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(54) Title: PHARMACEUTICAL SAFETY DOSAGE FORMS

(57) Abstract: Pharmaceutical safety dosage forms are provided which include a pharmaceutical and an antagonist to the pharmaceutical. The safety dosage forms are such that the antagonist has no significant bioavailability when the pharmaceutical safety dosage form is administered as intended. However, the antagonist is released and becomes bioavailable if the dosage form is disrupted. Methods of administering pharmaceuticals by providing pharmaceutical safety dosage forms are also provided.

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PHARMACEUTICAL SAFETY DOSAGE FORMS

Related Cases

[0001] This application claims priority to U.S. Serial No. 10/339,977, filed on January 10, 2003, entitled "Pharmaceutical Safety Dosage Forms".

Field Of The Invention

[0002] The present invention relates to the field of pharmaceutical safety dosage forms.

Background Of The Invention

[0003] Many pharmaceuticals are prone or potentially subject to misuse or abuse when the intended dosing instructions are ignored and/or the written instructions are disregarded. For example, it is well known that sustained-release narcotics, such as OXYCONTIN® ER tablets (supplied by Perdue Pharma), are prone to abuse and misuse when their dosage units are broken, chewed, crushed, dissolved, or otherwise disrupted, rather than being taken whole as intended. Other narcotic and analgesic drugs are liable to similar misuse. Other types of drugs, including those which are not amenable to abuse, may, nonetheless, be inappropriately used. Such inappropriate use can lead to adverse reactions in

persons so using the drugs and can give rise to adverse reactions and even death. One example of this is the inappropriate use of metformin sustained-release (e.g., GLUCOPHAGE® XR, metformin hydrochloride extended-release tablets supplied by Bristol-Myers Squibb), a common diabetes drug. If metformin sustained-release is chewed, or the tablets otherwise disrupted prior to ingestion, rather than the tablets being swallowed whole, dangerous lowering of a person's blood glucose level may result. Very large numbers of pharmaceuticals may be inappropriately ingested in this way and a method for reducing or eliminating the undesired effects has long been desired.

[0004] Many pharmaceutical products, which have been introduced into the pharmaceutical market in an immediate-release tablet or capsule form, have subsequently been reformulated into a sustained-release form. The sustained-release form has provided the advantages of more convenient dosing schedules, increased patient compliance, more even blood levels, improved therapeutic activity, or others. Typically, the dosage of active pharmaceutical ingredient in these sustained-release formulations is greater than the dosage of the corresponding immediate-release formulation. This presents the danger of "dumping" in which the sustained-release mechanism fails, either intentionally or unintentionally, so that potentially dangerous dosages of the active pharmaceutical ingredient (agonist) are delivered to the patient causing dangerously high blood levels of the agonist. For example, the *Physicians' Desk Reference (PDR)*, 56th Edition, states for GLUCOTROL® XL Extended Release Tablets (supplied by Pfizer), under "Information for Patients", that "Patients should be informed that GLUCOTROL XL Extended Release Tablets should be swallowed whole. Patients should not chew, divide, or crush tablets." For the product RITALIN-SR® (supplied by Novartis) under "DOSAGE AND ADMINISTRATION", it is written, "Ritalin-SR tablets must be swallowed whole and never crushed or chewed." For OXYCONTIN® ER tablets (supplied by Perdue Pharma) there has been much recent controversy and numerous

published reports of narcotic abuse through mechanical disruption of the sustained-release mechanism thereby enabling the abuser to receive a relatively larger immediate dose of narcotic.

[0005] Some attempts at providing dosage forms for preventing abuse of narcotics have been offered by the prior art. For example, U.S. Patent No. 4,457,933, Gordon et al., discusses both oral and parenteral abuse of strong analgesics, such as oxycodone, propoxyphene and pentazocine. Gordon et al. discuss oral administration of compositions containing specific ratios of oxycodone to naloxone, a narcotic antagonist. According to Gordon et al., the antagonist, naloxone, is supplied in an amount to deter either oral or parenteral abuse of an analgesic without substantially affecting the analgesic activity. Gordon et al., therefore, contemplates that the antagonist be absorbed into the blood in normal use along with the analgesic.

[0006] U.S. Patent No. 5,375,957 in the name of Kaiko et al. recognizes that oral and parenteral abuse of oral opioid formulations can occur by self-administration of more than the prescribed oral dosage. Kaiko et al. discusses an appropriate ratio between analgesic agonist and antagonist in such dosage forms to ensure analgesic efficacy is maintained. Thus, Kaiko et al. contemplates that the antagonist be absorbed into the blood in normal use along with the agonist. Kaiko et al. distinguishes itself over prior art that teaches inclusion of antagonists in oral opioid analgesic dosage forms, which are themselves not orally active, but which counteract the analgesic effects of the opioid upon parenteral administration. As an example, Kaiko et al. describes the commercially available combination of pentazocine and naloxone, wherein the amount of naloxone does not interfere with the pentazocine upon oral administration. As such, it is understood that the antagonist would still be absorbed into the blood in normal use along with the agonist, but would not provide any pharmacological activity.

[0007] Pharmaceutical dosage forms that permit absorption into the blood of an antagonist are inefficient because of the resulting potential to hinder the activity of the agonist during normal use. This limits the amount of antagonist that can be used. This also limits the potential amount of antagonist activity that can be incorporated into the dosage form to less than the amount of activity that will substantially inhibit the agonist activity. Even if, as in Gordon et al., the antagonist, naloxone, can be present in amounts that are not orally active, this may not be possible or desirable with antagonists for other drugs. Also, even if the antagonist is not orally active, it may still be absorbed by the blood and impact the patient during normal use of the dosage form. Additionally, as in Gordon et al., if the antagonist is inactive with oral use then it cannot provide protection against dumping of the agonist if the sustained-release tablet is mechanically disrupted. Furthermore, lack of oral activity may not deter oral abuse.

[0008] There remains a great need for dosage forms which can minimize or eliminate the effects of abusive or otherwise inappropriate use of pharmaceuticals. A need exists for dosage forms which may be employed for the delivery of a wide range of drugs and which do not require the coadministration of a separate second pharmaceutically active dosage unit in addition to the desired pharmaceutical. Dosage forms which ensure the safe administration of drugs without unnecessarily loading the bloodstream of a person taking the drug with additional dosage units are objects of this invention. A further object is to provide dosage forms which block an avenue of abusive value to a person in possession of the dosage unit. Other objects will become apparent from a review of the present specification.

Summary Of The Invention

[0009] Pharmaceutical safety dosage forms are provided by the present invention. Such pharmaceutical safety dosage forms include a pharmaceutical as well as an antagonist for the pharmaceutical. In normal use, that is when the dosage forms are administered or

taken by the person in need of drug treatment, the antagonist has no significant bioavailability. The antagonist has significant bioavailability only when the pharmaceutical safety dosage form is disrupted. Disruption of the dosage form means in this context the mechanical, chemical or other alteration of the dosage form in such a fashion as to release or make biologically available the antagonist. Disruption does not mean the dissolution of the dosage form or its delivery of the pharmaceutical in accordance with the intended mechanism of use of the dosage form.

[0010] The pharmaceutical safety dosage forms of the present invention can be administered orally, parenterally, rectally, vaginally, transdermally, via aerosol, via nasal spray, or otherwise such as via implantation. In connection with each route of administration, a normal mechanism of delivery of the pharmaceutical is intended consistent with good medical and pharmaceutical practices. Delivery of the pharmaceutical in any of these intended ways for the dosage forms of the invention does not deliver a substantial amount of the antagonist into the bloodstream. Rather, the antagonist is maintained in such a way as not to be substantially bioavailable via such intended method of administration. In short, it is intended that the antagonist "pass through" the patient and be substantially eliminated thereby. Thus, the antagonist is intended not to become bioavailable to the patient and not to require systemic inactivation or excretion therefrom. The overall loading of active compounds is, thus, minimized and limited to only the intended pharmaceutical when the dosage form is used as intended.

[0011] The present invention generally contemplates placing one or more antagonist pharmaceutical products within the dosage formulation of the agonist pharmaceutical product so that, under normal conditions, the antagonist is substantially not bioavailable. However, disruption of the formulation, through any of a variety of means, will release the antagonist thereby diminishing the effects of the agonist. For example, for the case of OXYCONTIN®

(supplied by Perdue Pharma) Extended Release tablets abuse, narcotic abusers are crushing the tablets to disrupt the sustained-release mechanism thereby gaining a large immediate dose of narcotic. This invention contemplates, in one example, placing a narcotic antagonist in coated beads in OXYCONTIN® (supplied by Perdue Pharma) Extended Release tablets for which the coating maintains the beads intact throughout the digestive system, under normal use, thereby blocking any significant bioavailability of the antagonist. However, when the narcotic abuser crushes the tablets, the abuser will also crush the beads thereby exposing the antagonist within the beads to dissolution in the gastrointestinal tract thereby facilitating bioavailability of the antagonist. There are numerous such examples including, but not limited to, the following: blood glucose lowering drugs such as metformin (e.g., GLUCOPHAGE® XR supplied by Bristol-Myers Squibb) or glipizide (e.g., GLUCOTROL XL® Extended Release Tablets supplied by Pfizer) containing beads of a hyperglycemic agent such as epinepherine or others; anti-hypertensive drugs such as propranolol (e.g., INDERAL® LA Long-Acting capsules supplied by Wyeth-Ayerst), metoprolol (e.g., TOPROL-XL® supplied by AstraZeneca), nifedipine (e.g., PROCARDIA XL® Extended Release tablets supplied by Pfizer, ADALAT® CC supplied by Bayer), diltiazem (e.g., CARDIZEM® CD supplied by Biovail), or nisoldipine (e.g., SULAR® supplied by AstraZeneca) containing beads of antagonist sympathomimetic drugs such as epinepherine or others; methylphenidate (e.g., RITALIN-SR® tablets supplied by Novartis) containing an adrenergic beta blocking drug in beads; any antihistamine with a sympathomimetic decongestant such as cetirizine HCl/pseudoephedrine HCl (e.g., ZYRTEC-D 12Hour™ Extended Relief tablets supplied by Pfizer), fexofenadine HCl/pseudoephedrine HCl (ALLEGRA-D® Extended-Release tablets supplied by Aventis), or others containing beads containing one or more adrenergic beta receptor blocker drugs; any sustained-release drug

could contain an emetic agent within the normally non-bioavailable beads; and numerous other possibilities.

[0012] In all of these cases, the effects of the dumping of the active ingredient, whether through intentional abuse, unintentional misuse, or other mechanism could be offset by the resultant release of the antagonist thereby undermining the motivation for abuse or protecting the patient against the harmful effects of dumping of the intended dose.

Brief Description Of The Drawings

[0013] Figure 1 shows a dosage form of the invention containing pluralities of microdosage forms.

[0014] Figure 1A depicts two different types of bead types of microdosage forms.

[0015] Figure 1B shows a multi–layered bead for use in one embodiment of the invention.

[0016] Figure 2 depicts an osmotic drug dosage form in accordance with the invention.

[0017] Figure 3 shows a dosage form of the invention containing microdosage forms and particulated forms.

[0018] Figure 4 shows a dosage form of the invention containing two different types of microdosage forms.

[0019] In accordance with the invention, antagonist is delivered from the dosage form, (i.e., becomes bioavailable), only when the dosage form is physically or otherwise disrupted through use in a manner not intended by the drug manufacturer. For example, by reference to only one type of pharmaceutical, with oxycodone sustained-release, for which the present dosage forms are applicable, in normal use, the oxycodone is delivered over a period of time to a patient ingesting a dosage form so as to provide extended narcotic effect to such patient. An antagonist for the narcotic, naloxone, is present in the dosage form, but is

not released from the dosage form; it does not become bioavailable, in normal use. However, if the oxycodone dosage form is disrupted, e.g. physically comminuted, in an attempt to release immediately the entire amount of the narcotic in order to abuse the drug, the antagonist, naloxone, is also released. The naloxone is preferably present in an amount sufficient to interfere with the narcotic effect of the oxycodone, thus frustrating the attempted abuse of the drug.

[0020] The present dosage forms are amenable to the delivery of a wide variety of narcotic and non-narcotic drugs in a manner having improved safety. The only requirement is a practical one. Thus, a drug which is capable of abuse or of significant adverse effect if inappropriately ingested during or following disruption of the dosage form must be one which has an antagonist. In this context, an antagonist is preferably a compound or composition which is capable of interfering or negating all or some of the effects of the therapeutic drug. This may be achieved either biochemically, physically, physiologically, or otherwise. Thus, while the exemplary narcotic antagonist, naloxone, operates biochemically, it is believed, through interfering with a biochemical (receptor) pathway for narcotics, an effective antagonist, in the context of this invention, may act otherwise, e.g. through stimulation of an excretion or breakdown mechanism for the drug. The mechanism of action of antagonists which may be employed herein is not intended to be limiting in any way. Any compound, group of compounds or composition which can interfere effectively with the action of a drug may be considered to be an antagonist for the drug, providing the overall objectives of this invention are met.

[0021] While physical disruption of dosage forms, e.g. comminution or "grinding them up," is an important path undertaken for the abuse or inappropriate use of drugs, non-physical means may also be employed. Thus, dissolution in solvent systems in order to extract drug may be performed. It is preferred that the dosage forms of the present invention

release their antagonist component when subjected to such solvent action if the particular intended activity of the antagonist is to counteract the effects of this solvent disruption. Conceivably, a dosage form could be melted or sublimed to release a drug. In such cases, it may be preferred that dosage forms be available which can release antagonist under such conditions if this is the particular activity that is intended to be counteracted by inclusion of the antagonist in the dosage form. The antagonist can be formulated to protect against one or more such disruption activities.

[0022] Many pharmaceuticals are provided in capsule dosage forms containing within them microdosage forms. One embodiment of the present invention provides a pharmaceutical and an antagonist for the pharmaceutical in a dosage form where each is contained within microdosage forms, e.g., coated beads, mini tablets, and tablets. Thus, for example, the beads containing the drug are coated or formulated so as to release the drug on an intended time profile. The beads containing the antagonist, however, are either formulated or coated so as to prevent significant bioavailability of the antagonist when the dosage form is consumed as intended. Specific coatings which can attain the foregoing objectives are numerous and well-known to pharmaceutical chemists and formulators. Their identity and use in achieving coatings or formulations in accordance with the present requirements are not a central part of this invention and it is to be understood that all such coatings and formulations are comprehended hereby. It is understood, for example, that it may be desirable in some formulations to use only a single coating, whereas it may be desirable in other formulations to use multiple coatings, and the embodiments of the present invention are not intended to be limited thereby.

[0023] An exemplary, but by no means exhaustive, compilation of coatings and formulations for solid dosage forms, and the like is contained within *Remington: The Science and Practice of Pharmacy* by Alfonso R. Gennar, editor, (19th edition 2000) (Chapters 45-

46) and *Pharmaceutical Dosage Forms and Drug Delivery Systems* by Howard C. Ansel, et al. (Chapters 6-7), each incorporated herein by reference to provide guidance on such technologies.

[0024] An exemplary dosage form employing beads in accordance with the foregoing discussion is presented in Figure 1. Figure 1 depicts a conventional capsule dosage form comprising a shell, 10 and containing pluralities of microdosage forms, e.g. beads, 12. There are preferably at least two different kinds of beads, beads (or other microdosage forms) containing the drug and beads (or other microdosage forms) containing antagonist. The drug–containing beads are formulated so as to release drug when administered to a patient in accordance with conventional practice. The antagonist–containing beads are formulated so as not to deliver antagonist to a patient in normal use. Thus, for example, as shown in Figure 1A, beads 16 can represent a formulated drug 24 within a saccharide, polymer, or other matrix designed to deliver the drug, e.g. in the small intestine of a patient. Another type of bead 14 comprises antagonist for the drug 20 coated by coating 22 the whole being formulated to resist antagonist delivery until all beads are eliminated from the patient, e.g. in the stool. As discussed, however, the drug–containing beads may be coated and the antagonist not coated as may be desired by the routineer in the art. Moreover, three or more different types of beads may be employed, for example, when extended-release of drug is desired or there are different active ingredients. As stated, the preparation of diverse types of beads and the use of a wide variety of coatings and formulation components is an advanced art and is well known to persons skilled in drug formulation. All such may find utility herein.

[0025] A further exemplification of the invention is shown in Figure 1B. The figure depicts a multi-layer microdosage form or bead 30. Drug 32 is coated by coating 34 designed to deliver the drug to a patient at a desired time and in a desired location, e.g. the stomach. The whole, in this embodiment, preferably surrounds a formulation of antagonist 36 for the

drug which is so formulated as not to release antagonist when ingested under normal conditions. Thus, the antagonist is designed to pass through the body of the patient unabsorbed.

[0026] If any of these exemplary embodiments are subjected to physical disruption, e.g. by being ground up, both the drug and the antagonist are likely to be released. The dosage forms are, thus, less amenable to abuse if crushed or chewed by a patient. Furthermore, such dosage forms provide protection against unexpected dosing upon crushing or chewing because the patient will receive both the unexpected dosing and the antagonist which will diminish the effect of the unexpected dosage. Increased resistance to abuse and overdose result.

[0027] Another exemplary dosage form using different types of microdosage forms is shown in Figure 4. Figure 4 presents a conventional capsule dosage form comprising a shell 70, and containing two different types of microdosage forms, e.g., tablets 74 and beads 78. It is understood that neither the drug nor its antagonist are limited to certain microdosage forms. Thus, in one instance, a drug 72 may be contained in tablets 74 which are formulated for time-release, and its antagonist 76 may be contained in beads 78 formulated or coated to not deliver the antagonist during normal use of the dosage form. On the other hand, it is possible that the drug may be contained in beads formulated for time-release and its antagonist may be contained in tablets coated to prevent significant bioavailability when the dosage form is used as intended.

[0028] Many pharmaceuticals are also provided in tabletted or capsule dosage forms comprising some particulated forms of ingredients. A further embodiment of the present invention comprises a drug in the form of a powder, in an amorphous form or with one or more polymorphs, in tabletable form together with antagonist in a microdosage form such that it is substantially insoluble in gastric or other fluid. Thus, for example, a powdered drug,

along with excipients, such as fillers, binders, disintegration agents, lubricants, colorants, or other conventional adjuvants, is combined with one or more beads, mini tablets, powder, or other forms containing antagonist. The antagonist forms are formulated or coated in such a way as to render them substantially insoluble in the gastrointestinal tract or other locus of administration. An antagonist that is substantially insoluble in the human body, for example, is prevented from being released before the antagonist is excreted from the body. It is understood in the art that powders can be formulated so as to prevent dissolution in bodily fluids and/or prevent significant bioavailability. Solubility of polymorphs or solvates, for example, are dependent on the crystallized structure of the molecules, and thus, have different solubilities. Hence, certain polymorphs or solvates may be insoluble in the body, but readily soluble in specific solvents. The preparation of polymorphs or solvates are discussed by numerous patents on numerous molecules, e.g. U.S. Patent Nos. 6,472,563; 6,440,459; 6,337,422; 6,133,289; and 5,900,423. Also contemplated is using one or more polymorphic or solvate forms of one or more antagonists wherein the utilized polymorphic or solvate forms are not readily bioavailable under normal use.

[0029] In Figure 3, a tabletted dosage form in accordance with one embodiment of the invention is provided. The tabletted dosage form 60 is formed from powdered drug 62 together with conventional adjuvants, such as excipients and the like. Beads, mini tablets, or the like 64 comprising antagonist for the drug 66 are included within the tablet. Other variations of such tabletted dosage forms may also be employed. It is understood that neither the drug nor its antagonist are limited to certain particulated forms or microdosage forms. Thus, a drug may be present in time-release powder form and its antagonist may be present as a polymorph which is insoluble in the body, but readily soluble in specific solvents. Furthermore, pharmaceutical safety dosage forms themselves are not limited in the types of microdosage forms or particulated forms contained therein. As such, a conventional capsule

dosage form, for example, may contain a drug in time-release powdered form and an antagonist to the drug in tabletted form, shellacked to prevent bioavailability upon normal use of the dosage form.

[0030] A further dosage form in accordance with this invention is depicted in Figure 2. This is a type of osmotic pump drug delivery dosage form 40. Thus, a shell 41 contains a compartment containing drug 42 as well as a compartment containing an osmotic agent 50. The two compartments are preferably separated by a piston 48. Preferably, both the drug–containing compartment and the osmotic agent–containing compartment have an orifice sealed by plugs 46 and 52, respectively. Upon administration, such as oral administration, the plugs 46 and 52 dissolve, exposing both the drug–containing compartment and the osmotic agent–containing compartment to body fluid. Absorption of water by the osmotic agent with concomitant swelling pushes upon the piston 48, expelling the drug through the orifice to its compartment. The geometry of the dosage form, orifice sizes, identity of the drug and osmotic agent and other factors are typically designed and optimized for a desired delivery location and timing. The art of osmotic drug delivery is relatively mature and an extensive patent literature has arisen. Moreover, commercial sources for such dosage forms are available, e.g. the Alza Corporation. One exemplary patent showing such dosage forms is U.S. patent 6,132,420.

[0031] The present invention may be applied to such osmotic drug dosage forms. In one embodiment, shown in Figure 2, a formulation of antagonist, 54 surrounds the dosage form. In view of the importance of the orifices to operation of the dosage form, the antagonist formulation is generally kept away from those orifices as shown. Since osmotic drug delivery vehicles may take a diversity of physical shapes, the shape and location of antagonist will reflect such geometry. While, as shown, the antagonist formulation is one which does not release antagonist to the body of a person correctly ingesting the dosage form,

it may also be coated if preferred to achieve a similar result. In any event, physical or other disruption of the dosage form will release the antagonist as well as the drug. Another example could be coated beads of the antagonist that reside in one or more compartments of the osmotic drug delivery vehicle.

[0032] Another aspect of the present invention is a method of administering pharmaceuticals by providing pharmaceutical safety dosage forms that include a pharmaceutical and an antagonist for the pharmaceutical where the microdosage forms provide insignificant bioavailability when the dosage form is administered as intended.

[0033] Insignificant bioavailability in the context of this invention is intended to mean that the antagonist does not interfere with the drug in a meaningful way and that the person to whom the dosage form is administered is not burdened with a significant loading of antagonist.

[0034] Drug dosage forms of this invention are preferably administered through the alimentary canal orally or anally. Delivery otherwise to the body from outside of the digestive tract, parenteral administration, may also benefit from this invention and employs, e.g. subcutaneous, intravenous, intravaginal, intramuscular, transdermal, nasal, aerosol, or other routes of administration.

[0035] The use of the present pharmaceutical safety dosage forms is directly applicable to administration of drugs prone to drug abuse, such as narcotics and amphetamines. One combination of agonist and antagonist contemplated by the present invention includes narcotics and narcotic antagonists. Examples of narcotics include, but are not limited to, codeine, oxycodone, propoxyphene, pentazocine, and derivatives thereof. Examples of narcotic antagonists include, but are not limited to, naloxone, nalmefene, and derivatives thereof. Another combination of agonist and antagonist is sympathomimetics, e.g. amphetamines, and adrenergic beta blockers. Sympathomimetic agonists along with

antihistamines can also be combined with adrenergic beta blockers. Reference to derivatives of chemicals discussed herein include, but are not limited to, chemical derivatives and salts and bases thereof.

[0036] Drugs which are not prone to abuse may also be administered using the safety dosage forms hereof. Thus, drugs intended for sustained-release in the body can give rise to unpleasant and undesired reactions if over-administered. Thus, the disruption of dosage forms containing, e.g. diabetes drugs, blood pressure lowering drugs and many other types of pharmaceuticals can give rise to diabetic shock or shock–inducing low blood pressure. Such conditions can be fatal. Examples of diabetes drugs include, but are not limited to, hypoglycemic agents, and examples of antagonists to hypoglycemic agents include, but are not limited to, hyperglycemic agents. Examples of blood pressure-lowering drugs include, but are not limited to, adrenergic beta blockers, calcium channel blockers, and ACE inhibitors. Examples of antagonists to blood pressure-lowering drugs include, but are not limited to, sympathomimetics. Including antagonists for these drugs as taught hereby can guard against accidental overdose, if, for example, sustained-release tablets are chewed.

[0037] Furthermore, in accordance with the present invention, dosage forms can include any pharmaceutical combined with an emetic agent, e.g., ipecac, which is released upon disruption of the dosage forms.

[0038] While not intended to be limiting, an exemplary list of drugs (as bases or any salts thereof) and their antagonists are set forth which may find utility through delivery via the safety dosage forms of this invention.

DRUG	ANTAGONIST
Codeine, Oxycodone, Propoxyphene, Pentazocine, Buprenorphine, Morphine, Oxymorphone	Naloxone, Nalmefene, Naltrexone
Methamphetamine, amphetamine, dextroamphetamine, methylphenidate	Propranolol, Atenolol, Metoprolol, or other adrenergic beta blocker
Insulin, Metformin, Glipizide	Epinepherine, Glucagon
Propranolol, Metoprolol, Nifedipine,	Dopamine, Epinepherine or other

Diltiazem, Nisoldipine, Timolol Maleate	sympathomimetic
Methylphenidate	Adrenergic beta blocker
Cetirizine HCl/pseudoephedrine HCl, fexofenadine HCl/pseudoephedrine HCl	Adrenergic beta blocker
Any drug	Ipecac or other emetic agent

[0039] Other aspects of the invention will be apparent from review of the present specification and claims and all such falling within the spirit of the invention are comprehended hereby.

What is Claimed is:

1. A pharmaceutical safety dosage form comprising a pharmaceutical and an antagonist for said pharmaceutical wherein said antagonist has significant bioavailability only when said pharmaceutical safety dosage form is disrupted.

2. The pharmaceutical safety dosage of claim 1 wherein said pharmaceutical is adapted for time-release, or said antagonist comprises an insoluble coating, or both.

3. The pharmaceutical safety dosage form of claim 1 wherein said bioavailability occurs upon mechanical disruption.

4. The pharmaceutical safety dosage form of claim 1 wherein said bioavailability occurs upon extraction by a chemical.

5. The pharmaceutical safety dosage form of claim 1 adapted to be administered orally.

6. The pharmaceutical safety dosage form of claim 1 adapted to be administered rectally, parenterally, vaginally, transdermally, intranasally, or via aerosol.

7. The pharmaceutical safety dosage form of claim 1 wherein said antagonist comprises an emetic agent.

8. The pharmaceutical safety dosage form of claim 7 wherein said emetic agent is ipecac or derivatives thereof.

9. The pharmaceutical safety dosage form of claim 1 wherein said pharmaceutical comprises a narcotic.

10. The pharmaceutical safety dosage form of claim 9 wherein said narcotic is codeine, oxycodone, propoxyphene, pentazocine, derivatives thereof, or combinations thereof.

11. The pharmaceutical safety dosage form of claim 9 wherein said antagonist is naloxone, nalmefene, derivatives thereof, or combinations thereof.

12. The pharmaceutical safety dosage form of claim 1 wherein said pharmaceutical comprises a sympathomimetic.

13. The pharmaceutical safety dosage form of claim 12 further comprising an antihistamine.

14. The pharmaceutical safety dosage form of claim 13 wherein said sympathomimetic is pseudoephedrine HCl or derivatives thereof, and said antihistamine is cetirizine HCl, fexofenadine HCl, derivatives thereof, or combinations thereof.

15. The pharmaceutical safety dosage form of claim 13 wherein said antagonist comprises an adrenergic beta blocker.

16. The pharmaceutical safety dosage form of claim 12 wherein said sympathomimetic comprises methylphenidate.

17. The pharmaceutical safety dosage form of claim 16 wherein said antagonist comprises an adrenergic beta blocker.

18. The pharmaceutical safety dosage form of claim 12 wherein said sympathomimetic comprises an amphetamine.

19. The pharmaceutical safety dosage form of claim 18 wherein said amphetamine is methamphetamine, amphetamine, dextroamphetamine, derivatives thereof, or combinations thereof.

20. The pharmaceutical safety dosage form of claim 18 wherein said antagonist comprises an adrenergic beta blocker.

21. The pharmaceutical safety dosage form of claim 20 wherein said adrenergic beta blocker is propranolol, atenolol, metoprolol, derivatives thereof, or combinations thereof.

22. The pharmaceutical safety dosage form of claim 1 wherein said pharmaceutical comprises a blood pressure-lowering medication.

23. The pharmaceutical safety dosage form of claim 22 wherein said blood pressure-lowering medication is an adrenergic beta blocker, a calcium channel blocker, or an ACE inhibitor.

24. The pharmaceutical safety dosage form of claim 23 wherein said blood pressure-lowering medication is propranolol, metoprolol, nifedipine, diltiazem, nisoldipine, timolol maleate, derivatives thereof, or combinations thereof.

25. The pharmaceutical safety dosage form of claim 22 wherein said antagonist comprises a sympathomimetic.

26. The pharmaceutical safety dosage form of claim 25 wherein said sympathomimetic is dopamine, epinepherine, derivatives thereof, or combinations thereof.

27. The pharmaceutical safety dosage form of claim 1 wherein said pharmaceutical comprises a hypoglycemic agent.

28. The pharmaceutical safety dosage form of claim 27 wherein said hypoglycemic agent is insulin, metformin, glipizide, glyburide, derivatives thereof, or combinations thereof.

29. The pharmaceutical safety dosage form of claim 27 wherein said antagonist comprises a hyperglycemic agent.

30. The pharmaceutical safety dosage form of claim 29 wherein said hyperglycemic agent is epinepherine, glucagon, derivatives thereof, or combinations thereof.

31. A pharmaceutical safety dosage form comprising a pharmaceutical contained within a first microdosage form, said first microdosage form being adapted for release of said pharmaceutical within a patient, together with an antagonist for said pharmaceutical, said antagonist being contained within a second microdosage form, said second microdosage form being substantially insoluble in gastric fluid.

32. The pharmaceutical safety dosage form of claim 31 wherein said pharmaceutical is adapted for time-release, or said second microdosage form comprises a coating which is substantially insoluble in gastric fluid, or both.

33. The pharmaceutical safety dosage form of claim 31 wherein said first microdosage form comprises beads, tablets, mini tablets, or combinations thereof; or second microdosage forms comprises beads, tablets, mini tablets, or combinations thereof; or both.

34. The pharmaceutical safety dosage form of claim 31 adapted to be administered orally.

35. The pharmaceutical safety dosage form of claim 31 adapted to be administered rectally, parenterally, vaginally, transdermally, intranasally, or via aerosol.

36. The pharmaceutical safety dosage form of claim 31 wherein said antagonist comprises an emetic agent.

37. The pharmaceutical safety dosage form of claim 36 wherein said emetic agent is ipecac or derivatives thereof.

38. The pharmaceutical safety dosage form of claim 31 wherein said pharmaceutical comprises a narcotic.

39. The pharmaceutical safety dosage form of claim 38 wherein said narcotic is codeine, oxycodone, propoxyphene, pentazocine, derivatives thereof, or combinations thereof.

40. The pharmaceutical safety dosage form of claim 38 wherein said antagonist is naloxone, nalmefene, derivatives thereof, or combinations thereof.

41. The pharmaceutical safety dosage form of claim 31 wherein said pharmaceutical comprises a sympathomimetic.

42. The pharmaceutical safety dosage form of claim 41 further comprising an antihistamine.

43. The pharmaceutical safety dosage form of claim 42 wherein said sympathomimetic is pseudoephedrine HCl or derivatives thereof, and said antihistamine is cetirizine HCl, fexofenadine HCl, derivatives thereof, or combinations thereof.

44. The pharmaceutical safety dosage form of claim 42 wherein said antagonist comprises an adrenergic beta blocker.

45. The pharmaceutical safety dosage form of claim 41 wherein said sympathomimetic comprises methylphenidate.

46. The pharmaceutical safety dosage form of claim 45 wherein said antagonist comprises an adrenergic beta blocker.

47. The pharmaceutical safety dosage form of claim 41 wherein said sympathomimetic comprises an amphetamine.

48. The pharmaceutical safety dosage form of claim 47 wherein said amphetamine is methamphetamine, amphetamine, dextroamphetamine, derivatives thereof, or combinations thereof.

49. The pharmaceutical safety dosage form of claim 47 wherein said antagonist comprises an adrenergic beta blocker.

50. The pharmaceutical safety dosage form of claim 49 wherein said adrenergic beta blocker is propranolol, atenolol, metoprolol, derivatives thereof, or combinations thereof.

51. The pharmaceutical safety dosage form of claim 31 wherein said pharmaceutical comprises a blood pressure-lowering medication.

52. The pharmaceutical safety dosage form of claim 51 wherein said blood pressure-lowering medication is an adrenergic beta blocker, a calcium channel blocker, or an ACE inhibitor.

53. The pharmaceutical safety dosage form of claim 52 wherein said blood pressure-lowering medication is propranolol, metoprolol, nifedipine, diltiazem, nisoldipine, timolol maleate, derivatives thereof, or combinations thereof.

54. The pharmaceutical safety dosage form of claim 51 wherein said antagonist comprises a sympathomimetic.

55. The pharmaceutical safety dosage form of claim 54 wherein said sympathomimetic is dopamine, epinepherine, derivatives thereof, or combinations thereof.

56. The pharmaceutical safety dosage form of claim 31 wherein said pharmaceutical comprises a hypoglycemic agent.

57. The pharmaceutical safety dosage form of claim 56 wherein said hypoglycemic agent is insulin, metformin, glipizide, glyburide, derivatives thereof, or combinations thereof.

58. The pharmaceutical safety dosage form of claim 56 wherein said antagonist comprises a hyperglycemic agent.

59. The pharmaceutical safety dosage form of claim 58 wherein said hyperglycemic agent is epinepherine, glucagon, derivatives thereof, or combinations thereof.

60. A pharmaceutical safety dosage form comprising a pharmaceutical contained within a first plurality of particulated forms, said first particulated forms being adapted for release of said pharmaceutical within a patient, together with an antagonist for said pharmaceutical, said antagonist being contained within a second plurality of particulated forms, said second particulated forms being substantially insoluble in gastric fluid.

61. The pharmaceutical safety dosage form of claim 60 wherein said pharmaceutical is adapted for time-release, or said second plurality of particulated forms comprise a polymorph or a solvate which is substantially insoluble in gastric fluid, or both.

62. The pharmaceutical safety dosage form of claim 61 wherein said first plurality of particulated forms comprises a sustained-release powder.

63. The pharmaceutical safety dosage form of claim 60 adapted to be administered orally.

64. The pharmaceutical safety dosage form of claim 60 adapted to be administered rectally, parenterally, vaginally, transdermally, intranasally, or via aerosol.

65. The pharmaceutical safety dosage form of claim 60 wherein said antagonist comprises an emetic agent.

66. The pharmaceutical safety dosage form of claim 65 wherein said emetic agent is ipecac or derivatives thereof.

67. The pharmaceutical safety dosage form of claim 60 wherein said pharmaceutical comprises a narcotic.

68. The pharmaceutical safety dosage form of claim 67 wherein said narcotic is codeine, oxycodone, propoxyphene, pentazocine, derivatives thereof, or combinations thereof.

69. The pharmaceutical safety dosage form of claim 67 wherein said antagonist is naloxone, nalmefene, derivatives thereof, or combinations thereof.

70. The pharmaceutical safety dosage form of claim 60 wherein said pharmaceutical comprises a sympathomimetic.

71. The pharmaceutical safety dosage form of claim 70 further comprising an antihistamine.

72. The pharmaceutical safety dosage form of claim 71 wherein said sympathomimetic is pseudoephedrine HCl or derivatives thereof, and said antihistamine is cetirizine HCl, fexofenadine HCl, derivatives thereof, or combinations thereof.

73. The pharmaceutical safety dosage form of claim 71 wherein said antagonist comprises an adrenergic beta blocker.

74. The pharmaceutical safety dosage form of claim 70 wherein said sympathomimetic comprises methylphenidate.

75. The pharmaceutical safety dosage form of claim 74 wherein said antagonist comprises an adrenergic beta blocker.

76. The pharmaceutical safety dosage form of claim 70 wherein said sympathomimetic comprises an amphetamine.

77. The pharmaceutical safety dosage form of claim 76 wherein said amphetamine is methamphetamine, amphetamine, dextroamphetamine, derivatives thereof, or combinations thereof.

78. The pharmaceutical safety dosage form of claim 76 wherein said antagonist comprises an adrenergic beta blocker.

79. The pharmaceutical safety dosage form of claim 78 wherein said adrenergic beta blocker is propranolol, atenolol, metoprolol, derivatives thereof, or combinations thereof.

80. The pharmaceutical safety dosage form of claim 60 wherein said pharmaceutical comprises a blood pressure-lowering medication.

81. The pharmaceutical safety dosage form of claim 80 wherein said blood pressure-lowering medication is an adrenergic beta blocker, a calcium channel blocker, or an ACE inhibitor.

82. The pharmaceutical safety dosage form of claim 81 wherein said blood pressure-lowering medication is propranolol, metoprolol, nifedipine, diltiazem, nisoldipine, timolol maleate, derivatives thereof, or combinations thereof.

83. The pharmaceutical safety dosage form of claim 80 wherein said antagonist comprises a sympathomimetic.

84. The pharmaceutical safety dosage form of claim 83 wherein said sympathomimetic is dopamine, epinepherine, derivatives thereof, or combinations thereof.

85. The pharmaceutical safety dosage form of claim 60 wherein said pharmaceutical comprises a hypoglycemic agent.

86. The pharmaceutical safety dosage form of claim 85 wherein said hypoglycemic agent is insulin, metformin, glipizide, glyburide, derivatives thereof, or combinations thereof.

87. The pharmaceutical safety dosage form of claim 85 wherein said antagonist comprises a hyperglycemic agent.

88. The pharmaceutical safety dosage form of claim 87 wherein said hyperglycemic agent is epinepherine, glucagon, derivatives thereof, or combinations thereof.

89. A pharmaceutical safety dosage form comprising a pharmaceutical contained within a microdosage form, said microdosage form being adapted for release of said pharmaceutical within a patient, together with an antagonist for said pharmaceutical, said antagonist being contained within a plurality of particulated dosage forms, said particulated dosage forms being substantially insoluble in gastric fluid.

90. The pharmaceutical safety dosage form of claim 89 wherein said pharmaceutical is adapted for time-release, or said plurality of particulated forms comprise a polymorph which is substantially insoluble in gastric fluid, or both.

91. The pharmaceutical safety dosage form of claim 89 wherein said microdosage form comprises beads, tablets, mini tablets, or combinations thereof.

92. The pharmaceutical safety dosage form of claim 89 adapted to be administered orally.

93. The pharmaceutical safety dosage form of claim 89 adapted to be administered rectally, parenterally, vaginally, transdermally, intranasally, or via aerosol.

94. The pharmaceutical safety dosage form of claim 89 wherein said antagonist comprises an emetic agent.

95. The pharmaceutical safety dosage form of claim 94 wherein said emetic agent is ipecac or derivatives thereof.

96. The pharmaceutical safety dosage form of claim 89 wherein said pharmaceutical comprises a narcotic.

97. The pharmaceutical safety dosage form of claim 96 wherein said narcotic is codeine, oxycodone, propoxyphene, pentazocine, derivatives thereof, or combinations thereof.

98. The pharmaceutical safety dosage form of claim 96 wherein said antagonist is naloxone, nalmefene, derivatives thereof, or combinations thereof.

99. The pharmaceutical safety dosage form of claim 89 wherein said pharmaceutical comprises a sympathomimetic.

100. The pharmaceutical safety dosage form of claim 99 further comprising an antihistamine.

101. The pharmaceutical safety dosage form of claim 100 wherein said sympathomimetic is pseudoephedrine HCl or derivatives thereof, and said antihistamine is cetirizine HCl, fexofenadine HCl, derivatives thereof, or combinations thereof.

102. The pharmaceutical safety dosage form of claim 100 wherein said antagonist comprises an adrenergic beta blocker.

103. The pharmaceutical safety dosage form of claim 99 wherein said sympathomimetic comprises methylphenidate.

104. The pharmaceutical safety dosage form of claim 103 wherein said antagonist comprises an adrenergic beta blocker.

105. The pharmaceutical safety dosage form of claim 99 wherein said sympathomimetic comprises an amphetamine.

106. The pharmaceutical safety dosage form of claim 105 wherein said amphetamine is methamphetamine, amphetamine, dextroamphetamine, derivatives thereof, or combinations thereof.

107. The pharmaceutical safety dosage form of claim 105 wherein said antagonist comprises an adrenergic beta blocker.

108. The pharmaceutical safety dosage form of claim 107 wherein said adrenergic beta blocker is propranolol, atenolol, metoprolol, derivatives thereof, or combinations thereof.

109. The pharmaceutical safety dosage form of claim 89 wherein said pharmaceutical comprises a blood pressure-lowering medication.

110. The pharmaceutical safety dosage form of claim 109 wherein said blood pressure-lowering medication is an adrenergic beta blocker, a calcium channel blocker, or an ACE inhibitor.

111. The pharmaceutical safety dosage form of claim 110 wherein said blood pressure-lowering medication is propranolol, metoprolol, nifedipine, diltiazem, nisoldipine, timolol maleate, derivatives thereof, or combinations thereof.

112. The pharmaceutical safety dosage form of claim 109 wherein said antagonist comprises a sympathomimetic.

113. The pharmaceutical safety dosage form of claim 112 wherein said sympathomimetic is dopamine, epinepherine, derivatives thereof, or combinations thereof.

114. The pharmaceutical safety dosage form of claim 89 wherein said pharmaceutical comprises a hypoglycemic agent.

115. The pharmaceutical safety dosage form of claim 114 wherein said hypoglycemic agent is insulin, metformin, glipizide, glyburide, derivatives thereof, or combinations thereof.

116. The pharmaceutical safety dosage form of claim 114 wherein said antagonist comprises a hyperglycemic agent.

117. The pharmaceutical safety dosage form of claim 116 wherein said hyperglycemic agent is epinepherine, glucagon, derivatives thereof, or combinations thereof.

118. A pharmaceutical safety dosage form comprising a pharmaceutical contained within a plurality of particulated forms, said particulated forms being adapted for release of said pharmaceutical within a patient, together with an antagonist for said pharmaceutical, said antagonist being contained within a microdosage form, said microdosage form being substantially insoluble in gastric fluid.

119. The pharmaceutical safety dosage form of claim 118 wherein said plurality of particulated forms comprise a polymorph which is substantially insoluble in gastric fluid, or said microdosage form comprises a coating which is substantially insoluble in gastric fluid, or both.

120. The pharmaceutical safety dosage form of claim 118 wherein said microdosage form comprises beads, tablets, mini tablets, or combinations thereof.

121. The pharmaceutical safety dosage form of claim 118 adapted to be administered orally.

122. The pharmaceutical safety dosage form of claim 118 adapted to be administered rectally, parenterally, vaginally, transdermally, intranasally, or via aerosol.

123. The pharmaceutical safety dosage form of claim 118 wherein said antagonist comprises an emetic agent.

124. The pharmaceutical safety dosage form of claim 123 wherein said emetic agent is ipecac or derivatives thereof.

125. The pharmaceutical safety dosage form of claim 118 wherein said pharmaceutical comprises a narcotic.

126. The pharmaceutical safety dosage form of claim 125 wherein said narcotic is codeine, oxycodone, propoxyphene, pentazocine, derivatives thereof, or combinations thereof.

127. The pharmaceutical safety dosage form of claim 125 wherein said antagonist is naloxone, nalmefene, derivatives thereof, or combinations thereof.

128. The pharmaceutical safety dosage form of claim 118 wherein said pharmaceutical comprises a sympathomimetic.

129. The pharmaceutical safety dosage form of claim 128 further comprising an antihistamine.

130. The pharmaceutical safety dosage form of claim 129 wherein said sympathomimetic is pseudoephedrine HCl or derivatives thereof, and said antihistamine is cetirizine HCl, fexofenadine HCl, derivatives thereof, or combinations thereof.

131. The pharmaceutical safety dosage form of claim 129 wherein said antagonist comprises an adrenergic beta blocker.

132. The pharmaceutical safety dosage form of claim 128 wherein said sympathomimetic comprises methylphenidate.

133. The pharmaceutical safety dosage form of claim 132 wherein said antagonist comprises an adrenergic beta blocker.

134. The pharmaceutical safety dosage form of claim 128 wherein said sympathomimetic comprises an amphetamine.

135. The pharmaceutical safety dosage form of claim 134 wherein said amphetamine is methamphetamine, amphetamine, dextroamphetamine, derivatives thereof, or combinations thereof.

136. The pharmaceutical safety dosage form of claim 134 wherein said antagonist comprises an adrenergic beta blocker.

137. The pharmaceutical safety dosage form of claim 136 wherein said adrenergic beta blocker is propranolol, atenolol, metoprolol, derivatives thereof, or combinations thereof.

138. The pharmaceutical safety dosage form of claim 118 wherein said pharmaceutical comprises a blood pressure-lowering medication.

139. The pharmaceutical safety dosage form of claim 138 wherein said blood pressure-lowering medication is an adrenergic beta blocker, a calcium channel blocker, or an ACE inhibitor.

140. The pharmaceutical safety dosage form of claim 139 wherein said blood pressure-lowering medication is propranolol, metoprolol, nifedipine, diltiazem, nisoldipine, timolol maleate, derivatives thereof, or combinations thereof.

141. The pharmaceutical safety dosage form of claim 138 wherein said antagonist comprises a sympathomimetic.

142. The pharmaceutical safety dosage form of claim 141 wherein said sympathomimetic is dopamine, epinepherine, derivatives thereof, or combinations thereof.

143. The pharmaceutical safety dosage form of claim 118 wherein said pharmaceutical comprises a hypoglycemic agent.

144. The pharmaceutical safety dosage form of claim 143 wherein said hypoglycemic agent is insulin, metformin, glipizide, glyburide, derivatives thereof, or combinations thereof.

145. The pharmaceutical safety dosage form of claim 143 wherein said antagonist comprises a hyperglycemic agent.

146. The pharmaceutical safety dosage form of claim 145 wherein said hyperglycemic agent is epinepherine, glucagon, derivatives thereof, or combinations thereof.

147. A pharmaceutical safety dosage form comprising a pharmaceutical in a first form adjacent to an antagonist for said pharmaceutical in a second form wherein said antagonist has significant bioavailability only when said pharmaceutical safety dosage form is disrupted.

148. The pharmaceutical safety dosage of claim 147 wherein said first form is time-release, or said second form comprises an insoluble coating, or both.

149. The pharmaceutical safety dosage form of claim 147 wherein said first form is substantially layered over said second form.

150. The pharmaceutical safety dosage form of claim 147 wherein said second form is substantially layered over said first form.

151. The pharmaceutical safety dosage form of claim 147 wherein said bioavailability occurs upon mechanical disruption.

152. The pharmaceutical safety dosage form of claim 147 wherein said bioavailability occurs upon extraction by a chemical.

153. The pharmaceutical safety dosage form of claim 147 adapted to be administered orally.

154. The pharmaceutical safety dosage form of claim 147 adapted to be administered rectally, parenterally, vaginally, transdermally, intranasally, or via aerosol.

155. The pharmaceutical safety dosage form of claim 147 wherein said antagonist comprises an emetic agent.

156. The pharmaceutical safety dosage form of claim 155 wherein said emetic agent is ipecac or derivatives thereof.

157. The pharmaceutical safety dosage form of claim 147 wherein said pharmaceutical comprises a narcotic.

158. The pharmaceutical safety dosage form of claim 157 wherein said narcotic is codeine, oxycodone, propoxyphene, pentazocine, derivatives thereof, or combinations thereof.

159. The pharmaceutical safety dosage form of claim 157 wherein said antagonist is naloxone, nalmefene, derivatives thereof, or combinations thereof.

160. The pharmaceutical safety dosage form of claim 147 wherein said pharmaceutical comprises a sympathomimetic.

161. The pharmaceutical safety dosage form of claim 160 further comprising an antihistamine.

162. The pharmaceutical safety dosage form of claim 161 wherein said sympathomimetic is pseudoephedrine HCl or derivatives thereof, and said antihistamine is cetirizine HCl, fexofenadine HCl, derivatives thereof, or combinations thereof.

163. The pharmaceutical safety dosage form of claim 161 wherein said antagonist comprises an adrenergic beta blocker.

164. The pharmaceutical safety dosage form of claim 160 wherein said sympathomimetic comprises methylphenidate.

165. The pharmaceutical safety dosage form of claim 164 wherein said antagonist comprises an adrenergic beta blocker.

166. The pharmaceutical safety dosage form of claim 160 wherein said sympathomimetic comprises an amphetamine.

167. The pharmaceutical safety dosage form of claim 166 wherein said amphetamine is methamphetamine, amphetamine, dextroamphetamine, derivatives thereof, or combinations thereof.

168. The pharmaceutical safety dosage form of claim 166 wherein said antagonist comprises an adrenergic beta blocker.

169. The pharmaceutical safety dosage form of claim 168 wherein said adrenergic beta blocker is propranolol, atenolol, metoprolol, derivatives thereof, or combinations thereof.

170. The pharmaceutical safety dosage form of claim 147 wherein said pharmaceutical comprises a blood pressure-lowering medication.

171. The pharmaceutical safety dosage form of claim 170 wherein said blood pressure-lowering medication is an adrenergic beta blocker, a calcium channel blocker, or an ACE inhibitor.

172. The pharmaceutical safety dosage form of claim 171 wherein said blood pressure-lowering medication is propranolol, metoprolol, nifedipine, diltiazem, nisoldipine, timolol maleate, derivatives thereof, or combinations thereof.

173. The pharmaceutical safety dosage form of claim 170 wherein said antagonist comprises a sympathomimetic.

174. The pharmaceutical safety dosage form of claim 173 wherein said sympathomimetic is dopamine, epinepherine, derivatives thereof, or combinations thereof.

175. The pharmaceutical safety dosage form of claim 147 wherein said pharmaceutical comprises a hypoglycemic agent.

176. The pharmaceutical safety dosage form of claim 175 wherein said hypoglycemic agent is insulin, metformin, glipizide, derivatives thereof, or combinations thereof.

177. The pharmaceutical safety dosage form of claim 175 wherein said antagonist comprises a hyperglycemic agent.

178. The pharmaceutical safety dosage form of claim 177 wherein said hyperglycemic agent is epinepherine, glucagon, derivatives thereof, or combinations thereof.

179. A method of administering a pharmaceutical comprising:

providing a pharmaceutical safety dosage form comprising a pharmaceutical in a first form, said first form providing a prescribed bioavailability; and

providing an antagonist for said pharmaceutical in a second form, said second form providing insignificant bioavailability when administered; and

wherein disruption to said pharmaceutical safety dosage form may result in significant bioavailability of said antagonist.

180. The method of claim 179 wherein said significant bioavailability occurs upon mechanical disruption.

181. The method of claim 179 wherein said significant bioavailability occurs upon extraction by a chemical.

182. The method of claim 179 wherein said pharmaceutical safety dosage form is adapted to be administered orally.

183. The method of claim 179 wherein said pharmaceutical safety dosage form is adapted to be administered rectally, parenterally, vaginally, transdermally, intranasally, or via aerosol.

184. The method of claim 179 wherein said antagonist comprises an emetic agent.

185. The method of claim 184 wherein said emetic agent is ipecac or derivatives thereof.

186. The method of claim 179 wherein said pharmaceutical comprises a narcotic.

187. The method of claim 186 wherein said narcotic is codeine, oxycodone, propoxyphene, pentazocine, derivatives thereof, or combinations thereof.

188. The method of claim 186 wherein said antagonist is naloxone, nalmefene, derivatives thereof, or combinations thereof.

189. The method of claim 179 wherein said pharmaceutical comprises a sympathomimetic.

190. The method of claim 189 wherein said pharmaceutical safety dosage form further comprises an antihistamine.

191. The method of claim 190 wherein said sympathomimetic is pseudoephedrine HCl or derivatives thereof, and said antihistamine is cetirizine HCl, fexofenadine HCl, derivatives thereof, or combinations thereof.

192. The method of claim 190 wherein said antagonist comprises an adrenergic beta blocker.

193. The method of claim 189 wherein said sympathomimetic comprises methylphenidate.

194. The method of claim 193 wherein said antagonist comprises an adrenergic beta blocker.

195. The method of claim 189 wherein said sympathomimetic comprises an amphetamine.

196. The method of claim 195 wherein said amphetamine is methamphetamine, amphetamine, dextroamphetamine, derivatives thereof, or combinations thereof.

197. The method of claim 196 wherein said antagonist comprises an adrenergic beta blocker.

198. The method of claim 197 wherein said adrenergic beta blocker is propranolol, atenolol, metoprolol, derivatives thereof, or combinations thereof.

199. The method of claim 179 wherein said pharmaceutical comprises a blood pressure-lowering medication.

200. The method of claim 199 wherein said blood pressure-lowering medication is an adrenergic beta blocker, a calcium channel blocker, or an ACE inhibitor.

201. The method of claim 200 wherein said blood pressure-lowering medication is propranolol, metoprolol, nifedipine, diltiazem, nisoldipine, timolol maleate, derivatives thereof, or combinations thereof.

202. The method of claim 199 wherein said antagonist comprises a sympathomimetic.

203. The method of claim 202 wherein said sympathomimetic is dopamine, epinepherine, derivatives thereof, or combinations thereof.

204. The method of claim 179 wherein said pharmaceutical comprises a hypoglycemic agent.

205. The method of claim 204 wherein said hypoglycemic agent is insulin, metformin, glipizide, glyburide, derivatives thereof, or combinations thereof.

206. The method of claim 204 wherein said antagonist comprises a hyperglycemic agent.

207. The method of claim 206 wherein said hyperglycemic agent is epinepherine, glucagon, derivatives thereof, or combinations thereof.

208. A method of delivering a drug to a patient comprising placing said drug into a pharmaceutical safety dosage form further comprising an antagonist for said drug, said antagonist being insubstantially bioavailable when said dosage form is not disrupted; and administering said safety dosage form to the patient.

209. The method of claim 208 wherein said antagonist comprises an emetic agent.

210. The method of claim 209 wherein said emetic agent is ipecac or derivatives thereof.

211. A method of delivering a narcotic to a patient comprising placing said narcotic into a pharmaceutical safety dosage form further comprising a narcotic antagonist, said narcotic

antagonist being insubstantially bioavailable when said dosage form is not disrupted; and administering said safety dosage form to the patient.

212. The method of claim 211 wherein said narcotic is codeine, oxycodone, propoxyphene, pentazocine, derivatives thereof, or combinations thereof.

213. The method of claim 211 wherein said antagonist is naloxone, nalmefene, derivatives thereof, or combinations thereof.

214. A method of delivering a sympathomimetic to a patient comprising placing said sympathomimetic into a pharmaceutical safety dosage form further comprising an adrenergic beta blocker, said adrenergic beta blocker being insubstantially bioavailable when said dosage form is not disrupted; and administering said safety dosage form to the patient.

215. The method of claim 214 further delivering an antihistamine along with said sympathomimetic.

216. The method of claim 215 wherein said sympathomimetic and said antihistamine are cetirizine HCl/pseudoephedrine HCl, fexofenadine HCl/pseudoephedrine HCl, derivatives thereof, or combinations thereof.

217. The method of claim 214 wherein said sympathomimetic comprises methylphenidate.

218. The method of claim 214 wherein said sympathomimetic comprises an amphetamine.

219. The method of claim 218 wherein said amphetamine is methamphetamine, amphetamine, dextroamphetamine, derivatives thereof, or combinations thereof.

220. The method of claim 219 wherein said adrenergic beta blocker is propranolol, atenolol, metoprolol, derivatives thereof, or combinations thereof.

221. A method of delivering a blood pressure-lowering medication to a patient comprising placing said blood-pressure lowering medication into a pharmaceutical safety dosage form further comprising a sympathomimetic, said sympathomimetic being insubstantially bioavailable when said dosage form is not disrupted; and administering said safety dosage form to the patient.

222. The method of claim 221 wherein said blood pressure-lowering medication is an adrenergic beta blocker, a calcium channel blocker, or an ACE inhibitor.

223. The method of claim 222 wherein said blood pressure-lowering medication is propranolol, metoprolol, nifedipine, diltiazem, nisoldipine, timolol maleate, derivatives thereof, or combinations thereof.

224. The method of claim 221 wherein said sympathomimetic is dopamine, epinepherine, derivatives thereof, or combinations thereof.

225. A method of delivering a hypoglycemic agent to a patient comprising placing said hypoglycemic agent into a pharmaceutical safety dosage form further comprising a hyperglycemic agent, said hyperglycemic agent being insubstantially bioavailable when said dosage form is not disrupted; and administering said safety dosage form to the patient.

226. The method of claim 225 wherein said hypoglycemic agent is insulin, metformin, glipizide, glyburide, derivatives thereof, or combinations thereof.

227. The method of claim 225 wherein said hyperglycemic agent is epinepherine, glucagon, derivatives thereof, or combinations thereof.

228. A method of making a pharmaceutical safety dosage form comprising a pharmaceutical and an antagonist for said pharmaceutical wherein said antagonist has significant bioavailability only when said pharmaceutical safety dosage form is disrupted.

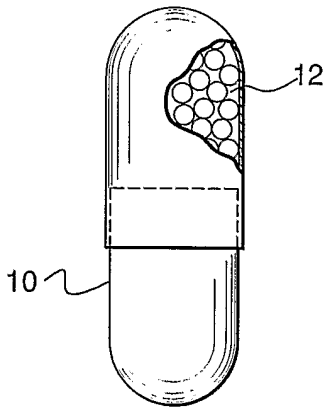

FIG. 1

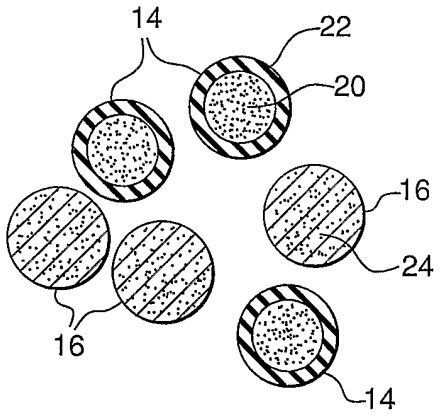

FIG. 1A

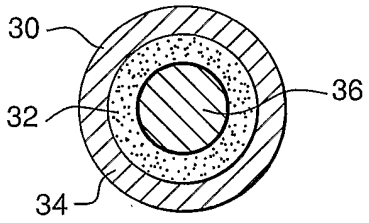

FIG. 1B

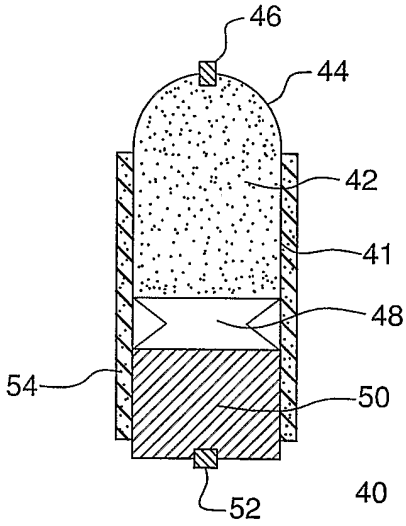

FIG. 2

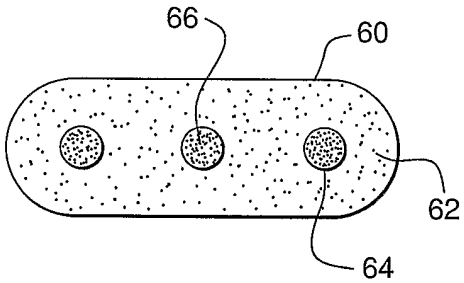

FIG. 3

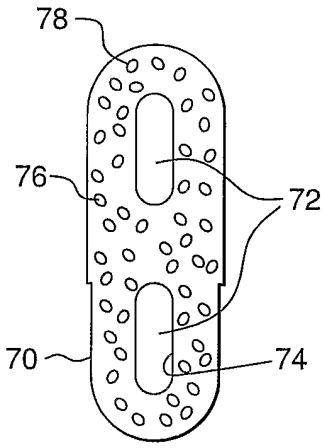

FIG. 4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/40990

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 9/14, 9/16, 9/20, 9/22, 9/26, 9/28, 9/30, 9/48, 9/52, 9/54, 9/60
US CL : 424/451, 452, 457, 458, 459, 464, 465, 468, 469, 474, 475, 489, 490, 491

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)
U.S. : 424/451, 452, 457, 458, 459, 464, 465, 468, 469, 474, 475, 489, 490, 491

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 practicable, search terms used)
West

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6,228,863 B1 (PALERMO et al.) 08 May 2001 (08.05.2001), columns 5-6, 8-10, 13-15, 20-21, claims 1-34.	1-6, 9-11, 31-35, 38-40, 60-64, 67-69, 89-93, 96-98, 118-122, 125-127, 147-154, 157-159, 179-183, 186-188, 208-213, 228
A,E	US 2003/0035839 A1 (HIRSH et al.) 20 February 2003 (20.02.2003), see entire document.	1-228
A	US 6,255,502 B1 (PENKLER et al.) 03 July 2001 (03.07.2001), see entire document.	1-228
A,E	US 2004/0006091 A1 (KYLE et al.) 08 January 2004 (08.012004), see entire document.	1-228
A	US 5,795,909 A (SHASHOUA et al.) 18 August 1998 (18.08.1998), see entire document.	1-228

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

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

"E" earlier application or patent published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
10 June 2004 (10.06.2004)

Date of mailing of the international search report
02 JUL 2004

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Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/40990

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

PCT/US03/40990

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claims 1-30 are drawn to a pharmaceutical agent and its' antagonist in a single dosage form.

Group II, claims 31-59 are drawn to a dosage form of first and second microdosage.

Group III, claims 60-88, drawn to a dosage form of first and second plurality of particulated forms.

Group IV, claims 89-146 are drawn to a microdosage form of a pharmaceutical agent and its' antagonist.

Group V, claims 147-178 are drawn to a pharmaceutical agent in a first dosage form and its' antagonist in a second dosage form.

Group VI, claims 179-207 are drawn to method of administering a pharmaceutical.

Group VII, claims 208-227 are drawn to method of delivering a drug to a patient.

Group VIII, claim 228 is drawn to method of making a pharmaceutical dosage form.

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In order for more than one species to be examined, the appropriate additional examination fees must be paid. The species are as follows: narcotic, sympathomimetic agent, blood pressure-lowering agent and hypoglycemic agent.

The claims are deemed to correspond to the species listed above in the following manner:
Narcotic: claims 211-213.
Sympathomimetic agent: claims 214-220.
Blood pressure-lowering agent: claims 221-224.
Hypoglycemic agent: claims 225-227.

The following claim is generic: 208.

The inventions listed as Groups I-VIII do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: they do not share the same essential elements that define the "special technical feature" necessary to specify a contribution over the prior art. The element common to all the groups is a pharmaceutical dosage form containing active agent and its' antagonist, which is known in the art and therefore, cannot be said to be the special technical feature that makes a contribution over the prior art (see for example, Kao et al. and Oshlack et al.). All other elements differ from each other, *e.g.*, dosage form with first and second composition, multiparticulate, method of using and method of making the dosage form, each of which are known in the prior art. Thus, these claims lack the corresponding special technical features necessary to link them together to fulfill the Unity of Invention requirement.

This application contains the above identified inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. in accordance to 37CFR 1.499 and under 35 U.S.C. 121 and 372, the applicants are required, in response to this Office Action, to elect a single invention to which the claims must be restricted.