive amlodipine besylate, the anti-inflammatories iroxicam, valdecoxib and celicoxib, and the antibiotics carbenicillin indanyl sodium, bacampicillin hydrochloride, troleandomycin, and doxycycline hyclate.

THE DISPERSION POLYMER

Suitable polymers for forming the solid dispersion of drug are preferably polymeric, concentration-enhancing, non-aqueous solvent-processable, non-toxic and inert. By "non-aqueous solvent" is meant solvents comprising up to about 30 wt% water.

By "non-aqueous solvent-processable" is meant the polymer is capable of being processed with the drug in a common non-aqueous solvent to form the solid dispersion, *i.e.*, it is generally adaptable to techniques utilizing non-aqueous solvents in the formation of solid dispersions. Such techniques include spray-drying or spray coating. The polymer has a preferred solubility in the non-aqueous solvent of at least 0.1 mg/mL, more preferably greater than 1 mg/mL and most preferably greater than 10 mg/mL. This property is critical for forming the solid amorphous dispersion of the drug and dispersion polymer via solvent processing as the drug and dispersion polymer must be dissolved in a common solvent and such solvents cannot be substantially aqueous as the drugs by definition have a relatively low aqueous solubility.

Such dispersion polymers are aqueous-soluble in the sense that they are sufficiently soluble (≥1 mg/mL) in at least a portion of the 1 to 8 pH range that they exhibit a "concentration-enhancing" property. By "concentration-enhancing" is meant the concentration of

drug provided by a solid dispersion of the drug in aqueous media is at least 1.5-fold that provided by an equivalent quantity of undispersed drug.

By "non-toxic" is meant that they should be acceptable for oral administration to a mammal, especially a human.

By "inert" is meant not adversely reactive or bioactive, yet still capable of positively affecting the drug's bioavailability.

The amount of the concentration-enhancing dispersion polymer present in the dispersion generally ranges from about 10 to about 95 wt%, preferably 30 to 80 wt%.

A preferred class of concentration-enhancing polymers comprises ionizable cellulosic polymers (including those with ether or ester or a mixture of ester/ether substituents and copolymers thereof, which includes both so-called "enteric" and "non-enteric" polymers).

Exemplary ionic cellulosics include carboxymethylcellulose (CMC) and its sodium salt, carboxyethylcellulose (CEC), hydroxyethylmethylcellulose acetate phthalate (HEMCAP), hydroxyethylmethylcellulose acetate succinate (HEMCAS), hydroxypropylmethylcellulose phthalate (HPMCP), hydroxypropylmethylcellulose succinate (HPMCS), hydroxypropylcellulose acetate phthalate (HPCAP), hydroxypropylcellulose acetate succinate (HPCAS), hydroxypropylmethylcellulose acetate phthalate (HPMCAP), hydroxypropylmethylcellulose acetate succinate (HPMCAS), hydroxypropylmethylcellulose acetate trimellitate (HPMCAT), hydroxypropylmethylcellulose acetate phthalate (HPMCAP), hydroxypropylcellulose butyrate phthalate (HPCBP), carboxymethylethylcellulose (CMEC) and its sodium salt, cellulose acetate phthalate (CAP), methylcellulose acetate phthalate (MCAP), cellulose acetate trimellitate (CAT), cellulose acetate terephthalate, cellulose acetate isophthalate, cellulose

propionate phthalate, cellulose propionate trimellitate, and cellulose butyrate trimellitate.

Of these ionic cellulosics, it has been found that an even more preferred class of concentration-enhancing polymers are those ionic cellulosics that have a significant substitution by both an alkylate substituent and an ester-linked carboxylic acid substituent. Exemplary alkylate substituents are acetate, propionate and butyrate. Exemplary ester-linked carboxylic acid substituents and phthalate, succinate, trimellitate, terephthalate, isophthalate, pyridinedicarboxylate, and salicylate. Such polymers are preferred as they generally produce drug dispersions that have a particularly advantageous combination of excellent concentration-enhancement properties as well as good physical stability. By "good physical stability" is meant the drug present in the solid amorphous dispersions tends to remain in its amorphous state upon storage relative to dispersion of other polymers. Good physical stability for solid amorphous dispersions of drug and such ionic cellulosics with both alkylate and ester-linked carboxylic acid substituents may well be a result of the relatively high glass-transition temperature of such dispersions, especially in the presence of moisture, as well as their tendency to inhibit drug crystallization. In addition, their tendency to inhibit the crystallization of drug from aqueous solution may also lead to their excellent concentration-enhancing properties and in turn their tendency to promote enhanced bioavailability for low-solubility drugs.

Exemplary ionic cellulosics with both alkylate and ester-linked carboxylic acid substituents include HEMCAP, HEMCAS, HPCAP, HPCAS, HPMCAP, HPMCAS, HPMCAT, HPMCAP, HPCBP, CAP, MCAP, CAT, cellulose acetate terephthalate, cellulose acetate isophthalate, cellulose propionate phthalate, cellulose propionate trimellitate, cellulose butyrate trimellitate and mixtures thereof. Of these, the most preferred are HPMCAS, CAP and CAT.

It should be noted that in the above polymer nomenclature, ether-linked substituents are recited prior to "cellulose" as the moiety attached to the ether group (e.g., "ethylbenzoic acid cellulose" has ethoxybenzoic acid substituents) and ester-linked substituents are recited after "cellulose" as the carboxylate (*e.g.*, "cellulose phthalate" has one carboxylic acid of each phthalate moiety ester-linked to the polymer and the other carboxylic acid unreacted).

It should further be noted that a polymer name such as "cellulose acetate phthalate" refers to any of the family of cellulosic polymers that have acetate and phthalate groups attached via ester linkages to a significant fraction of the cellulosic polymer's hydroxyl groups. Generally, the degree of substitution of each substituent group can range from 0.1 to 2.8 as long as the other criteria of the polymer are met. "Degree of substitution" refers to the average number of the three hydroxyls per saccharide repeat unit on the cellulose chain that have been substituted. For example, if all of the hydroxyls on the cellulose have been phthalate-substituted, the phthalate degree of substitution is 3. Also included within each polymer family type are cellulosic polymers that have additional substituents added in relatively small amounts that do not substantially alter the performance of the polymer.

THE SOLID AMORPHOUS DISPERSION

The solid dispersion generally contains from about 5 to about 90 wt% drug, preferably 20 to 70 wt%. However, when the drug dose is less than 25 mg, the drug content of the dispersion may be less than 5 wt%.

The solid amorphous dispersion of drug may in some cases be prepared by essentially any known method such as melt fusion, ball-milling or solvent processing. However, the preferred method is by solvent processing such as spray-drying or spray-coating that remove solvent

relatively rapidly. When prepared by such rapid solvent processing, a major portion (>60%) of the drug is almost always in an amorphous state, and often substantially all (>75%) if not essentially all (>90%) of the drug is in an amorphous state. By "amorphous" is meant the drug may be present in the dispersion in any of three broad classes of forms: (a) in discrete, drug-rich domains; (b) homogeneously distributed in the dispersion, *i.e.*, a solid solution; or (c) any state or combination of states between the extremes of (a) and (b).

As mentioned previously, the solid amorphous dispersion is preferably substantially homogenous. Solvent processing is preferred because it tends to yield more homogeneous dispersions and because melt fusion is not suitable for use with many of the preferred concentration-enhancing dispersion polymers. In particular, solvent processing in a manner such as spray-drying or spray-coating wherein the polymer/drug solution is solidified by rapid removal of solvent (preferably in less than 1 second) is preferred because it has been found to lead to more homogeneous dispersions.

When prepared by such solvent processing a homogenous solution of drug and the dispersion polymer is formed in a common solvent, alone or along with other excipients that may or may not be dissolved, followed by relatively rapid solvent removal by precipitation or evaporation. By "common solvent" is meant one or more solvents in which both drug and dispersion polymer are soluble at a given temperature and pressure.

The reason that such solvent processing is preferred is that it permits the drug and dispersion polymer to be intimately mixed at the molecular level thereby achieving homogeneity (difficult to accomplish by mechanical processing), without application of excessive heat (required by melt fusion processing), and results in a major portion (>60%) of the drug being in an amorphous, as opposed to a crystalline, state. Precipitation is

typically induced by contacting the drug/matrix solution with a non-solvent such as water, a liquid hydrocarbon or super-critical CO_2.

A particularly preferred method of forming the dispersion is by dissolving the drug and matrix polymer in a common solvent, then removing the solvent by spray-drying or spray-coating the mixture. Spray-drying and spray-coating processes and equipment are described generally in *Perry's Chemical Engineer's Handbook*, pages 20-54 to 20-57 (6th Ed. 1984). More details on spray-drying processes and equipment are reviewed by Marshal in 50 Chem. Eng. Prog. Monogr. Series 2 (1954).

The terms "spray-drying" and "spray-coating" in connection with the present invention are used conventionally and broadly refer to processes involving breaking up liquid mixtures into small droplets (atomization) and rapidly removing solvent from the mixtures in a vessel such as a spray-drying apparatus, fluidized bed- or pan-coater where there is a strong driving force for evaporation of solvent from the droplets. In the case of spray-coating the droplets impinge on a particle, bead, pill, tablet, or capsule, resulting in a coating comprising the solid amorphous dispersion. Spray-coating may also be conducted on a metal, glass or plastic surface and the coated layer may subsequently be removed and milled to the desired particle size. In the case of spray-drying, the droplets generally dry prior to impinging on a surface, thus forming particles of solid amorphous dispersion on the order of 1 to 100 μm in diameter. The strong driving force for solvent evaporation is generally provided by maintaining the partial pressure of solvent in the spray-drying apparatus well below the vapor pressure of the solvent at the temperature of the drying droplets. This is accomplished by either (1) maintaining the pressure in the spray-drying apparatus at a partial-vacuum (*e.g.*, 0.01 to 0.50 atm); (2) mixing the liquid droplets with a

warm drying gas; or (3) both. For example, a solution of drug and a dispersion polymer such as HPMCAS in acetone may be suitably spray-dried by spraying the solution at a temperature of 50°C (the vapor pressure of acetone at 50°C is about 0.8 atm) into a chamber held at 0.01 to 0.2 atm total pressure by connecting the outlet to a vacuum pump. Alternatively, such a solution may be sprayed into a chamber where it is mixed with nitrogen gas at a temperature of 80°C to 250°C and a pressure of 1.0 to 1.2 atm.

Generally, the temperature and flow rate of the drying gas is chosen so that dispersion polymer/drug solution droplets are dry enough by the time they reach the wall of the apparatus that they are essentially solid, so that they form a fine powder and do not stick to the apparatus wall. The actual length of time to achieve this level of dryness depends on the size of the droplets. Droplet sizes generally are larger than about 1 μm in diameter, with 5 to 100 μm being typical. The large surface-to-volume ratio of the droplets and the large driving force for evaporation of solvent leads to actual drying times of a few seconds or less. For some mixtures of drug/dispersion polymer/solvent this rapid drying is critical to the formation of a uniform, homogeneous composition and generally preventing the mixture from separating into drug-rich and polymer-rich phases, although a limited degree of phase separation is permissible. Such dispersions having a homogenous composition can be considered solid solutions and may be supersaturated in drug. Such homogeneous dispersions are preferred in that the maximum drug concentration (MDC) value obtained when a large amount of drug is dosed can be higher for such dispersions relative to dispersions for which at least a portion of the drug is present as a drug-rich amorphous or crystalline phase.

Solidification times should be less than 100 seconds, preferably less than a few seconds, and more preferably less than 1 second. In general, to achieve

such rapid solidification of the drug/polymer solution, it is preferred that the diameter of droplets formed during the spray-drying process are less than 100 μm, preferably less than 50 μm, and most preferably less than 25 μm. The so-formed solid particles resulting from solidification of these droplets generally tend to be 2 to 40 μm in diameter.

Following solidification, the solid powder typically remains in the spray-drying chamber for 5 to 60 seconds, evaporating more solvent. The final solvent content of the solid dispersion as it exits the dryer should be low, since low solvent content tends to reduce the mobility of drug molecules in the dispersion, thereby improving its stability. Generally, the residual solvent content of the dispersion should be less than 10 wt% and preferably less than 2 wt%.

The solution spray-dried to form the polymer/drug dispersion can be quite simple, containing only drug and polymer in a solvent. Generally, the ratio of polymer to drug in the solution ranges from 0.1 to 20 and preferably ranges from 0.5 to 5. However, when the drug dose is low (less than 20 mg), the polymer to drug ratio may be even greater than 5.

Other excipients may be added to the spray solution, either co-dissolved in the solvent along with the drug and dispersion polymer or suspended in the solution to form a slurry. Such excipients may include: acids, bases or buffers to modify the ionic state and dissolution properties of the resulting dispersion; fillers, binders, disintegrants or other materials to improve the tableting process or final properties of the dosage form; antioxidants to improve the dispersions stability; osmotic agents, including both water-swellable hydrophilic polymers and osmogens such as hygroscopic sugars, organic acids and polyols; and surfactants to affect the wetting of the dosage form.

Solvents suitable for spray-drying may generally be characterized as "non-aqueous" in the same

sense mentioned above, *i.e.*, comprising <30 wt% water. They may be essentially any organic compound in which the drug and polymer are mutually soluble or mixtures of water and/or organic compounds. In the case of mixtures of water and organic compounds, up to about 30 wt% water may advantageously be included, particularly in those cases where the organic solvent is more hydrophobic than the drug. Preferably, the solvent is also relatively volatile with a boiling point of 150°C or less. Although lower volatility solvents may also be used, they are generally less preferred. In those cases where the solubility of the drug in the volatile solvent is low, it may be desirable to include a small amount, say 2 to 25 wt%, of a low volatility solvent such as N-methylpyrrolidone (NMP) or dimethylsulfoxide (DMSO) in order to enhance drug solubility. In addition, the solvent should have relatively low toxicity and be removed from the dispersion to a level that is acceptable according to the International Committee on Harmonization (ICH) guidelines. Removal of solvent to this level may require a processing step such as spray-drying subsequent to the spray-drying or spray-coating dispersion formulation process.

Preferred solvents include alcohols such as methanol, ethanol, n-propanol, isopropanol, and butanol; ketones such as acetone, methyl ethyl ketone and methyl isobutyl ketone; esters such as ethyl acetate and propylacetate; and various other solvents such as acetonitrile, methylene chloride, toluene, and 1,1,1-trichloroethane. Lower volatility solvents such as dimethyl acetamide or DMSO may also be used. Mixtures of solvents may also be used, as may mixtures up to 30 wt% with water as long as the polymer and drug are sufficiently soluble to make the spray-drying process practical.

In general, the solid amorphous dispersion provides a C_{max} in a use environment that is at least

1.25-fold that of a control dosage form comprising an equivalent amount of undispersed drug (typically the control is simply the crystalline drug alone in its thermodynamically most stable form unless the crystalline form of the drug is unknown, in which case the control is the amorphous drug alone).

Alternatively, the dispersion of the present invention when tested *in vitro* in a physiologically relevant aqueous solution provides an AUC value at least 1.5-fold that measured for an equivalent quantity of undispersed drug. Preferably, when orally administered, the dispersion also provides an AUC *in vivo* (area under the blood drug concentration vs. time plot) that is at least 1.25-fold that observed when an equivalent quantity of undispersed drug is dosed.

OTHER DISPERSION COMPONENTS

The solid amorphous drug dispersion of the drug delivery device may contain a wide variety of additives and excipients, generally aimed at enhancing the bioavailability of the drug.

The dispersion may include osmotically effective solutes, often referred to as "osmogens." Typical useful osmogens include magnesium sulfate, magnesium chloride, calcium chloride, sodium chloride, lithium chloride, potassium sulfate, sodium carbonate, sodium sulfite, lithium sulfate, potassium chloride, sodium sulfate, d-mannitol, urea, sorbitol, inositol, raffinose, sucrose, glucose, fructose and mixtures thereof. Particularly preferred osmagens are glucose, lactose, sucrose, sodium chloride, mannitol and xylitol.

The solid dispersion may also include about 1 to about 20 wt% solubility-enhancing or -reducing agents that promote or retard the dissolution rate of the dispersion, including the drug. Examples of suitable solubility-enhancing agents include surfactants; pH control agents such as buffers, organic acids and organic

acid salts and organic and inorganic bases; glycerides; partial glycerides; glyceride derivatives; polyhydric alcohol esters; PEG and PPG esters; sorbitan esters; polyoxyethylene sorbitan esters; carbonate salts; alkyl sulfonates; and cyclodextrins.

Exemplary solubility-enhancing or -reducing agents are: organic acids such as citric acid; organic acid salts such as calcium acetate; partial glycerides such as glyceryl monostearate; glycerides such as triacetin; glyceride derivatives such as glyceryl succinate; polyethylene glycol esters such as polyoxyethylene laurate; polypropylene glycol esters such as polyoxypropylene stearate; polyhydric alcohol esters such as glucose laurate; sorbitan esters such as polysorbate 80; carbonate salts such as calcium carbonate; alkyl sulfonates such as sodium lauryl sulfate; and cyclodextrins such as sulphobutylether beta-cyclodextrin.

The solid dispersion may include additives or excipients that promote stability, tableting or processing of the dispersion. Such components include tableting aids, surfactants, water-soluble polymers, pH modifiers, fillers, binders, pigments, disintegrants, lubricants and flavorants. Exemplary of such components are microcrystalline cellulose; metallic salts of acids such as aluminum stearate, calcium stearate, magnesium stearate, sodium stearate, and zinc stearate; fatty acids, hydrocarbons and fatty alcohols such as stearic acid, palmitic acid, liquid paraffin, stearyl alcohol, and palmitol; fatty acid esters such as glyceryl (mono- and di-) stearates, triglycerides, glyceryl (palmiticstearic) ester, sorbitan monostearate, saccharose monostearate, saccharose monopalmitate, and sodium stearyl fumarate; alkyl sulfates such as sodium lauryl sulfate and magnesium lauryl sulfate; and inorganic materials such as talc and dicalcium phosphate.

All such additives and excipients may be added directly to the spray-drying solution such that the

additive is dissolved or suspended in the solution as a slurry. Alternatively, such components may be added following the spray-drying process to aid in forming the final dosage form.

THE ERODIBLE MATRIX

The erodible polymeric matrix into which the solid dispersion is incorporated may generally be described as a set of excipients that are mixed with the dispersion following its formation that, when contacted with the aqueous environment of use imbibes water and forms a water-swollen gel or "matrix" that entraps the dispersion. Drug release may occur by a variety of mechanisms: the matrix may disintegrate or dissolve from around the dispersion particles or granules; or the drug may dissolve in the imbibed aqueous solution and diffuse from the tablet, beads or granules of the dosage form. A key ingredient of this water-swollen matrix is the water-swellable, erodible, or soluble polymer which may generally be described as a osmopolymer, hydrogel or water-swellable polymer. Such polymers may be linear, branched, or crosslinked. They may be homopolymers or copolymers. Although they may be synthetic polymers derived from vinyl, acrylate, methacrylate, urethane, ester and oxide monomers, they are most preferably derivatives of naturally occurring polymers such as polysaccharides or proteins.

Such materials include naturally occurring polysaccharides such as chitin, chitosan, dextran and pullulan; gum agar, gum arabic, gum karaya, locust bean gum, gum tragacanth, carrageenans, gum ghatti, guar gum, xanthan gum and scleroglucan; starches such as dextrin and maltodextrin; hydrophilic colloids such as pectin; phosphatides such as lecithin; alginates such as ammonia alginate, sodium, potassium or calcium alginate, propylene glycol alginate; gelatin; collagen; and cellulosics.

A preferred class of cellulosics for the erodible matrix comprises aqueous-soluble and aqueous-erodible cellulosics such as ethyl cellulose (EC), methylethyl cellulose (MEC), CMC, CMEC, hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), cellulose acetate (CA), cellulose propionate (CP), cellulose butyrate (CB), cellulose acetate butyrate (CAB), CAP, CAT, HPMC, HPMCP, HPMCAS, HPMCAT, and ethylhydroxy ethylcellulose (EHEC). A particularly preferred class of such cellulosics comprises various grades of low viscosity (MW ≤50,000 daltons) and high viscosity (MW ≥50,000 daltons) HPMC. Commercially available low viscosity HPMC polymers include the Dow METHOCEL* series E5, E15LV, E50LV and K100LY, while high viscosity HPMC polymers include E4MCR, E10MCR, K4M, K15M and K100M; especially preferred in this group are the METHOCEL™ K series. Other commercially available types of HPMC include the Shinetsu METOLOSE 90SH* series.

Although the primary role of the erodible matrix material is to control the rate of release of drug to the environment of use, the inventors have found that the choice of matrix material can have a large effect on the maximum drug concentration attained by the controlled-release dosage form as well as the maintenance of a high drug concentration. The proper choice of polymer in turn affects the bioavailability of the drug. We have found that water-soluble cellulosics such as certain grades of methyl cellulose (MC) or HPMC, when used as the primary rate-controlling matrix material, can result in higher maximum drug concentrations *in vitro* relative to other conventional matrix polymers such as polyoxamers (*e.g.*, PEO or PEG) or carboxylic acid polymers such as CMC or calcium CMC or polyacrylic acids such as Carbopol*. Thus, an especially preferred embodiment of the invention comprises a solid substantially amorphous dispersion of drug in a cellulosic polymer incorporated into controlled-release

*Trade-mark

beads, granules, or tablets wherein the matrix polymer comprises an aqueous-soluble cellulosic. It has been found that in an aqueous use environment such dosage forms provide an area under the drug concentration versus time plot that is at least 1.25-fold that of an identical control dosage composition except that the polymeric matrix comprises PEO, wherein the PEO has a molecular weight such that the time to release 50% of the drug from the control is greater than 80% but less than 120% the time to release 50% of the drug from the dosage composition of the present invention. Exemplary of such cellulosics are MC, HEC, HPC, hydroxyethylmethyl cellulose, HPMC, and other closely related water-soluble polymers. Preferably, the matrix material comprises MC or HPMC.

Other materials useful as the erodible matrix material include, but are not limited to, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyvinyl acetate, glycerol fatty acid esters, polyacrylamide, polyacrylic acid, copolymers of ethacrylic acid or methacrylic acid (EUDRAGIT®, Rohm America, Inc., Piscataway, New Jersey) and other acrylic acid derivatives such as homopolymers and copolymers of butylmethacrylate, methylmethacrylate, ethylmethacrylate, ethylacrylate, (2-dimethylaminoethyl)methacrylate, and (trimethylaminoethyl) methacrylate chloride.

The erodible matrix polymer may contain concentration-enhancing dispersion polymers of the type discussed above. In addition, the erodible matrix polymer may contain a wide variety of the same types of additives and excipients known in the pharmaceutical arts and discussed above, including osmopolymers, osmagens, solubility-enhancing or -retarding agents and excipients that promote stability or processing of the dosage form.

ENTERIC COATINGS

The dosage compositions of the present invention may also be overcoated with one or more pH-sensitive coating compositions, commonly referred to in the art as "enteric coatings," according to conventional procedures in order to delay the release of drug. Suitable pH-sensitive polymers include those which are relatively insoluble and impermeable at the pH of the stomach, but which are more soluble or disintegrable or permeable at the pH of the small intestine and colon. Such pH-sensitive polymers include polyacrylamides, phthalate derivatives such as acid phthalate of carbohydrates, amylose acetate phthalate, cellulose acetate phthalate (CAP), other cellulose ester phthalates, cellulose ether phthalates, hydroxypropylcellulose phthalate (HPCP), hydroxypropylethylcellulose phthalate (HPECP), hydroxyproplymethylcellulose phthalate (HPMCP), HPMCAS, methylcellulose phthalate (MCP), polyvinyl acetate phthalate (PVAcP), polyvinyl acetate hydrogen phthalate, sodium CAP, starch acid phthalate, cellulose acetate trimellitate (CAT), styrene-maleic acid dibutyl phthalate copolymer, styrene-maleic acid/polyvinylacetate phthalate copolymer, styrene and maleic acid copolymers, polyacrylic acid derivatives such as acrylic acid and acrylic ester copolymers, polymethacrylic acid and esters thereof, polyacrylic and methacrylic acid copolymers, shellac, and vinyl acetate and crotonic acid copolymers.

Preferred pH-sensitive polymers include shellac; phthalate derivatives; CAT; HPMCAS, polyacrylic acid derivatives, particularly copolymers comprising acrylic acid and at least one acrylic acid ester; polymethyl methacrylate blended with acrylic acid and acrylic ester copolymers; and vinyl acetate and crotonic acid copolymers.

A particularly preferred group of pH-sensitive polymers includes CAP, PVAcP, HPMCP, HPMCAS, anionic acrylic copolymers of methacrylic acid and

methylmethacrylate, and osmopolymers comprising acrylic acid and at least one acrylic acid ester.

Cellulose acetate phthalate may be applied as an enteric coating to the dosage forms of the invention to provide delayed release of drug until the dosage form has exited the stomach. The CAP coating solution may also contain one or more plasticizers, such as diethyl phthalate, polyethyleneglycol-400, triacetin, triacetin citrate, propylene glycol, and others as known in the art. Preferred plasticizers are diethyl phthalate and triacetin. The CAP coating formulation may also contain one or more emulsifiers, such as polysorbate-80.

Anionic acrylic copolymers of methacrylic acid and methylmethacrylate are also particularly useful enteric coating materials for delaying the release of drug until the tablets have moved to a position in the GI tract which is distal to the stomach. Copolymers of this type are available from Rohm America, Inc., under the trade names EUDRAGIT-L® and EUDRAGIT-S®. EUDRAGIT-L® and EUDRAGIT-S® are anionic copolymers of methacrylic acid and methylmethacrylate. The ratio of free carboxyl groups to the esters is approximately 1:1 in EUDRAGIT-L® and approximately 1:2 in EUDRAGIT-S®. Mixtures of EUDRAGIT-L® and EUDRAGIT-S® may also be used. For coating these acrylic coating polymers can be dissolved in an organic solvent or mixture of organic solvents or suspended in aqueous media. Useful solvents for this purpose are acetone, isopropyl alcohol, and methylene chloride. It is generally advisable to include 5-20 wt% plasticizer in coating formulations of acrylic copolymers. Useful plasticizers include polyethylene glycols, propylene glycols, diethyl phthalate, dibutyl phthalate, castor oil, and triacetin. EUDRAGIT-L® is preferred because it dissolves relatively quickly at intestinal pH.

In addition to the pH-sensitive polymers listed above, delayed release coatings may consist of a mixture

or blend of two or more pH-sensitive polymers or may consist of a mixture of one or more pH-sensitive polymers and one or more non-pH-sensitive polymers. Addition of a non-pH-sensitive polymer to the pH-sensitive polymer is useful in modulating the duration of the delay or rate of release of drug from the granule, bead or tablet. For example, the delay can be lengthened by blending an aqueous-insoluble polymer with the pH-sensitive polymers, while the delay can be shortened by blending a water-soluble polymer with the pH-sensitive polymers. Preferred non-pH-sensitive aqueous-insoluble polymers include cellulose esters, cellulose ethers, polyacrylates, polyamides, polyesters, and vinyl polymers. Preferred non-pH-sensitive aqueous-soluble polymers include hydroxyalkyl-substituted cellulosics such as HPC, HEC and HPMC, PVA, PEG, PEO, PEG/PPG copolymers, and aqueous-soluble polyamides, polysaccharides, and polyacrylates. Various additives may be included in such coatings, including emulsifiers, plasticizers, surfactants, fillers and buffers.

Finally, the polymeric coating may be described as being "quasi-enteric" in the sense that it remains substantially intact for a significant period of time (e.g., greater than an hour) after the dosage form exits the stomach, thereafter becoming sufficiently drug-permeable to permit gradual release of drug by diffusion through the coating.

USE AND FABRICATION

In use, the solid dispersion in the erodible matrix absorbs water from the environment of use to form a water-swollen mass. Drug may be released by diffusion from the dispersion or by the dispersion slowly eroding into the environment of use. Thus drug is released either primarily as a solution of drug or as a suspension of drug; when delivered as a suspension, the drug formulation subsequently dissolves in the environment of use, such as the GI tract.

Dosage forms of the present invention may be made by essentially any known process suitable for fabrication of pharmaceutical tablets, caplets, capsules, beads, multiparticulates, powders for suspensions or unit dosage packets, commonly referred to as sachets, wherein the solid dispersion is substituted for crystalline drug. For example, the ingredients may be blended, milled and wet- or dry-granulated to form a homogeneous blend of ingredients. Blended ingredients may be compressed into tablets using conventional tablet presses or ingredients may be segregated and then compressed to form tablets with a layered or coated geometry. Additionally, when the dosage form comprises multiparticulates, beads or powders, such materials are prepared, for example, by melt-congealing from a spinning disc, extrusion-spheronization, or fluid-bed granulation, or by coating nonpareil seeds with a mixture of water or organic solvent and the dosage form components.

Following formation of the solid drug dispersion and erodible polymeric matrix in tablet, caplet, bead, powder, multiparticulate or capsule form, it may additionally be coated with a pH-sensitive enteric or quasi-enteric coating, or with a coating to mask taste, improve appearance, or facilitate swallowing of the dosage form. Such coatings may be fabricated by any conventional means including fluidized bed coating, spray-coating, pan-coating and powder-coating using aqueous or organic solvents. Additionally, the dosage form may comprise an immediate release layer of the same or different drug from that used to form the solid dispersion, the drug(s) being in crystalline, amorphous or dispersion form.

The dosage forms of this invention are useful in treating a variety of conditions and diseases, including those exemplified herein, by administering the dosage forms described herein to a mammal in need of such treatment.

EXAMPLE 1

Exemplary dosage forms of the present invention were fabricated by first forming a batch of 1:2 solid dispersion ("SD") comprising 1 part of a low solubility drug to 2 parts of dispersion polymer by mixing the drug 5-chloro-1H-indole-2-carboxylic acid [(1S) -benzyl-3-((3R,4S) -dihydroxypyrrolidin-1-yl-) - (2R) -hydroxy-3-oxypropyl]amide (a glycogen phosphorylase inhibitor from Pfizer, Inc.) having a water solubility of 80 μg/mL, in the solvent acetone together with a "medium fine" (MF) grade of HPMCAS (AQUOT*, Shinetsu, Tokyo, Japan) to form a solution. The makeup of the solution was 2.5 wt% drug, 5 wt% polymer and 92.5 wt% solvent. This solution was then spray-dried by directing an atomizing spray via a Niro two-fluid nozzle at 2.8 bar and 200 g/min feed rate into a stainless steel chamber of a Niro portable spray-dryer maintained at 180°C at the inlet and 70°C at the outlet. Portions of the drug dispersion were held back and subjected to analysis by imaging the dispersion using scanning electron microscopy, and so verified to be in an amorphous, non-crystalline state.

To incorporate the resulting SD into the erodible polymeric matrix, 1.05 g of the SD particles were then mixed with 1.7 g HPMC (METHOCEL K 100 LV prem., Dow Chemical, Midland, Michigan), 0.70 g of the lactose filler FAST FLOW (Foremost/Van Water and Rogers, Baraboo, Wisconsin), and 0.0525 g of the lubricant magnesium stearate, all blended for 20 minutes in a TURBULA blender (Willy A. Bachofen AG Muschinenfabrik, Basel, Switzerland) to render the mixture homogeneous. The so-formed homogeneous core mixture contained 10 wt% drug, 20 wt% HPMCAS-MF, 48.5% METHOCEL, 20 wt% lactose and 1.5 wt% magnesium stearate. This homogeneous mixture was formed into tablets using an F-3 Press (Manesty, Liverpool, England) with 11/32" tooling. The tablet weight was about 350 mg.

As a control (Control A), tablets were similarly prepared except rather than using the

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drug/HPMCAS-MF SD, an undispersed mixture of 1 part crystalline drug to 2 parts dispersion polymer (HPMCAS-MF) was used. As a second control (Control B), 37.4 mg of crystalline drug with no erodible matrix was used. As a third control (Control C), 106.1 mg of the SD with no erodible matrix polymer was used.

Phosphate buffered saline solution (PBS) was prepared comprising 20 mM sodium phosphate, 466 mM potassium phosphate, 87 mM NaCl and 0.2 mM KCl, adjusted to pH 6.5. Four *in vitro* dissolution tests were performed in 35 mL of the PBS solution at 37°C to test the effectiveness of drug release from the dosage composition of the invention as measured against Controls A, B and C. Drug concentrations over time were determined by periodically withdrawing samples of each of the four solutions, centrifuging the samples for 1 minute at 13,000 rpm to pellet any undissolved drug, sampling the supernate, and analyzing the sample by High Performance Liquid Chromatography (HPLC) to thereby calculate drug concentrations.

The results are set forth in Table 1 and graphically illustrated in Figure 1. As is apparent from Table 1 and Figure 1, the dosage form of the present invention exhibited a gradual and continuous increase in drug concentration in the PBS solution over a period of about 8 hours, reaching a maximum value of about 563 μg/mL, or about three-fold that achieved by either Control A or Control B. Finally, the data obtained demonstrate that supersaturated drug concentrations are achievable by the present invention. The matrix tablets were completely disintegrated over the course of the 12 hour dissolution tests, indicating that the mechanism of controlled release was primarily by erosion.

Table 1

Dosage Form	Time (min)	[Drug]*	AUC**
Example 1 of invention; SD in erodible matrix	0	0.0	0
	4	0.0	0
	10	11.2	34
	20	25.3	217
	40	52.9	999
	90	136.3	5730
	120	178.3	10449
	180	277.7	24131
	240	365.6	43432
	360	496.8	95177
	525	563.2	182625
	720	562.9	292415
Control A; Crystalline drug mixed with dispersion polymer	0	0.0	0
	4	0.0	0
	10	0.0	0
	20	13.2	66
	40	41.7	614
	90	77.9	3605
	120	90.8	6135
	180	114.5	12293
	240	132.8	19711
	360	165.8	37627
	525	196.0	67473
	720	212.3	107280
Control B; Crystalline drug alone	0	0.0	0
	4	90.1	180
	10	101.0	754
	20	98.8	1753
	40	166.1	4402
	90	147.9	12252
	120	164.5	16937
	180	137.3	25991
	240	141.8	34362
	360	161.0	52528
	525	179.0	80574
	720	157.2	113346
Control C SD alone	0	0.0	0
	4	0.0	0
	10	44.1	1324
	20	468.0	5870
	40	479.0	15338
	90	505.5	39945
	120	492.6	54916
	180	536.6	85792
	240	531.8	117840
	360	556.8	183153
	525	550.7	274517
	720	523.1	379210

* μg/mL
**min•μg/mL

EXAMPLE 2

Exemplary dosage forms of the present invention were fabricated by first forming a batch of 2:1 SD comprising 2 parts of a low solubility drug to 1 part of dispersion polymer by mixing HPMCAS-MF with the drug [R-(R*S*)]-5 chloro-N-[2-hydroxy-3-[(methoxymethylamino)-3-oxo-1(phenylmethyl)propyl]propyl]-1H-indole-2-carboxymide, (another glyocogen phosphorylase inhibitor from Pfizer, Inc.) having a water solubility of 1 μg/mL. The solid dispersion was made as described in Example 1 except that the makeup of the solution was 5.0 wt% drug, 2.5 wt% HPMCAS-MF and 92.5 wt% solvent and the solution was spray-dried using a rotary atomizer nozzle set at 7.5 bar with an inlet temperature of 120°C. The drug dispersion was verified to be in an amorphous, non-crystalline state.

To incorporate the resulting SD into an erodible matrix, 1.05 g of the resulting solid particles were then mixed with 1.7 g METHOCEL K100LV Prem, 0.70 g of the filler FAST FLOW lactose, and 0.0525 g of the lubricant magnesium stearate, then tableted as described in Example 1. The resulting tablets were 20 wt% drug, 10 wt% HPMCAS-MF, 48.5 wt% METHOCEL, 20 wt% lactose and 1.5 wt% magnesium stearate. The tablet weight was 350 mg.

As a control (Control D), tablets were prepared similarly except rather than using the drug/HPMCAS-MF SD, a mixture of 2 parts crystalline drug to 1 part HPMCAS-MF was used. As a second control (Control E), 70 mg of the undispersed crystalline drug with no erodible matrix was used. As a third control (Control F), 107 mg of the SD with no erodible matrix was used.

A Model Fasted Duodenum (MFD) solution which mimics the chemical environment in the small intestine was prepared, comprising the PBS solution described in Example 1 mixed with 14.7 mM sodium taurocholic acid and 2.8 mM of 1-palmitoyl-2-oleyl-sn-glycero-3-phosphocholine. Four *in vitro* dissolution tests were

performed in 500 mL of the so-prepared MFD solution to test the effectiveness of drug release from the dosage composition of the invention against Controls D, E and F. The sampling and analysis were carried out as in Example 1.

The results are set forth in Table 2 and graphically illustrated in Figure 2. As is apparent from Table 2 and Figure 2 the dosage form of the present invention exhibited a gradual and continuous increase in drug concentration in the MFD solution over a period of 20 hours, reaching a maximum value of about 82 μg/mL, 12 times that achieved by Control D and 4.6 times that achieved by Control E.

Table 2

Dosage Form	Time (min)	[Drug]*	AUC**
Example 2 of invention; SD in erodible matrix	0	0.0	0
	10	0.0	0
	20	0.0	0
	40	2.3	23
	90	5.2	212
	120	7.1	397
	180	10.9	936
	240	14.8	1706
	360	23.6	4011
	525	6.9	9458
	720	46.2	16939
	1200	82.4	
Control D; Crystalline drug mixed with dispersion polymer	0	0.0	0
	10	0.0	0
	20	0.0	0
	40	0.0	0
	90	0.0	0
	120	0.0	47
	180	1.6	154
	240	2.0	462
	360	3.1	1135
	525	4.4	1985
	720	5.1	2439
	1200	6.6	
Control E; Crystalline drug alone	0	0.0	0
	10	6.9	21
	20	3.2	72
	40	6.8	172
	90	18.1	795
	120	14.3	1281
	180	17.0	2219
	240	8.8	2992
	360	8.5	4030
	525	10.7	5756
	720	9.0	7525
	1200	8.0	
Control F; SD alone	0	0.0	0
	10	37.0	0
	20	43.6	111
	40	72.5	514
	90	102.4	1674
	120	103.6	6046
	180	105.8	9136
	240	108.2	15418
	360	117.8	
	525	124.0	21838
	720	126.3	35401
	1220	78.0	57168

* μg/mL
**min•μg/mL

This Example also demonstrates that the dosage form of the present invention is capable of a much more desirable t_{max} as compared to that of an SD alone, reaching its maximum concentration in at least 20 hours, whereas drug released from the SD alone (Control F) reached a plateau concentration near its maximum concentration in less than 90 minutes. The matrix tablets were completely disintegrated over the course of the 20 hours, indicating that the mechanism of controlled release was primarily by erosion.

EXAMPLE 3

Exemplary dosage forms of the present invention were fabricated by first forming a batch of 1:3 SD of 1 part of a low solubility drug to 3 parts of the dispersion polymer by mixing the same drug as in Example 1 with CAP to form a solution. The spray-drying was carried out as described in Example 1 except that the solution was 0.75 wt% drug, 2.25 wt% CAP and 97 wt% acetone and the spray apparatus was set at 1.9 bar. Formation of an amorphous, noncrystalline drug dispersion was confirmed.

To incorporate the solid dispersion into an erodible matrix, 1.071 g of the resulting solid particles were then mixed with 1.7315 g METHOCEL, 0.714 g of lactose filler, and 0.0536 g of the lubricant magnesium stearate. The tablet weight was 350 mg.

As a control (Control G), tablets were similarly prepared except rather than using the drug/CAP solid dispersion, a mixture of 1 part crystalline drug to 3 parts CAP was used. As a second control (Control H), 26 mg of crystalline drug alone was used. As a third control (Control I), 105.3 mg of the solid dispersion with no erodible matrix was used. In order to determine the drug release profile of the dosage form of the present invention as compared to the controls, in vitro dissolution tests in 40 mL of the PBS solution of Example 1 at 37°C were performed as in Example 1.

The results are set forth in Table 3 and graphically illustrated in FIG. 3, and as is apparent therefrom, the dosage form of the present invention exhibited a gradual and continuous increase in drug concentration in the MFD solution over a period of about 9 hours, reaching a maximum value of about 560 μg/mL--more than three-fold greater than that achieved by either Control G or Control H. This Example further demonstrates that the dosage form of the present invention has a much more desirable t_{max} than does the SD alone, reaching its maximum drug concentration in about 9 hours, whereas maximum concentration for the SD alone (Control I) is reached in less than 10 minutes. Finally, the data obtained show that supersaturated drug concentrations are attainable, more than three-fold that achieved by the crystalline drug alone (Control H) or the crystalline drug mixed with CAP (Control G). The matrix tablets were completely disintegrated over the course of the 12 hours, indicating that the mechanism of controlled release was primarily by erosion.

Table 3

Dosage Form	Time (min)	[Drug]*	AUC**
Example 4 of invention; SD in erodible matrix	0	0.0	0
	10	6.8	21
	20	18.8	149
	40	46.3	799
	90	107.9	4654
	120	157.8	8640
	180	248.4	20826
	240	328.5	38131
	360	474.7	86322
	525	557.0	171442
	720	545.3	278918
Control G; Crystalline drug mixed with dispersion polymer	0	0.0	0
	10	2.9	9
	20	9.7	72
	40	25.4	423
	90	60.7	2575
	120	76.7	4636
	180	105.2	10091
	240	125.2	17003
	360	146.1	33282
	540	174.2	59702
	720	177.5	93992
Control H; Crystalline drug alone	0	0.0	0
	10	107.8	0
	20	130.1	323
	40	109.1	1513
	90	118.1	3906
	120	121.8	9587
	180	151.7	13186
	240	170.4	21392
	360	135.3	31055
	540	134.8	49395
	720	168.3	73701
Control I; SD alone	0	0.0	0
	10	589.7	0
	20	560.6	1769
	40	566.4	7520
	90	549.2	18790
	120	543.1	46680
	180	540.3	63064
	240	526.2	95564
	360	487.6	127556
	525	412.6	188381
	720	242.0	262646

* μg/mL
**min•μg/mL

EXAMPLE 4

Tablets of a solid drug dispersion incorporated into an erodible matrix were prepared as in Example 2, then coated with a 100 Å-thick enteric coating to delay drug release, comprising 90 wt% CAP and 10 wt% triacetin. The coating was applied by spraying a solution comprising 9 wt% CAP and 1 wt% triacetin in acetone onto the tablet cores using a conventional pan coater. The drug release profile of this coated dosage form was tested by exposing the tablets to USP simulated gastric buffer for two hours and then transferring the tablets to the MFD solution of Example 2. Release of drug was delayed by two to four hours, showing the effectiveness of the coating for retarding drug release while the tablets are in the gastric environment.

EXAMPLE 5

Exemplary dosage forms of the present invention were fabricated as in Example 1 by first forming a batch of SD comprising 1 part of the low solubility drug (1S-*cis*)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-napthalenamine hydrochloride having a water solubility of 70 μg/mL and 1 part of the dispersion polymer HPMCP-55 except that drug and polymer were sprayed from a 1:1 mixture (by weight) of MeOH:acetone with a solution composition of 2.5 wt% drug, 2.5 wt% polymer and 92.5 wt% solvent. The solution was sprayed at a pressure of 1.8 bar with a 190 g/min feed rate, a 230°C inlet temperature, and a 70°C outlet temperature. The drug dispersion was verified to be in an amorphous, non-crystalline state.

To incorporate the resulting SD into an erodible matrix, a homogeneous mixture of 30% SD, 48.5% METHOCEL K100LV Prem, 20% FAST FLO lactose and 1.5% magnesium stearate was made. Tablets were made as described in Example 1.

As a control (Control J), tablets were prepared similarly except rather than using the drug/HMPCP SD, a mixture of 1 part crystalline drug to 1 part of the same grade of HPMCP was used. As a second control (Control K), 62 mg of the undispersed crystalline drug alone was used. As a third control (Control L), 122 mg of the SD with no erodible matrix was used.

An MFD solution was prepared as in Example 2. Four *in vitro* dissolution tests were performed in 30 ml of the MFD solution to test the effectiveness of drug release from the dosage composition of the invention against Controls J, K and L. The sampling and analysis were carried out as in Example 1.

The results are set forth in Table 4 and graphically illustrated in FIG. 4, and as is apparent therefrom the dosage form of the present invention exhibited a gradual and continuous increase in drug concentration in the MFD solution over a period of 12 hours, reaching its maximum value of about 600 μg/mL at 12 hours. At 9 hours the drug concentratin achieved by the dosage composition of the invention was 4-fold that of Control K.

Table 4

Dosage Form	Time (min)	[Drug]*	AUC**
Example 6 of invention; SD in erodible matrix	0	0	0
	10	35	104
	20	74	650
	40	118	2570
	90	245	11629
	120	166	17785
	180	395	34613
	240	436	59546
	360	523	117090
	540	573	215775
	720	600	321320
	1200	380	
Control J; Crystalline drug mixed with dispersion polymer	0	0	0
	10	27	82
	20	88	656
	40	145	2981
	90	277	13522
	120	283	21922
	180	421	43043
	240	503	70742
	360	506	131280
	540	454	217682
	720	579	310606
	1200	485	
Control K; Crystalline drug alone	0	0	0
	10	0	1073
	20	358	5459
	40	520	16706
	90	605	37083
	120	210	40231
	240	130	52796
	360	159	70528
	540	136	108647
	1200	128	
Control L; SD alone	0	0	0
	10	0	1076
	20	359	4751
	40	376	12704
	90	419	33693
	120	421	46399
	180	426	72602
	240	447	99737
	360	457	154514
	540	456	226262
	720	342	277001
	1200	222	

* μg/mL
**min•μg/mL

The terms and expressions which have been employed in the foregoing specification are used therein as terms of description and not of limitation, and there is no intention, in the use of such terms and expressions, of excluding equivalents of the features shown and described or portions thereof, it being recognized that the scope of the invention is defined and limited only by the claims which follow.

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CLAIMS:

1. A controlled release dosage composition comprising:

(a) a solid dispersion comprising a low solubility drug dispersed in a cellulosic polymer, a major portion of said drug being amorphous; and

(b) an aqueous-soluble cellulosic erodible polymeric matrix having said dispersion incorporated therein.

2. A controlled release dosage composition comprising:

(a) a solid dispersion comprising a low solubility drug substantially homogeneously dispersed in an ionizable cellulosic polymer, said drug being amorphous; and

(b) an erodible polymeric matrix having said dispersion incorporated therein.

3. A controlled release dosage composition comprising:

(a) a solid dispersion comprising a low solubility drug dispersed in an ionizable cellulosic polymer having an alkylate substituent and an ester-linked carboxylic acid substituent, a major portion of said drug being amorphous; and

(b) an erodible polymeric matrix having said dispersion incorporated therein.

4. The dosage composition of claim 1 wherein said cellulosic polymer of said dispersion is an ionizable cellulosic polymer.

5. The dosage composition of claim 2 or 4 wherein said ionizable cellulosic polymer of said dispersion has an alkylate substituent and an ester-linked carboxylic acid substituent.

6. The dosage composition of claim 3 or 5 wherein said alkylate substituent is selected from the group consisting of acetate, propionate, and butyrate and the degree of substitution for said alkylate substituent is at least 0.1.

7. The dosage composition of claim 3 or 5 wherein said ester-linked carboxylic acid substituent is selected from the group consisting of phthalate, trimellitate, succinate, terephthalate, and isophthalate and the degree of substitution for said ester-linked carboxylic acid substituent is at least 0.1.

8. The dosage composition of any one of claims 2-4 wherein said ionizable cellulosic polymer of said dispersion is selected from the group consisting of hydroxyethylmethylcellulose acetate phthalate, hydroxyethylmethylcellulose acetate succinate, hydroxypropylcellulose acetate phthalate, hydroxypropylcellulose acetate succinate, hydroxypropylmethylcellulose acetate phthalate, hydroxypropylmethylcellulose acetate succinate, hydroxypropylmethylcellulose acetate trimellitate, hydroxypropylcellulose butyrate phthalate, cellulose acetate phthalate, methylcellulose acetate phthalate, cellulose acetate trimelliate, cellulose acetate terephthalate, cellulose acetate isophthalate, cellulose propionate phthalate, cellulose propionate trimellitate and cellulose butyrate trimellitate.

9. The dosage composition of any one of claims 2-4 wherein said ionizable cellulosic polymer of said dispersion is selected from the group consisting of

cellulose acetate phthalate, cellulose acetate trimellitate and hydroxypropylmethylcellulose acetate succinate.

10. The dosage composition of claims 2 or 3 wherein said polymeric matrix comprises a second ionizable cellulosic polymer.

11. The dosage composition of claim 1 wherein said aqueous-soluble cellulosic polymer is selected from the group consisting of methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxyethylmethylcellulose and hydroxypropylmethylcellulose.

12. The dosage composition of claim 4 wherein said aqueous-soluble cellulosic polymer is selected from the group consisting of methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxyethylmethylcellulose and hydroxypropylmethylcellulose.

13. The dosage composition of claims 1 or 3 wherein substantially all of said drug is substantially amorphous.

14. The dosage composition of claims 1 or 3 wherein essentially all of said drug is substantially amorphous.

15. The dosage composition of claims 2 or 3 wherein said erodible polymeric matrix is formed from a polymer selected from the group consisting of polyoxamers; aqueous-soluble cellulosics; aqueous-erodible cellulosics; acrylic acid derivatives and polymers of the same; naturally occurring polysaccharides and derivatives thereof; and naturally occurring proteins.

16. The dosage composition of claim 15 wherein said erodible polymeric matrix is formed from a polymer selected from the group consisting of aqueous-soluble cellulosics; aqueous-erodible cellulosics; and naturally occurring polysaccharides and derivatives thereof.

17. The dosage composition of claim 16 wherein said erodible polymeric matrix is formed from a polymer selected from the group consisting of methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxyethylmethylcellulose and hydroxypropylmethylcellulose.

18. The dosage composition of any one of claims 1-3 wherein said polymeric matrix is coated with a pH-sensitive polymer to delay the release of said drug.

19. The dosage composition of claim 18 wherein said pH-sensitive polymer is selected from the group consisting of amylose acetate phthalate, cellulose acetate phthalate and its sodium salt, cellulose ester phthalates, cellulose ether phthalates, hydroxypropylcellulose phthalate, hydroxypropylethylcellulose phthalate, hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose acetate succinate, methylcellulose phthalate, polyvinyl acetate phthalate, polyvinyl acetate hydrogen phthalate, starch acid phthalate, cellulose acetate trimellitate, styrene-maleic acid dibutyl phthalate copolymer, styrene-maleic acid/polyvinylacetate phthalate copolymer, styrene and maleic acid copolymers, acrylic acid and acrylic ester copolymers, polymethacrylic acid and esters thereof, polyacrylic and methacrylic acid copolymers, shellac, and vinyl acetate and crotonic acid copolymers.

20. The dosage composition of claim 18 wherein said pH-sensitive polymer is selected from the group

consisting of cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose acetate succinate, anionic acrylic copolymers of methacrylic acid and methylmethacrylate, and copolymers comprising acrylic acid and at least one acrylic acid ester.

21. The dosage composition of claim 18 wherein said coating further comprises at least one non-pH-sensitive polymer to modulate either the delay of release or the rate of release of said drug.

22. The dosage composition of any one of claims 1-3 in a form selected from the group consisting of a tablet, a caplet, a capsule, a bead, a sachet, a multiparticulate and combinations thereof.

23. The dosage composition of any one of claims 1-3 wherein said dispersion includes a solubility-enhancing agent.

24. The dosage composition of claim 23 wherein said solubility-enhancing agent is selected from a group consisting of organic acids and organic acid salts; partial glycerides; glycerides; glyceride derivatives; polyethylene glycol esters; polypropylene glycol esters; polyhydric alcohol esters; sorbitan esters; carbonate salts; alkyl sulfonates; and cyclodextrins.

25. The dosage composition of any one of claims 1-3 wherein said dispersion is formed by spray-drying.

26. The dosage composition of claim 25 wherein said dispersion comprises said drug dispersed in hydroxypropylmethylcellulose acetate succinate.

27. The dosage composition of claim 25 wherein, prior to formation of said dispersion, said drug in its pure state is amorphous.

28. The dosage composition of claim 25 wherein, prior to formation of said dispersion, said drug in its pure state is crystalline.

29. The dosage composition of any one of claims 1-3 wherein said dispersion includes excipients.

30. The dosage composition of claim 29 wherein said excipients are selected from the group consisting of surfactants, aqueous-soluble polymers, pH modifiers, fillers, binders, pigments, lubricants, antioxidants and flavorants.

31. The dosage composition of any one of claims 1-3 wherein said drug is selected from the group consisting of an anti-hypertensive, an antianxiety agent, an anticlotting agent, a blood glucose-lowering agent, a decongestant, an antihistamine, an antitussive, an anti-inflammatory, an antipsychotic agent, a cognitive enhancer, a cholesterol-reducing agent, an antiobesity agent, an autoimmune disorders agent, a hypnotic agent, an anti-Parkinsonism agent, an antibiotic agent, an antiviral agent, an anti-impotence agent, an anti-neoplastic, a sedative, a barbiturate, a nutritional agent, a beta-blocker, an emetic, an anti-emetic, a diuretic, an anticoagulant, a cardiotonic, an androgen, a corticoid, an anabolic agent, an anti-depression agent, an anti-infective agent, a coronary vasodilator, a carbonic anhydrase inhibitor, an antifungal, an antiprotozoal, a gastrointestinal agent, a dopaminergic agent, an anti-Alzheimer's Disease agent, an anti-ulcer agent, a platelet inhibitor, and a glycogen phosphorylase inhibitor.

32. The dosage composition of claim 31 wherein said drug is an antihypertensive selected from the group consisting of prazosin, nifedipine, trimazosin and doxazosin.

33. The dosage composition of claim 31 wherein said drug is an antianxiety agent selected from the group consisting of fluoextine, pyroxidine, sertraline, venlafaxine, [3,6-dimethyl-2-(2,3,6-trimethylphenoxy)-pyridi-4-yl]-(1-ethylpropyl)-amine and 3,5-dimethyl-4(3'-pentoxy)-2-(2',4',6'-trimethylphenoxy)pyridine.

34. The dosage composition of claim 31 wherein said drug is the antipsychotic agent selected from the group consisting of ziprasidone and its pharmaceutically acceptable salts.

35. The dosage composition of claim 31 wherein said drug is the anti-impotence agent selected from the group consisting of sildenafil and its pharmaceutically acceptable salts.

36. The dosage composition of claim 31 wherein said drug is the blood glucose-lowering agent glipizide.

37. The dosage composition of claim 31 wherein said drug is a glycogen phosphorylase inhibitor selected from the group consisting of [R-(R*,S*)]-5-chloro-N-[2-hydroxy-3-[methoxymethylamino)-3-oxo-1-(phenylmethyl)propyl)propyl]-1H-indole-2-carboxamide and 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-3-(3R,4S)-dihydroxypyrrolidin-1-yl-)-(2R)-hydroxy-3-oxypropyl]amide.

38. The dosage composition of any one of claims 1-3 wherein said dosage composition provides a maximum concentration of said drug in an aqueous *in vitro* test

which is at least 1.5-fold that achieved by an identical dosage composition containing the same quantity of drug in an undispersed state.

39. The dosage composition of any one of claims 1-3 wherein, when orally dosed to a mammal, said dosage composition provides a maximum concentration of said drug in the blood which is at least 1.25-fold that achieved by an identical dosage composition containing the same quantity of drug in an undispersed state.

40. The dosage composition of any one of claims 1-3 wherein, when orally dosed to a mammal, said dosage composition provides an area under the blood drug concentration vs. time plot of said drug which is at least 1.25-fold that achieved by an identical dosage composition containing the same quantity of drug in an undispersed state.

41. The dosage composition of claim 1 wherein, in an aqueous use environment, said dosage composition provides an area under the drug concentration versus time plot that is at least 1.25-fold that of a control dosage composition that is identical except that said polymeric matrix comprises polyethylene oxide having a molecular weight such that the time to release 50% of said drug from said control is greater than 80% but less than 120% the time to release 50% of said drug from said dosage composition.

42. Use of a controlled release dosage composition of any one of claims 1-41 for treating a disease or disorder in a mammal.

FIG. 1

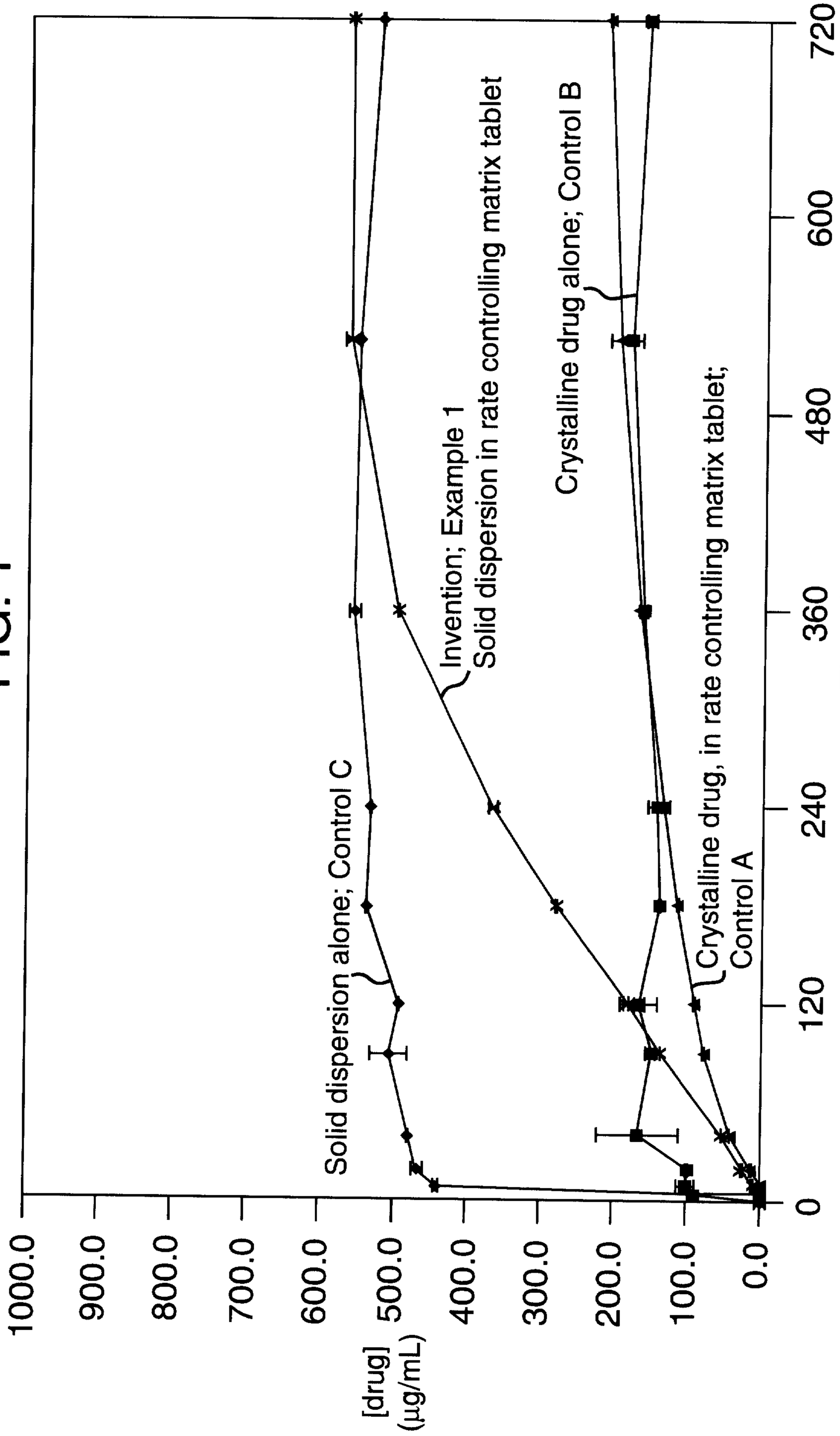

[drug] (µg/mL)
1000.0
900.0
800.0
700.0
600.0
500.0
400.0
300.0
200.0
100.0
0.0
0
120
240
360
480
600
720
Time (min)
Solid dispersion alone; Control C
Invention; Example 1
Solid dispersion in rate controlling matrix tablet
Crystalline drug alone; Control B
Crystalline drug, in rate controlling matrix tablet; Control A

FIG. 2

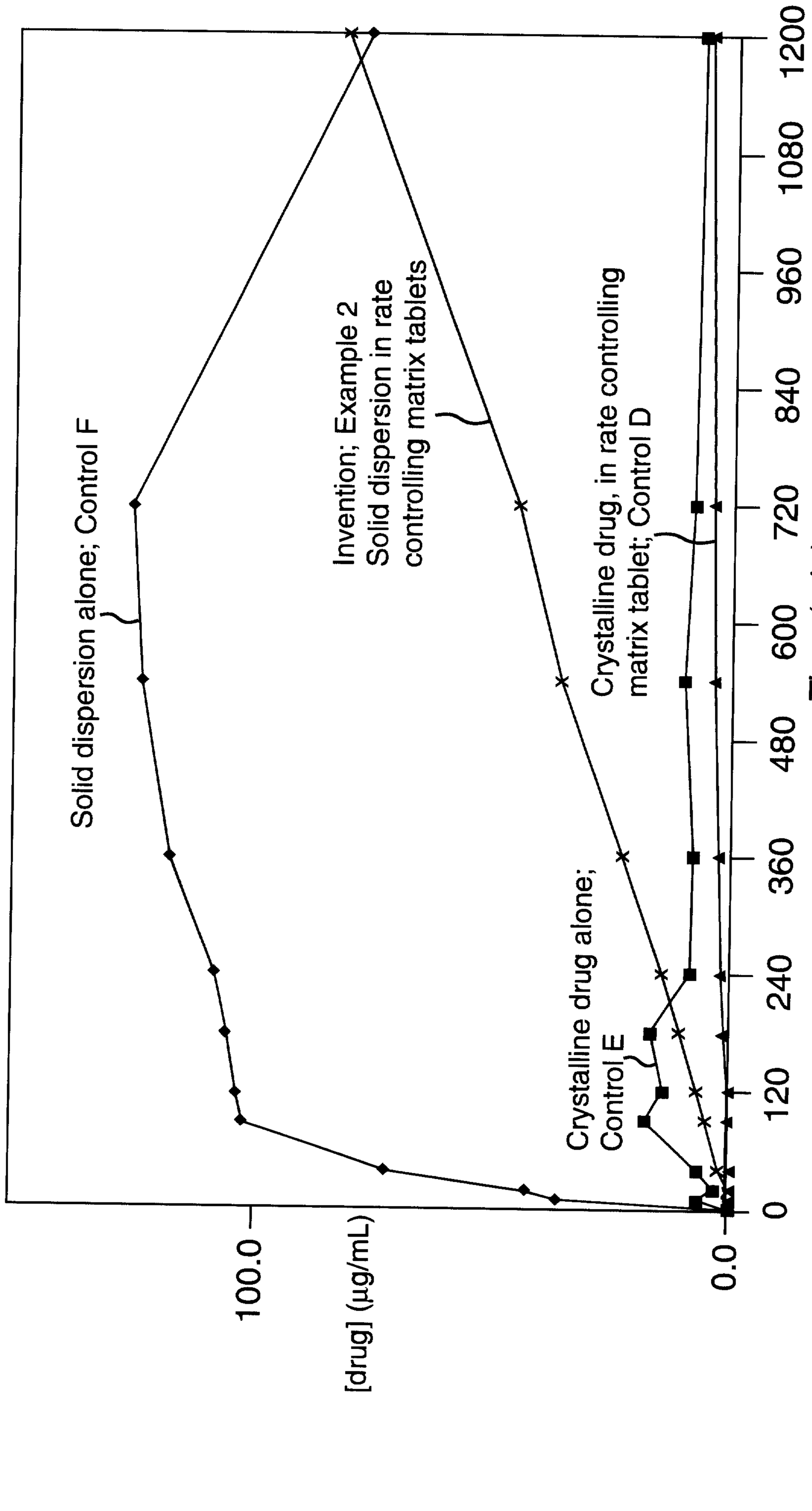

Solid dispersion alone; Control F
Invention; Example 2
Solid dispersion in rate
controlling matrix tablets
Crystalline drug, in rate controlling
matrix tablet; Control D
Crystalline drug alone;
Control E
100.0
0.0
[drug] (µg/mL)
0
120
240
360
480
600
720
840
960
1080
1200
Time (min)

FIG. 3

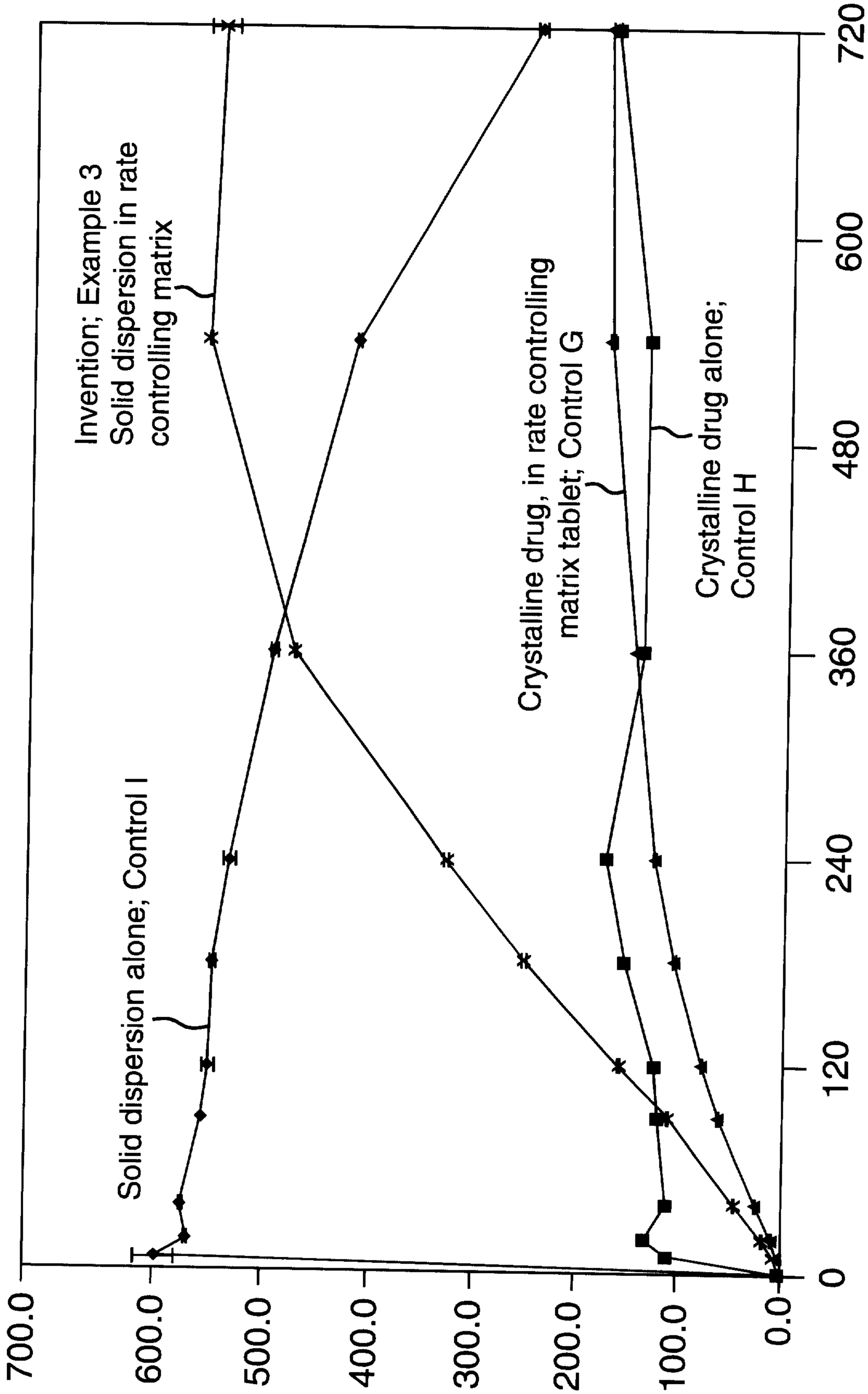
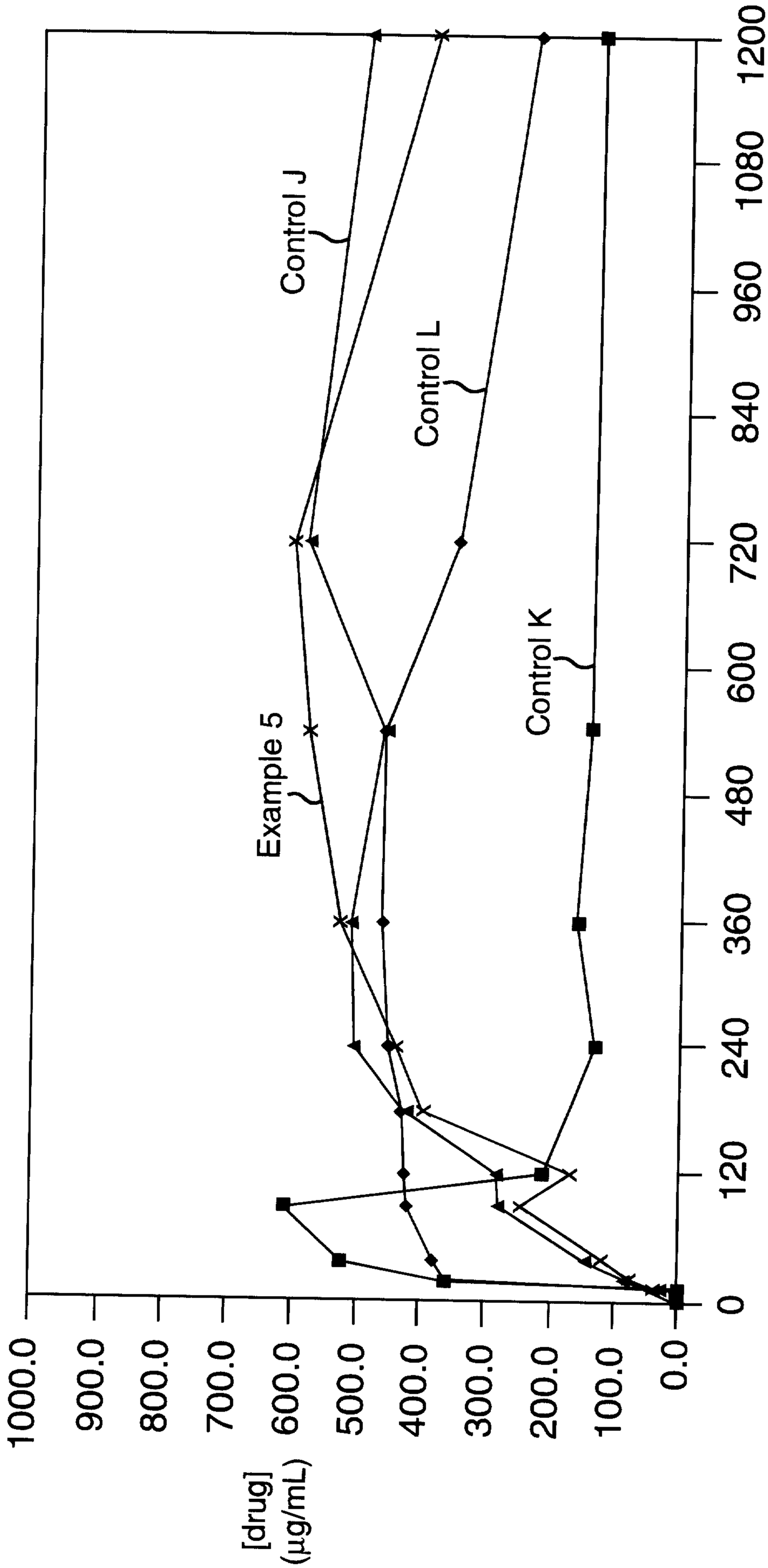
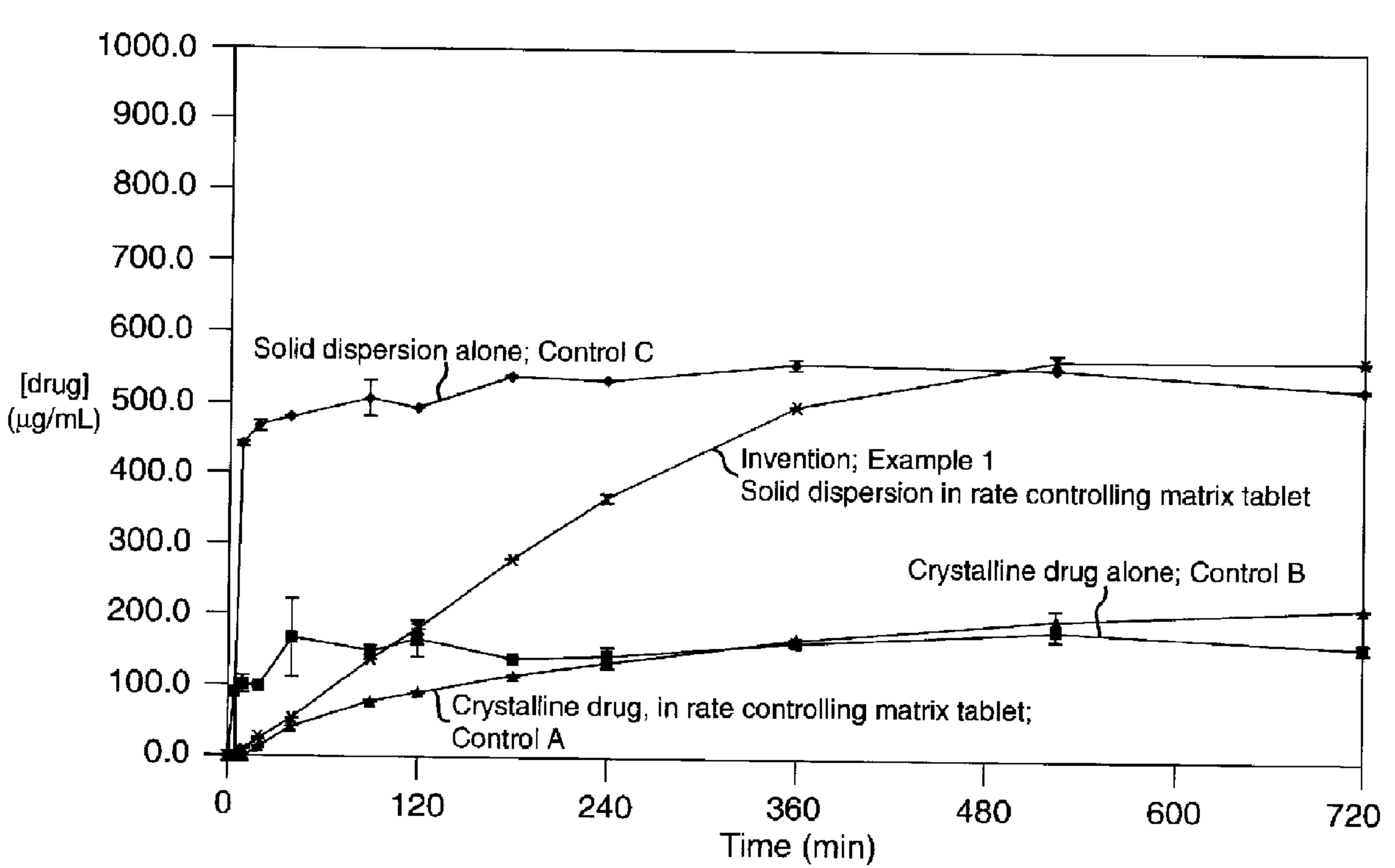

Solid dispersion alone; Control I
Invention; Example 3 Solid dispersion in rate controlling matrix
Crystalline drug, in rate controlling matrix tablet; Control G
Crystalline drug alone; Control H
[drug] (µg/mL)
Time (min)
700.0
600.0
500.0
400.0
300.0
200.0
100.0
0.0
0
120
240
360
480
600
720

FIG. 4


Control J
Example 5
Control L
Control K
Time (min)
[drug] (µg/mL)
0
120
240
360
480
600
720
840
960
1080
1200
0.0
100.0
200.0
300.0
400.0
500.0
600.0
700.0
800.0
900.0
1000.0


1000.0
900.0
800.0
700.0
600.0
500.0
400.0
300.0
200.0
100.0
0.0
[drug]
(µg/mL)
Solid dispersion alone; Control C
Invention; Example 1
Solid dispersion in rate controlling matrix tablet
Crystalline drug alone; Control B
Crystalline drug, in rate controlling matrix tablet;
Control A
0
120
240
360
480
600
720
Time (min)