

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
3 November 2005 (03.11.2005)

PCT

(10) International Publication Number
WO 2005/102272 A2

(51) International Patent Classification⁷: **A61K 9/00**

(21) International Application Number:
PCT/IB2005/001010

(22) International Filing Date: 11 April 2005 (11.04.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/564,139 21 April 2004 (21.04.2004) US

(71) Applicant (for all designated States except US): **PFIZER PRODUCTS INC.** [US/US]; Eastern Point Road, Groton, CT 06340 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **MURPHY, Thomas, K.** [US/US]; Eastern Point Road, Groton, CT 06340 (US).
EISENHART, Eric, K. [US/US]; Eastern Point Road, Groton, CT 06340 (US).

(74) Agents: **FULLER, Grover, F., Jr.** et al.; Pfizer Inc., P.O. Box 1027, St. Louis, MO 63006 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished upon receipt of that report

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

(54) Title: SUSTAINED-RELEASE DOSAGE FORMS FOR CABERGOLINE

(57) Abstract: The present invention in one embodiment is directed to sustained-release dosage forms of cabergoline and other ergoline derivatives, which provide a zero-order or near zero-order release profile. The invention in another embodiment is directed to a method for treating Parkinson's disease, Progressive Supranuclear Palsy, Multisystemic Atrophy, Restless Legs Syndrome, Fibromyalgia, Chronic Fatigue Syndrome, stroke and nervous system disorders, including addictive disorders, using sustained-release dosage forms containing cabergoline or a pharmaceutically acceptable salts thereof.

WO 2005/102272 A2

SUSTAINED-RELEASE DOSAGE FORMS FOR CABERGOLINE

FIELD OF THE INVENTION

The present invention relates to sustained release dosage forms suitable for administration of a wide range of therapeutically active medicaments, especially ergoline derivatives such as cabergoline, and to a process of making same.

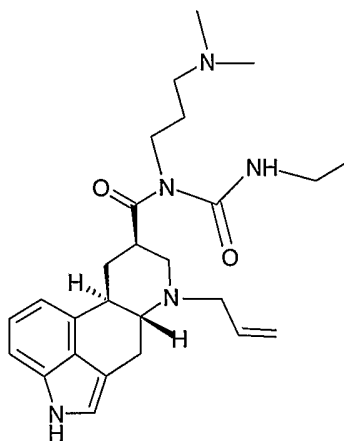
BACKGROUND OF THE INVENTION

There exists a significant need for a pharmaceutical delivery system which releases therapeutically active medicaments, especially cabergoline and other ergoline derivatives, in sustained-release profile such as zero-order release profile and over an extended period of time.

Cabergoline is an ergoline derivative which interacts with D2 dopamine receptors and which is used in the treatment of hyperprolactinemia, central nervous system (CNS) disorders, and other related diseases. Cabergoline is the generic name of the active ingredient in DOSTINEX® Tablets, marketed by Pfizer, Inc. in the United States as a treatment for hyperprolactinemic disorders, and CABASER®, marketed by Pfizer Products, Inc. in Europe as a treatment for Parkinson's disease. A package insert describing CABASER®, its pharmacokinetics, Parkinson's disease patients, clinical studies, indications and usage, contraindication and warnings is provided by Pfizer Products, Inc. This package insert, which is incorporated by reference herein, provides, for example, that a CABASER® 4 mg tablet is useful for the treatment of Parkinson's disease, and as adjuvant therapy to levodopa plus dopa-decarboxylase inhibitor, in patients affected by "on-off" mobility problems with daily fluctuations in motor performance. The tablet is for oral administration.

The synthesis and use of cabergoline is disclosed and claimed in U.S. Pat. No. 4,526,892, which is incorporated herein by reference. The chemical name for the compound is 1-[(6-allylergolin-8-yl) -carbonyl] -1- [3-(dimethylamino)propyl] -3-ethylurea. The synthesis of cabergoline is reported also in Eur. J. Med. Chem., 24, 421, (1989) and in GB-2,103,603-B.

Cabergoline has the following structural formula:



The use of cabergoline to treat Parkinson's disease, Progressive Supranuclear Palsy, and Multisystemic Atrophy is described in U.S. Patent No. 6,503,920, which is incorporated herein by reference. The use of cabergoline to treat Restless Leg Syndrome is described in U.S. Patent No. 6,114,326, which is incorporated herein by reference. The use of cabergoline and related compounds to treat Fibromyalgia and Chronic Fatigue Syndrome is described in U.S. Patent No. 6,555,548, which is incorporated herein by reference. The use of cabergoline and related compounds to treat other nervous system disorders, particularly addictive disorders, is described in PCT/US01/25603, which is incorporated herein by reference.

A drug dosage form which releases its drug content gradually and over an extended period of time after the drug makes contact with a use environment is called a sustained release dosage form. Sustained release dosage forms are well known in the art. The term "use environment", as used above, may refer to, for example, an aqueous solution, which corresponds to in vitro dissolution; a simulated gastric fluid, which may be used for testing purposes, or a gastrointestinal fluid, which corresponds to use of the dosage form in vivo. Sustained release dosage forms are desirable in the treatment of a number of diseases because the drug concentration is maintained in the body for longer periods of time, leading to reduction in the frequency of dosage. These dosage forms can be formulated into a variety of physical structures or forms, including tablets, lozenges, gelcaps, buccal patches, suspensions, solutions, gels, etc.

It is of great advantage to both the patient and the physician that medication be formulated so that it may be administered in a minimum number of daily doses from which the drug is uniformly released over a desired extended period of time. This effect is accomplished using sustained release compositions. Sustained release compositions containing pharmaceutical medicaments or other active ingredients are designed to contain higher concentrations of the medicament and are prepared in such a manner as to effect sustained release into the gastrointestinal digestive tract of humans or animals over an extended period of time.

Well-absorbed oral sustained release therapeutic drug dosage forms have inherent advantages over conventional, immediate release dosage forms. Those advantages include less frequent dosing of a medicament and resultant patient regime compliance, a more sustained drug blood level response, therapeutic action with less ingested drug, and the mitigation of side effects. By providing a steady release of the medicament over time, absorbed drug concentration "spikes" (sudden increases) are mitigated or eliminated by effecting a smoother and more sustained blood level response.

Cabergoline is known to exist in at least three crystalline forms. Form I is the earliest reported form. The discovery, preparation, and characterization of Form II are reported in

Tomasi et al., U.S. Patent No. 6,673,806, which is incorporated herein by reference. The discovery, preparation, and characterization of Form VII are reported in Candiani et al., U.S. Patent No. 6,680,327, which is incorporated herein by reference.

5 Cabergoline is unusual among D2 receptor family agonists in being a full D2 agonist with partial D1 activity. Cabergoline has an exceptionally long duration of action of at least 24 hours or longer, Ahlskog J E, Wright K F, Muentner M D, Adler C H (1996), "Adjunctive cabergoline therapy of Parkinson's disease: comparison with placebo and assessment of dose response and duration of effect" Clin. Neuropharmacol; 19: 202-212. (1996). As reported in U.S. Patent No. 6,114,326, clinically effective levels of cabergoline may last as
10 long as 65 hours, and one dose may be an effective treatment for RLS for 65 hours or more, possibly as long as a week.

Conventional pharmaceutical preparations of cabergoline, such as those containing an inert pharmaceutical carrier and an effective dose of the active substance: e.g., plain or coated tablets, capsules, lozenges, powders, solutions, suspensions, emulsions, syrups,
15 suppositories, and the like, are known. However, sustained release forms of cabergoline are heretofore unknown.

In view of the importance of cabergoline in treating a wide variety of CNS disorders, there exists a significant need for a delivery system which releases cabergoline, as well as other ergoline derivatives, over an extended period of time. Such a delivery system
20 advantageously provides a substantially steady release of cabergoline over time, effecting a smoother and more sustained blood drug level response and mitigating or eliminating concentration "spikes" or sudden increases. Most desirable is a system that releases cabergoline in a zero-order or near zero-order release profile.

SUMMARY OF THE INVENTION

25 In one aspect, the present invention is directed to a sustained-release dosage form suitable for administration to a mammal, comprising cabergoline, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In another aspect, the present invention is directed to a sustained-release dosage form suitable for oral administration to a mammal, comprising cabergoline, or a
30 pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, which dosage form releases cabergoline into a use environment at a rate not exceeding about 5 mgA/hr, provided said dosage form (1) releases not more than about 70% by weight of the cabergoline contained therein within the first hour following entry into said use environment and (2) releases cabergoline at a rate of at least about 0.01 mgA/hr.

35 In still another aspect, the present invention is directed to a sustained release dosage form suitable for oral administration to a mammal, comprising cabergoline or a

pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, which dosage form releases cabergoline at a rate less than about 10 mgA/hr in vitro when dissolution tested in an USP-2 apparatus containing 900 ml of an acetate buffer at pH 4.0, and containing NaCl in a concentration of 0.075 M at 37°C, wherein: (1) if said dosage form is a sustained release tablet or a non-disintegrating sustained release capsule, said USP-2 apparatus is equipped with a paddle stirring at 50 rpm; (2) if said dosage form is a multiparticulate comprises multiparticulates and is not a tablet, said USP-2 apparatus is equipped with a paddle stirring at 100 rpm; provided said dosage form (a) releases not more than about 70% by weight of the cabergoline contained therein within the first hour following initiation of the dissolution test and (b) releases cabergoline at a rate of at least about 0.01 mgA/hr.

In still yet another aspect, the present invention is directed to a sustained release dosage form suitable for oral administration to a mammal, said dosage form having an initial delay period prior to the onset of sustained release, comprising cabergoline or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, which dosage form releases cabergoline into 900 ml of 0.1 N HCl at a rate less than about 0.001 mgA/hr for at least 1 hour at 37° C in vitro when dissolution tested in an USP-2 apparatus and wherein said dosage form thereafter releases cabergoline into 900 ml of a phosphate buffer at a pH of 6.8 and containing 1% by weight of polysorbate 80 at 37° C, at a rate of from about 0.01mgA/hr to about 10 mgA/hr, provided said dosage form releases not more than about 70% by weight of the cabergoline within the first hour following the initial delay period, wherein: (1) if said dosage form is a sustained release tablet or a non-disintegrating sustained release capsule, said USP-2 apparatus is equipped with a paddle stirring at 50 rpm; (2) if said dosage form is a multiparticulate comprises multiparticulates and is not a tablet, said USP-2 apparatus is equipped with a paddle stirring at 100 rpm.

The invention also includes in another embodiment a sustained release dosage form suitable for oral administration to a mammal, comprising cabergoline or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, which dosage form, following ingestion by said mammal, releases cabergoline into said mammal's stomach at a rate less than about 0.01 mgA/hr, and which, after having passed into said mammals' duodenum; releases cabergoline at a rate of from about 0.01 mgA/hr to about 10 mgA/hr, provided said dosage form releases not more than about 70% by weight of the cabergoline contained therein within the first hour after passing into said mammal's duodenum.

In a further aspect, the present invention is directed to a sustained release dosage form suitable for oral administration to a mammal, comprising cabergoline, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, which

dosage form, when orally administered to said mammal, results in a maximum cabergoline plasma concentration, $C_{\max}$, which is less than about 80% of the $C_{\max}$ determined when an equal dose of cabergoline is orally administered in the form of an immediate release bolus, provided said sustained release dosage form (1) releases not more than about 70% by weight
5 of the cabergoline contained therein within the first hour following ingestion and (2) releases cabergoline at a rate of at least about 0.01 mgA/hr.

In another aspect, the present invention provides a method for treating a disease or disorder selected from the group consisting of Parkinson's disease, Progressive Supranuclear Palsy, Multisystemic Atrophy, Restless Legs Syndrome, Fibromyalgia, Chronic Fatigue
10 Syndrome, stroke, nervous system disorders, and addictive disorders, comprising orally administering to a mammal in need of such treatment, a therapeutically effective amount of cabergoline in a sustained-release dosage form comprising cabergoline or a pharmaceutically acceptable salt thereof.

DETAILED DESCRIPTION OF THE INVENTION

15 This invention provides a sustained-release dosage form of cabergoline or a pharmaceutically acceptable salt thereof which advantageously achieves a more sustained drug blood level response while mitigating or eliminating drug concentration spikes by providing a substantially steady release of cabergoline over time.

As used herein, "mgA" is an abbreviation for "milligrams of active cabergoline". For
20 example, "200 mgA" means 200 mg of active cabergoline. Active cabergoline refers to the non-salt, non-hydrated free base. Accordingly, therapeutic amounts of "mgA" or release rates of "mgA/hr" refer to the non-salt, non-hydrated free base. For convenience, unless otherwise specified, "cabergoline" as used herein in reference to therapeutic amounts of "mgA" or release rates of "mgA/hr" refers to active cabergoline. Amounts in mgA can conveniently be
25 converted to equivalent weights for whatever salt form is desired. The cabergoline employed is preferably the free base, hydrochloride, aspartate, acetate, or lactate salt.

Dosage forms which release more than about 70% by weight of the cabergoline contained therein within one hour or less are not "sustained release" as used herein.

For the dosage form that releases cabergoline into a use environment at a rate not
30 exceeding about 5 mgA/hr, provided said dosage form (1) releases not more than about 70% by weight of the cabergoline contained therein within the first hour following entry into said use environment and (2) releases cabergoline at a rate of at least about 0.01 mgA/hr release rates range from about .01 to about 5 mgA/hr, such as, for example, from about .01 mgA/hr to about 2.0 mgA/hr, about .02 mgA/hr to about 3 mgA/hr, about .02 mgA/hr to about 1.5
35 mgA/hr, and about .02 mgA/hr to about 1 mgA/hr. The range about .01 mgA/hr to about 2.0 mgA/hr is preferred. The range about .02 mgA/hr to about 1.0 mgA/hr is most preferred.

Cabergoline may be released, for example, to a mammal's gastrointestinal (GI) tract following ingestion, or into an in vitro test medium for analysis by an in vitro test as described below. Reference to a "use environment" can be, for example, to in vivo gastrointestinal fluids or to an in vitro test medium.

5 Low rates of cabergoline are within the scope of the invention particularly for low-weight and/or elderly patients. Thus a cabergoline release rate of about .01 mgA/hr after ingestion represents a release profile within the scope of the invention and may be even more efficacious in providing a more sustained drug blood level response. The rate must be sufficient to deliver a therapeutically sufficient amount of cabergoline before the dosage form
10 is excreted with the feces. Accordingly, in one embodiment, dosage forms according to the invention should release cabergoline at a rate of at least about .01 mgA/hr.

The unit "kg" as used herein in "mgA/hr/kg" refers to kilograms of body weight for the mammal, preferably a human, being treated.

As used herein, the term "tablet" is intended to embrace compressed tablets, coated
15 tablets, osmotic tablets, and other forms known in the art. See for example, Remington's Pharmaceutical Sciences (18th Ed. 1990).

In one embodiment of the invention, the dosage form is in the form of a tablet. In one embodiment, the tablet does not comprise multiparticulates.

In another embodiment, the tablet comprises multiparticulates that have been mixed
20 with a binder, disintegrants, or other excipients known in the art, and then formed into a tablet using compressive forces. Examples of binders include microcrystalline cellulose, starch, gelatin, polyvinyl pyrrolidinone, polyethylene glycol, and sugars such as sucrose, glucose, dextrose, and lactose. Examples of disintegrants include sodium starch glycolate, croscarmellose sodium, crospovidone, and sodium carboxymethyl cellulose. The tablet may
25 also include an effervescent agent (acid-base combinations) that generates carbon dioxide when placed in the use environment. The carbon dioxide generated helps in disintegration of the tablet. Other excipients, such as those discussed above, may also be included in the tablet.

The multiparticulates, binder, and other excipients that may be used in the tablet may
30 be granulated prior to formation of the tablet. Wet- or dry-granulation processes, well known in the art, may be used, provided the granulation process does not change the release profile of the multiparticulates. Alternatively, the materials may be formed into a tablet by direct compression.

The compression forces used to form the tablet should be sufficiently high to provide
35 a tablet with high strength, but not too high to damage the multiparticulates that may be used

in the tablet. Generally, compression forces that result in tablets with a hardness of about 3 to about 10 Kp are desired.

Alternatively, tablets may also be made using non-compression processes. In one embodiment, the tablet is formed by a lyophilization process. In this process, 5 multiparticulates are mixed with an aqueous solution or paste of water-soluble excipients and placed into a mold. The water is then removed by lyophilization, resulting in a highly porous, fast dissolving tablet containing the multiparticulates. Examples of water-soluble excipients used in such tablets include gelatin, dextran, dextrin, polyvinyl pyrrolidone, polyvinyl alcohol, trehalose, xylitol, sorbitol and mannitol.

10 Tablets according to the invention are disclosed herein in further detail.

In another embodiment, the dosage form is in the form of a capsule, well known in the art. See Remington's Pharmaceutical Sciences (18th Ed. 1990). The term "capsule" is intended to include solid dosage forms in which multiparticulates and optional excipients are enclosed in either a hard or soft, soluble container or shell. A "capsule" also includes dosage 15 forms for which the body of the dosage form remains substantially intact during its residence in the GI tract.

Upon administration to the use environment, the shell dissolves or disintegrates, releasing the contents of the capsule to the use environment. The hard capsule, typically made from gelatin, consists of two sections, one slipping over the other. The capsules are 20 made by first blending multiparticulates and optional excipients, such as those listed above. The ingredients may be granulated using wet- or dry-granulation techniques to improve the flow of the fill material. The capsules are filled by introducing the fill material into the longer end or body of the capsule and then slipping on the cap. For soft-gelatin capsules, the fill material may first be suspended in an oil or liquid prior to filling the capsule.

25 Capsules according to the invention are disclosed herein in further detail.

The dosage form may also be in the form of pills. The term "pill" is intended to embrace small, round solid dosage forms that comprise multiparticulates mixed with a binder and other excipients as described above. Upon administration to the use environment, the pill rapidly disintegrates, allowing the multiparticulates to be dispersed therein. Pills according to 30 the invention are disclosed herein in further detail.

The term "multiparticulate" refers to a plurality of particles wherein each particle is designed to yield controlled release of cabergoline. Ideally, each particle in a multiparticulate constitutes a self-contained unit of sustained release. The particles can be formed into larger units. The multiparticulate particles each comprise cabergoline and one or more excipients 35 as needed for fabrication and performance. The size of individual particles is generally between about 40 micrometers and about 5 mm, for example between about 50 micrometers

and about 3 mm, or as another example between about 50 micrometers and about 1 mm, or as another example between about 50 micrometers and about 300 micrometers. Multiparticulates predominantly composed of particles toward the low end of this size range is sometimes referred to herein as a powder. Multiparticulates predominantly composed of particles toward the high end of the size range are sometimes referred to herein as beads. Beads having a size outside the particle size range are also useful. The diameter of the multiparticulates can be used to adjust the release rate of cabergoline from the multiparticulates. Generally, the smaller the diameter of the multiparticulates, the faster will be the cabergoline release rate from a particular multiparticulate formulation. This is because the overall surface area in contact with the dissolution medium increases as the diameter of the multiparticulates decreases. Thus, adjustments in the mean diameter of the multiparticulates can be used to adjust the cabergoline release profile. Multiparticulates according to the invention and dosage forms comprising the multiparticulates are disclosed herein in further detail. Ideally, each particle in a multiparticulate constitutes a self-contained unit of sustained release. The particles can be formed into larger units as by being compressed into a larger tablet-like unit or placed into a capsule which is more convenient for swallowing. The larger units, however, disintegrate rapidly upon swallowing to give rise to the multiparticulate form. Dosage forms comprising multiparticulates include unit dose packets (also known in the art as "sachets") and powders for oral suspension.

It is noted that the mouth-to-anus transit time of a non-disintegrating dosage form is approximately 24 hours. Dosage forms of this invention release at least about 6%, preferably at least about 70%, by weight of their contained cabergoline within 24 hours. Accordingly, controlled release cabergoline dosage forms according to the invention release at least about 60%, preferably at least 70%, by weight of their contained cabergoline within 24 hours, preferably within 18 hours, most preferably within 16 hours.

Although dosage forms as defined above generally release at least about 70% by weight of their contained cabergoline within 24 hours, a dosage form according to the invention can release substantially all of its cabergoline well before 24 hours so long as it otherwise releases cabergoline at a rate not exceeding about 5 mgA/hr.

The invention is particularly useful for orally administering relatively large amounts of cabergoline to a patient. The amount of cabergoline contained within the dosage form is preferably at least about .25 mgA, and can be as high as about 10 mgA or more. The amount contained in the dosage form may be, for example, about .25 mgA to about 6 mgA, about .5 mgA to about 6 mgA, about .5 mgA to about 2 mgA, or within other ranges comprised between .25 mgA and 10 mgA. The dosage form can be unitary or divided e.g., constituted by two or more units (such as capsules or tablets which, taken together, constitute

the dosage form) which are taken at or about the same time. Cabergoline can be employed in the dosage forms of this invention in the form of its pharmaceutically acceptable salts, and also in anhydrous as well as hydrated forms. All such forms can be used within the scope of this invention.

5 As indicated above, cabergoline exists in at least three crystalline forms, known in the art as Form I, Form II, and Form VII. All such forms can be used within the scope of this invention. A preferred form for the purposes of this invention is Form II.

 Also contemplated by the invention are combination dosage forms, for example those comprising one or more sustained release tablets contained within a capsule shell such as a
10 gelatin capsule shell.

 In one embodiment, the present invention contemplates zero-order or near zero-order release dosage forms. Most sustained release systems currently available do not have a zero-order or near zero-order release profile. A drug with a zero-order or near zero-order release profile releases its drug content at a uniform or nearly uniform rate independent of the
15 drug concentration (in the dosage form) during a given period of release. By contrast, in most drug formulations the rate of drug release increases rapidly or "spikes". This is followed by an exponentially declining rate of release. This type of drug release is categorized as the first-order release.

 The zero-order or near zero-order release dosage forms contemplated by the present
20 invention allow a reduction in dosing frequency even beyond that obtainable with other sustained released dosage forms, thus improving the dosage compliance on the part of subjects. The contemplated zero-order or near zero-order release dosage forms in particular tend to maximize therapeutic value while minimizing any side effects.

 The USP-2 apparatus used to test the dosage forms of the invention is well known
25 and described in United States Pharmacopoeia XXIII (USP) Dissolution Test Chapter 711, Apparatus 2.

 Any of the dosage forms herein can be incorporated into a capsule. If the dosage form is in a capsule, then the dosage form may be tested in an apparatus, such as a USP-2 apparatus containing an acetate buffer, as described herein, as appropriate depending on the
30 exact dosage form. Trypsin may be added to the acetate buffer to a concentration of 0.1 mg/ml. Generally, the amount of or size of the dosage form tested should contain or be equivalent to 200 mgA of cabergoline or less. If the dosage form contains more than 200 mgA, then the amount of acetate buffer test medium should be increased proportionately.

 The test solution employed in the USP-2 apparatus, as described hereinabove, may
35 be an acetic acid/acetate buffer solution, pH 4.0, containing 0.075 M in NaCl, and which is intended to simulate gastrointestinal fluids. The test solution is prepared by making a 0.13M

5 solution of acetic acid in water and then making this solution into an acetic acid/acetate buffer by adding potassium hydroxide, typically as an 0.5M aqueous solution, until a pH of 4.0 has been attained. Sufficient sodium chloride is then added to make the solution 0.075M in NaCl. The temperature of the test solution is preferably maintained at 37 °C throughout the dissolution test.

10 The in vitro release rate is determined by multiplying the incorporated dose by 0.8, and dividing this number by the measured time at which 80% by weight of the incorporated dose has been released and dissolved, as further discussed below. If 80% by weight of the incorporated cabergoline is not released in 24 hr, then the mgA cabergoline released at 24 hr should be divided by 24 hr, to give the release rate. Preferably, no more than 40 mgA is released in any one hour. For example, if a 20 mgA cabergoline dosage form is tested in this fashion, and 80% of the incorporated cabergoline is released in 8 hr, then the release rate is $(20 \text{ mg} \times 0.8) / 8 \text{ hr}$, or 2 mgA/hr. This dosage form is thus within the scope of this embodiment of the invention. As another example, if a 20 mgA cabergoline dosage form is tested in vitro, and 80% of the incorporated cabergoline (as cabergoline base) is released in 0.2 hr, then the release rate is $(20 \text{ mg} \times 0.8) / 0.2 \text{ hr}$, or 80 mgA/hr, and the dosage form is not within the scope of this embodiment of the invention.

15 In an exemplary embodiment, a unitary dosage form is dissolution tested by placing it in a paddle-equipped USP-2 apparatus containing 900 ml of the test solution just described, the test solution having a temperature of 37 °C, with the paddle stirring at 50 rpm. If the dosage form is a capsule, it is tested in the same manner except that the test solution may also contain 0.1 mg/mL of trypsin. Filtered aliquots (typically 2 or 10 mL) of the dissolution medium are taken at various times, referred to herein as "pull points". The exact time at which an aliquot is removed is not particularly critical, although pull points may be standardized for convenience. The aliquot is filtered and assayed for cabergoline content utilizing an HPLC assay or other suitable assay. The data is plotted as mgA cabergoline (active cabergoline) released (or % by weight cabergoline base released) on the y-axis vs time on the x-axis. The time at which 80% by weight of the cabergoline dose is released is noted.

20 To assure accuracy of results, more than one, for example three, or more, preferably six, separate dissolution tests should be conducted and the rates determined and averaged.

While there are many methods of describing the in vitro-rate of drug release from a dosage form (e.g. first-order rate constant, zero-order rate constant, initial rate, etc.), the method described above provides a clear test which is independent of the mechanism of cabergoline release from the dosage form.

35

As disclosed hereinabove, this invention provides a sustained release dosage form of cabergoline suitable for administration, such as oral administration to a mammal, which results in a maximum cabergoline plasma concentration, C_{max} , which is less than about 80% of the C_{max} determined when an equal dose of cabergoline is administered to the mammal, in the form of an immediate release bolus (such as an immediate-release tablet) provided the sustained release dosage form (1) releases not more than about 70% by weight of the cabergoline contained therein within the first hour following ingestion and (2) releases cabergoline at a rate of at least about 0.01 mgA/hr. As used herein, the term "immediate release" means that the bolus does not include a component for slowing disintegration or dissolution of the bolus. This aspect of the invention defines a sustained release dosage form according to the invention by means of an appropriate in vivo test which is conducted in the mammalian species of interest. For example, to test a sustained release cabergoline dosage form in humans, the cabergoline test dosage form is dosed to half of a group of 12 or more humans and, after an appropriate washout period (e.g. 1 week) the same subjects are dosed with an immediate-release bolus dose at the same strength. The other half of the group is dosed with the immediate-release bolus dose first, followed by the cabergoline (sustained-release) test dosage form and the plasma cabergoline levels are measured as a function of time. After determining C_{max} for each individual on each treatment, an average C_{max} is determined. If C_{max} for the sustained release cabergoline test dosage form is less than about 80% of the C_{max} for the bolus dose, then the test dosage form is within the scope of the invention. In this embodiment, the dosage form may be sustained release, engineered with or without an initial delay period, as further disclosed below.

In a further embodiment, this invention provides a sustained release dosage form of cabergoline suitable for oral administration to a mammal, which results in a maximum cabergoline plasma concentration, C_{max} , of about 1 to about 100 picograms/ml, when administered as a single dose.

In a further embodiment, this invention provides a sustained release dosage form of cabergoline suitable for oral administration to a mammal, which results in a maximum cabergoline plasma concentration, C_{max} , of about 1 to about 100 picograms/ml, wherein cabergoline is released over 8 to 12 hours, when administered as a single dose.

In a further embodiment, this invention provides a sustained release dosage form of cabergoline suitable for oral administration to a mammal, which results in a maximum cabergoline plasma concentration, C_{max} , of about 50 to about 100 picograms/ml, wherein plasma levels in the 12 to 24 hour period following administration are about 1 to about 100 picograms/ml, when administered as a single dose.

In a further embodiment, this invention provides a sustained release dosage form of cabergoline suitable for oral administration to a mammal, which results in a maximum cabergoline plasma concentration, $C_{\max}$, of about 1 – 100 picograms/ml, wherein plasma levels at $C_{\max}$ do not exceed two times the plasma level 24 hours after administration.

5 As stated hereinabove, sustained release cabergoline dosage forms provide a decreased $C_{\max}$ relative to the $C_{\max}$ for immediate-release dosage forms containing equal amounts of cabergoline. That is, sustained-release dosage forms exhibit a $C_{\max}$ which is less than or equal to about 80% of the $C_{\max}$ provided by an equivalent amount of cabergoline in an immediate release form. Preferred dosage forms additionally provide a total blood drug
10 exposure which, relative to an equivalent amount of cabergoline in an immediate-release dosage form, is not proportionately decreased as much as the sustained release $C_{\max}$. A "total blood drug exposure" is determined as the area under the curve ("AUC") determined by plotting the concentration of drug in the plasma (Y-axis) vs. time (X-axis). AUC is generally an average value, and would, for example, be averaged over all the subjects in the crossover
15 study described above. The determination of AUCs is a well known procedure, and is described, for example, in "Pharmacokinetics; Processes and Mathematics", by Peter Welling (ACS Monograph 185, Amer. Chem. Soc., Wash. D.C.: 1986), incorporated by reference herein. By way of example, a sustained release 10 mgA cabergoline dosage form A exhibits a $C_{\max}$ that is 65% of the $C_{\max}$ produced by a 10 mgA immediate release cabergoline bolus.
20 Accordingly, in a preferred embodiment, sustained release dosage form A will also exhibit an AUC that is higher than 65% of that provided by the bolus.

The sustained release dosage form may be a form having an initial delay period, wherein "initial delay period" refers to the period of time between ingestion of the form and the onset of release of cabergoline or a pharmaceutically acceptable salt thereof. Such an initial
25 delay period may be achieved, for example, by providing a form containing cabergoline or a pharmaceutically acceptable salt thereof, wherein the form is coated with an enteric coating. Such an initial delay period may also be achieved, for example, by providing a matrix system in which cabergoline or a pharmaceutically acceptable salt thereof is dissolved, embedded or dispersed. The material of which the coating or matrix is made is a material that serves to
30 retard the release of cabergoline or a pharmaceutically acceptable salt thereof into an aqueous environment. Suitable materials are also disclosed in detail hereinbelow.

The initial delay period may be independent or substantially independent from the nature of the medium surrounding the form. For example, if the material used as a coating or a matrix is a wax or a polymer, such as a starch or a starch-based polymer, that does not
35 contain pH-sensitive groups, groups that are sensitive to enzymes, or both, the initial delay period is independent or substantially independent from the pH of the medium surrounding

the form, the presence of enzymes in the medium surrounding the form, or both the pH and the presence of enzymes. Suitable materials are also disclosed in detail hereinbelow.

Alternatively, the initial delay period may depend on the nature of the medium surrounding the form. For example, if the material used as a coating or a matrix is a polymer that contains pH-sensitive groups, the initial delay period may depend on the pH of the medium surrounding the form. As another example, if the material is a polymer that is sensitive to enzymes, the initial delay period may depend on the presence in the medium surrounding the form of enzymes suitable for triggering the onset of the sustained release. Suitable materials are also disclosed in detail hereinbelow.

10 A "spatially delayed" sustained release dosage form is one in which the initial delay period depends on the nature of the use environment surrounding the form. For example, spatially delayed forms include forms for which the rate of release of cabergoline is sensitive to their position along the GI tract. Such forms possess a mechanism that largely or completely prevents release of cabergoline in the stomach, wherein sustained release
15 initiates after the dosage form has passed into the duodenum. Once having sustained release of cabergoline initiates, the rate of sustained release may be limited as described above for sustained release cabergoline dosage forms that do not exhibit a spatial delay. For example, for spatially delayed sustained release dosage forms of this invention, sustained release of cabergoline may initiate within about 30 minutes, preferably within about 15
20 minutes, of passing out of the stomach into the duodenum.

A spatially delayed form may be, for example, a dosage form delayed with a pH-trigger. The embodiment of the invention disclosed hereinabove, wherein the dosage form comprises cabergoline or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, wherein the dosage form releases cabergoline into 900 ml of 0.1 N HCl at
25 a rate less than about 0.001 mgA/hr for at least about 1 hour at 37° C in vitro when dissolution tested in an USP-2 apparatus and wherein said dosage form thereafter releases cabergoline into 900 ml of a phosphate buffer at a pH of 6.8 and containing 1% by weight of polysorbate 80 at 37° C, at a rate of from about 0.01 mgA/hr to about 10 mgA/hr, provided said dosage form releases not more than about 70% by weight of the cabergoline within the first hour
30 following the initial delay period, wherein: (1) if said dosage form is a sustained release tablet or a non-disintegrating sustained release capsule, said USP-2 apparatus is equipped with a paddle stirring at 50 rpm; (2) if said dosage form is a multiparticulate comprises multiparticulates and is not a tablet, said USP-2 apparatus is equipped with a paddle stirring at 100 rpm, is an example of a spatially delayed form.

The dosage form as defined in the previous paragraph may be, for example, a form that is coated with a polymer that prevents release of cabergoline at the pH of the stomach of a mammal, but which is permeable to cabergoline at the pH of the duodenum of the mammal.

5 A spatially delayed form may be, for example, a dosage form delayed with an enzyme-trigger. For example, in the embodiment disclosed in the previous paragraphs, the phosphate buffer at pH 6.8 and containing 1% by weight polysorbate 80 may also contain an enzyme suitable for triggering the onset of said sustained release.

10 In the in vitro tests described herein, the rate of release of cabergoline in mgA/hr is calculated as the average hourly quantity of cabergoline released, calculated over the initial 1 hr or longer time period of the test following the initial delay period.

Another example of a spatially delayed form is the form described hereinabove, which is a sustained release dosage form suitable for oral administration to a mammal, comprising cabergoline or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, which dosage form, following ingestion by said mammal, releases cabergoline into
15 said mammal's stomach at a rate less than about 0.01 mgA/hr, and which, after having passed into said mammals' duodenum; releases cabergoline at a rate of from about 0.01 mgA/hr to about 10 mgA/hr, provided said dosage form releases not more than about 70% by weight of the cabergoline contained therein within the first hour after passing into said mammal's duodenum.

20 Materials useful for the manufacture of the dosage forms of the invention include diluents such as microcrystalline cellulose such as Avicel® FMC Corp., Philadelphia, Pa.), including grades of microcrystalline cellulose to which binders such as hydroxypropyl methyl cellulose have been added, waxes such as paraffin, modified vegetable oils, carnauba wax, hydrogenated castor oil, beeswax, and the like, as well as polymers such as cellulose,
25 cellulose esters, cellulose ethers, poly(vinyl chloride), poly(vinyl acetate), copolymers of vinyl acetate and ethylene, polystyrene, and the like. The mean particle size for the microcrystalline cellulose generally ranges from about 90 μ m to about 200 μ m. Generally, the microcrystalline cellulose is present in an amount from about 10 wt % to about 70 wt %, more preferably, microcrystalline cellulose is present in an amount of about 30-70 wt %.

30 Water soluble binders or release modifying agents which can optionally be formulated include water-soluble polymers such as celluloses such as ethylcellulose, hydroxymethylcellulose, hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), methyl cellulose, poly (N-vinyl-2-pyrrolidinone) (PVP), poly(ethylene oxide) (PEO), polypropylpyrrolidone, poly(vinyl alcohol) (PVA), polyethylene glycol, starch, natural and
35 synthetic gums (e.g., acacia, alginates, and gum arabic) and other such natural and synthetic materials, and waxes. In addition, materials which function as release-modifying agents

include water-soluble materials such as sugars or salts. Exemplary water-soluble materials include lactose, sucrose, glucose, and mannitol, as well as HPC, HPMC; and PVP.

Lubricants may also be used in dosage forms according to the invention, such as in a tablet formulation, to prevent the tablet and punches from sticking in the die. Suitable lubricants include calcium stearate, glyceryl monostearate, glyceryl palmitostearate, hydrogenated vegetable oil, light mineral oil, magnesium stearate, mineral oil, polyethylene glycol, sodium benzoate, sodium lauryl sulfate, sodium stearyl fumarate, stearic acid, talc and zinc stearate. A preferred lubricant is magnesium stearate which may be present, for example, in an amount from about 0.25 wt % to about 4.0% wt %.

Disintegrants may also be added to the composition to break up the dosage form and release the compound. Suitable disintegrants include sodium starch glycolate, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, croscarmellose sodium, polyvinylpyrrolidone, methyl cellulose, microcrystalline cellulose, powdered cellulose, lower alkyl-substituted hydroxypropyl cellulose, polacrilin potassium, starch, pregelatinized starch and sodium alginate. Of these, croscarmellose sodium and sodium starch glycolate are preferred, with croscarmellose sodium being most preferred. The croscarmellose sodium is generally present in an amount from about 0.5 wt % to about 6.0 wt %. The amount of disintegrant included in the dosage form will depend on several factors, including the properties of the dispersion, the properties of the porogen (discussed below), and the properties of the disintegrant selected. Generally, the disintegrant will comprise from 1 wt % to 15 wt %, preferably from 1 wt % to 10 wt % of the dosage form.

Solubilizing acid excipients such as malic acid, citric acid, erythorbic acid, ascorbic acid, adipic acid, glutamic acid, maleic acid, aconitic acid, and aspartic acid and solubilizing excipients such as partial glycerides, glycerides, glyceride derivatives, polyethylene glycol esters, polypropylene glycol esters, polyhydric alcohol esters, polyoxyethylene ethers, sorbitan esters, polyoxyethylene sorbitan esters, saccharide esters, phospholipids, polyethylene oxide-polypropylene oxide block co-polymers, and polyethylene glycols, can be incorporated into dosage forms to increase the release rate of cabergoline, increase the total quantity of cabergoline released, and potentially increase absorption and consequently the bioavailability of cabergoline, particularly from matrix formulations that release cabergoline over a period of six hours or longer.

The dosage forms of the invention may contain, for example, less than about 20% by weight of reducing carbohydrates, where reducing carbohydrates are sugars and their derivatives that contain a free aldehyde or ketone group capable of acting as a reducing agent through the donation of electrons. Examples of reducing carbohydrates include

monosaccharides and disaccharides and more specifically include lactose, glucose, fructose, maltose and other similar sugars.

The dosage forms of the invention may contain, for example, dicalcium phosphate as a diluent, such as, for example, an amount from about 10 % by weight to about 50 % by weight or an amount equal to or greater than about 20% by weight of dicalcium phosphate, such as about 20-40 % by weight. Suitable grades of dicalcium phosphate include anhydrous (about 135 to 180 μ m mean, available from PenWest Pharmaceuticals Co., Patterson, N.Y. or Rhodia, Cranbury, N.J.), and dihydrate (about 180 μ m, available from PenWest Pharmaceuticals Co., Patterson, N.Y. or Rhodia, Cranbury, N.J.).

Excipients that may be used include starch, mannitol, kaolin, calcium sulfate, inorganic salts (e.g., sodium chloride), powdered cellulose derivatives, tribasic calcium phosphate, calcium sulfate, magnesium carbonate, magnesium oxide, poloxamers such as polyethylene oxide and hydroxypropyl methylcellulose. A volume mean diameter drug substance particle size of less than or equal to about 30 microns is utilized in an exemplary embodiment of the invention.

Polymer-based release-controlling components may also be used in the dosage form of the invention. These are generally polymers which are insoluble in aqueous media and are which are thermoplastic. Preferred polymers include cellulose ethers such as cellulose acetate, cellulose propionate, cellulose butyrate, cellulose acetate butyrate, ethylcellulose, hydroxypropylmethylcellulose, etc. Ethylcellulose is a particularly preferred polymer for use in a polymer-based release- controlling component according to the invention.

Polymer-based release-controlling components are preferably prepared in the form of an aqueous polymer dispersion and, when used in a process of the invention, are preferably applied to a substrate, for example a bead or pellet, by spraying or coating the aqueous polymer dispersion onto the substrate. Illustratively, where the composition being prepared is in the form of a bead, such an aqueous polymer dispersion is sprayed onto the bead during one or more processing steps, for example using a fluid bed processor, and is simultaneously or subsequently dried thereon. The term "aqueous polymer dispersion" herein refers to a polymer-based release- controlling component that is in the form of an aqueous dispersion. Such an aqueous polymer dispersion comprises a plurality of polymer particles dispersed in a continuous aqueous phase. The dispersion preferably contains at least one pharmaceutically acceptable plasticizing agent (also referred to as a plasticizer). Illustrative plasticizers include carboxylic acids (e.g. fatty acids) and salts thereof, alkyl esters of carboxylic acids, in particular C₁-C₆ alkyl esters of fatty acids or C₁-C₄ alkyl esters of phthalic or sebacic acid, propylene glycol, castor oil, medium chain triglycerides (MCT, e.g. coconut oil). Preferred plasticizers include dibutylsebacate, propylene glycol, triethylcitrate, tributylcitrate, castor oil,

acetylated monoglycerides, acetyl triethylcitrate, acetyl butylcitrate, diethyl phthalate, dibutyl phthalate, triacetin, MCT, palmitic acid, oleic acid, stearic acid, linoleic acid, linolenic acid, ricinoleic acid, arachidonic acid, and palmitoleic acid. Oleic acid, MCT and dibutylsebacate are particularly preferred plasticizers.

5 One suitable aqueous polymer dispersion is Aquacoat® of FMC Corp. Aquacoat® is prepared by dissolving ethylcellulose in a water-immiscible organic solvent and then emulsifying the same in water in the presence of a surfactant and a stabilizer. After homogenization to generate submicron droplets, the organic solvent is evaporated under vacuum to form a pseudolatex. The plasticizer is not incorporated in the pseudolatex during
10 the manufacturing phase. Thus, prior to using the same as a coating, it is desirable to intimately mix the Aquacoat® with a suitable plasticizer.

 Another suitable aqueous polymer dispersion is commercially available as Surelease® (Colorcon, Inc.). Surelease® is prepared by incorporating plasticizer into the dispersion during the manufacturing process as is disclosed in U.S. Pat. No. 4,502,888,
15 hereby incorporated by reference herein in its entirety. A hot melt of a polymer, plasticizer (e.g. MCT), and stabilizer (e.g. oleic acid) is prepared as a homogeneous mixture, which is then diluted with an alkaline solution (ammoniated water) to obtain an aqueous polymer dispersion which can be applied directly onto substrates. The term Surelease® herein refers to products, of any grade, marketed under the trade-name, illustratively Surelease® E-7-
20 19010, Surelease® E-7-7050, and Surelease® E-7-19000. Surelease® and equivalents thereto are preferred aqueous polymer dispersions for use in processes and compositions of the invention. Surelease® E-7-19010 is a particularly preferred aqueous polymer dispersion.

 Lubricants, excipients, diluents, binders, disintegrants, and carriers described in US Patent Application Publication 2003/0180360, incorporated by reference herein, may be
25 incorporated in the dosage form of the present invention. Polymer-based releasing components and plasticizers described in US Patent Application Publication 2003/0152624, incorporated by reference herein, are within the scope of the present invention.

 In one embodiment, the invention provides a process for manufacture of controlled-release dosage forms. The process comprises co- formulating cabergoline or a
30 pharmaceutically acceptable salt thereof and a pharmaceutically acceptable polymer-based release-controlling component. At least about 70%, preferably at least about 80%, more preferably at least about 90%, and still more preferably substantially all or all of a polymer-based release-controlling component used in the process has an age, at time of dosage unit manufacture, which varies by not more than about 180 days, preferably not more than about
35 120 days, and more preferably not more than about 90 days. The age control element of this embodiment is suitable for any process which includes steps of co- formulating cabergoline or

a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable polymer-based release-controlling component. Dosage forms prepared by such a process are a further embodiment of the invention. A process in accordance with the present invention may also be the process illustrated by Figure 1 of U.S. Patent Application Publication 2003/0152624, incorporated by reference herein.

An exemplary dosage form is a controlled release bead. An illustrative process for preparing such a bead comprises the steps of: (a) providing a core unit of substantially water-soluble or water-swellaable material; (b) applying a first layer of a substantially water-insoluble polymer to said core; (c) applying onto said first layer a second layer comprising cabergoline or a pharmaceutically acceptable salt thereof and optionally a polymer binder; and (d) applying onto said second layer a third polymer layer comprising the aqueous polymer dispersion; wherein the amount of material in said first layer is selected to provide a layer thickness that permits control of water penetration into the core. Dosage forms prepared according to such a process represent a further embodiment of the invention. In such a dosage form, a core unit comprises any pharmaceutically acceptable excipient which can be molded to form a bead or pellet. Preferably, the core comprises sucrose and/or starch (e.g. sugar spheres NF), sucrose crystals, microcrystalline cellulose, lactose, etc. Preferably, the core unit is in the shape of a sphere and has a diameter of about 0.5 to about 2 mm. The substantially water-insoluble polymer present in the first layer is preferably insoluble in gastrointestinal fluids. Non-limiting examples of suitable polymers for use in the first layer include ethylcellulose, cellulose acetate, cellulose acetate butyrate, polymethacrylates such as ethyl acrylate/methyl methacrylate copolymer (e.g. Eudragit® NE-30-D) and ammonio methacrylate copolymer types A and B (e.g. Eudragit® RL-30-D and RS-30-D), and silicone elastomers. Preferably, a plasticizer is also present in the first layer. Illustratively, the first layer can include a component comprising both a polymer and one or more plasticizers (e.g. Surelease®). The first layer preferably constitutes about 2% to about 80%, and more preferably about 3% to about 80%, of the total bead weight. The second layer comprises cabergoline or a pharmaceutically acceptable salt thereof and optionally a polymer binder. The polymer binder, when present, is preferably hydrophilic but may be water-soluble or water-insoluble. Illustrative polymer binders for use in the second layer are hydrophilic polymers such as polyvinylpyrrolidone (PVP), polyalkylene glycols such as polyethylene glycol, gelatin, polyvinyl alcohol, starch and derivatives thereof, cellulose derivatives such as hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose, hydroxyethylcellulose, carboxyethylcellulose, carboxymethylhydroxyethylcellulose, acrylic acid polymers, polymethacrylates, etc. Preferably the second layer constitutes about 0.05% to about 60%, and more preferably about 0.1% to about 30%, of the total bead weight. The third layer

comprises a polymer-based release-controlling component as described hereinabove. Preferably, the third layer constitutes about 1% to about 50%, and more preferably about 2% to about 25%, of the total bead weight. Optionally, a bead according to this embodiment can further comprise a fourth layer to prevent agglomeration and sticking of individual beads (i.e. a coating layer). Such a coating layer can comprise a polymer or any other desired coating material. A preferred coating material is HPMC. A particularly preferred dosage unit according to this embodiment comprises a plurality of beads encapsulated in a hard capsule, for example a hard gelatin capsule.

The sustained-release dosage forms of this invention can be widely implemented. For purposes of discussion, not limitation, the many embodiments hereunder can be grouped into classes according to design and principle of operation.

A class of sustained release dosage forms contemplated by the present invention includes matrix systems, in which cabergoline is dissolved, embedded or dispersed in a matrix of another material that serves to retard the release of cabergoline into an aqueous environment, such as the luminal fluid of the GI tract.

A "matrix system", as used herein, refers to a dosage form where the drug is admixed with excipients, often in compressed or extruded form, such that the release of the drug from the dosage form is controlled by a combination of erosion and diffusion. Erosional control of drug delivery involves the slow removal of the matrix material by the GI fluids to gradually expose and release the drug from the matrix. Diffusional control of drug delivery involves diffusion of soluble drug through the network of matrix excipients in a controlled fashion. In practice, many matrix dosage forms involve some degree of combination of the two mechanisms.

A matrix system may be a hydrophilic matrix system, which is a matrix system where water-soluble or water-swelling polymers form a network containing the drug. The rate that drug diffuses to the surface of the dosage form and the rate that the matrix falls apart control the rate that drug is made available to the GI system.

A matrix system may be a hydrophobic matrix system, which is a matrix system where water-insoluble or only partially water-soluble materials slow the rate that a drug is exposed to the fluid environment of the GI system, thereby controlling the rate drug is available for absorption.

Matrix systems that are encompassed by the invention include matrix systems described in US Patent Application Publication 2003/0180360, incorporated by reference herein.

When cabergoline is dissolved, embedded or dispersed in a matrix as described above, release of the drug takes place principally from the surface of the matrix. Thus the

drug is released from the surface of a device which incorporates the matrix after it diffuses through the matrix into the surrounding fluid or when the surface of the device dissolves or erodes, exposing the drug. In some embodiments, both mechanisms can operate simultaneously. The matrix systems may be large, i.e., tablet sized (about 1 cm), or small (<0.3 cm). The system may be unitary, it may be divided as previously discussed by virtue of being composed of several sub-units (for example, several tablets-which constitute a single dose) which are administered substantially simultaneously, it may consist of several small tablets within a capsule, or it may comprise multiparticulates. The multiparticulate may be used as small beads or a powder for filling a capsule shell, it may be compressed into a tablet, or it may be used per se for mixing with food (for example ice cream) to increase palatability, or as a sachet that may be dispersed in a liquid, such as fruit juice or water.

The multiplicity of variables affecting release of cabergoline from matrix devices permits abundant flexibility in the design of devices of different materials, sizes, and release times. Examples of modifications of cabergoline release profiles from the specific embodiments of the examples within the scope of this invention are disclosed in detail below.

Matrix tablets may be matrix tablets that remain substantially intact during the period of sustained release. Matrix tablets may also be matrix tablets partially coated with a polymer which impedes the release of cabergoline.

Non-eroding matrix tablets that provide sustained-release of cabergoline can be made with cabergoline free base and with a wide range of cabergoline salts such as cabergoline HCl, cabergoline lactate, cabergoline acetate and cabergoline aspartate and water insoluble materials such as waxes, cellulose, or other water insoluble polymers. Matrix materials useful for the manufacture of these dosage forms include diluents such as microcrystalline cellulose such as Avicel® FMC Corp., Philadelphia, Pa.), including grades of microcrystalline cellulose to which binders such as hydroxypropyl methyl cellulose have been added, waxes such as paraffin, modified vegetable oils, carnauba wax, hydrogenated castor oil, beeswax, and the like, as well as polymers such as cellulose, cellulose esters, cellulose ethers, poly(vinyl chloride), poly(vinyl acetate), copolymers of vinyl acetate and ethylene, polystyrene, and the like. The mean particle size for the microcrystalline cellulose generally ranges from about 90 μm to about 200 μm . Generally, the microcrystalline cellulose is present in an amount from about 10 wt % to about 70 wt %, more preferably, microcrystalline cellulose is present in an amount of about 30-70 wt %.

In addition to components of the matrix system, the size of the matrix system can affect the rate of cabergoline release. Therefore, a large matrix system will, in general, have a different composition from a small one such as a system comprising multiparticulates to

achieve similar release profiles. The effect of the size of the matrix system on the kinetics of cabergoline release follows scaling behavior well known in the study of diffusion.

It is well known in the art that diffusion-coefficients necessary to achieve the target characteristic time of release can change by orders of magnitude as the desired size of the device changes. Matrix materials which can be used to provide a cabergoline diffusion coefficient at the low end of the diffusion coefficient scale are polymers such as cellulose acetate. Conversely, materials at the upper end of the scale are materials such as polymers which form hydrogels when hydrated. The rate of diffusion for any particular device can accordingly be tailored by the material or materials selected, and the structure of the matrix.

For purposes of further illustration, to obtain a sustained-release non-eroding matrix in a particle of about 50 μm in diameter, a matrix material of a polymer such as cellulose acetate or a similar material is required, the slow diffusing matrix material tending to offset the short distances characteristic of small particle size. By contrast in order to obtain sustained-release in a large (e.g., 1 cm) device, a material which is more liquid-like (e.g., a hydrogel, see below) or with greater porosity is required. For devices of an intermediate size, e.g., about 1 mm in diameter, a matrix composition of intermediate characteristics can be employed.

It is also noted that the effective diffusion coefficient of cabergoline in a matrix can be increased to the desired value by the addition of plasticizers, pores, or pore-inducing additives, as known in the art. Slow-hydrating materials can also be used to effectively reduce the diffusion rates of cabergoline, particularly at times shortly after administration. In addition to changing the effective diffusion coefficient, the release rate can also be altered by the inclusion of more soluble salt forms (relative to the free base) such as cabergoline lactate, cabergoline acetate, or cabergoline aspartate, or excipients such as acids and/or surfactant-like compounds that solubilize cabergoline and minimize gelation, particularly in the presence of chloride ions.

A further sustained release non-eroding matrix-system comprises cabergoline dispersed in a hydrogel matrix. This embodiment differs from the hydrophilic matrix tablet in that the hydrogel of this embodiment is not a compressed tablet of soluble or erodible granular material, but rather a monolithic polymer network. As known in the art, a hydrogel is a water-swellaable network polymer. Hydrogels can be made in many geometries. As an example, tablets can be prepared by standard techniques containing 10 to 80% of a crosslinkable polymer. Once tablets are formed the polymer can be crosslinked via a chemical crosslinking agent such as gluteraldehyde or via UV irradiation forming a hydrogel matrix. Hydrogels are preferred materials for matrix devices because they can absorb or be made to contain a large volume fraction of water, thereby permitting diffusion of solvated drug

within the matrix. Diffusion coefficients of drugs in hydrogels are characteristically high, and for highly water-swollen gels, the diffusion coefficient of the drug in the gel may approach the value of impure water. This high diffusion coefficient permits practical release rates from relatively large devices (i.e., it is not necessary to form microparticles). Although hydrogel
5 devices can be prepared, loaded with cabergoline, stored, dispensed and dosed in the fully hydrated state, it is preferred that they be stored, dispensed, and dosed in a dry state. In addition to stability and convenience, dry state dosing of hydrogel devices can provide good cabergoline release kinetics due to Case II transport (i.e. combination of swelling of hydrogel and diffusion of drug out through the swollen hydrogel). Preferred materials for forming
10 hydrogels include hydrophilic vinyl and acrylic polymers, polysaccharides such as calcium alginate, and poly(ethylene oxide). Especially preferred are poly(2-hydroxyethyl methacrylate), poly(acrylic acid), poly(methacrylic acid), poly(N-vinyl-2-pyrrolidinone), poly(vinyl alcohol) and their copolymers with each other and with hydrophobic monomers such as methyl methacrylate, vinyl acetate, and the like. Also preferred are hydrophilic polyurethanes
15 containing large poly(ethylene oxide) blocks. Other preferred materials include hydrogels comprising interpenetrating networks of polymers, which may be formed by addition or by condensation polymerization, the components of which can comprise hydrophilic and hydrophobic monomers such as those just enumerated.

Non-eroding matrix tablets can be made by tableting methods common in the
20 pharmaceutical industry. Preferred embodiments of non-eroding matrix tablets contain, by weight, 10 to 80% cabergoline, 5 to 50% insoluble matrix materials such as cellulose, cellulose acetate, or ethylcellulose, and optionally 5 to 85% plasticizers, pore formers or solubilizing excipients, and optionally about 0.25 to 2% of a tableting lubricant, such as magnesium stearate, sodium stearyl fumarate, zinc stearate, calcium stearate, stearic acid,
25 polyethyleneglycol-8000, talc, or mixtures of magnesium stearate with sodium lauryl sulfate. These materials can be blended, granulated, and tableted using a variety of equipment common to the pharmaceutical industry.

A non-eroding matrix comprising multiparticulates comprises a plurality of cabergoline-containing particles, each particle comprising a mixture of cabergoline with one or
30 more excipients selected to form a matrix capable of limiting the dissolution rate of the cabergoline into an aqueous medium. The matrix materials useful for this embodiment are generally water-insoluble materials such as waxes, cellulose, or other water-insoluble polymers. If needed, the matrix materials can optionally be formulated with water-soluble materials which can be used as binders or as permeability-modifying agents. Matrix materials
35 useful for the manufacture of these dosage forms include microcrystalline cellulose such as Avicel® FMC Corp., Philadelphia, Pa.), including grades of microcrystalline cellulose to which

binders such as hydroxypropyl methyl cellulose (HPMC) have been added, waxes such as paraffin, modified vegetable oils, carnauba wax, hydrogenated castor oil, beeswax, and the like, as well as synthetic polymers such as poly(vinyl chloride), poly(vinyl acetate), copolymer of vinyl acetate and ethylene, polystyrene, and the like. Water soluble release modifying agents which can optionally be formulated into the matrix include water-soluble polymers such as HPC, HPMC, methyl cellulose, PVP, PEO, PVA, xanthan gum, carrageenan, and other such natural and synthetic materials. In addition, materials which function as release-modifying agents include water-soluble materials such as sugars or salts. Preferred water-soluble materials include lactose, sucrose, glucose, and mannitol, as well as HPC, HPMC, and PVP. In addition any of the solubilizing acid or surfactant type excipients previously mentioned can be incorporated into matrix multiparticulates to increase the release rate of cabergoline, increase the total quantity of cabergoline released, and potentially increase absorption and consequently the bioavailability of cabergoline, particularly from matrix formulations that release cabergoline over a period of six hours or longer.

A preferred process for manufacturing matrix multiparticulates is the extrusion/spheronization process. For this process, the cabergoline is wet-massed with a binder, extruded through a perforated plate or die, and placed on a rotating disks. The extrudate ideally breaks into pieces which are rounded into spheres, spheroids, or rounded rods on the rotating plate. A preferred process and composition for this method involves using water to wet-mass a blend comprising about 20 to 75% , by weight, of microcrystalline cellulose blended with, correspondingly, about 25 to 80% , by weight, cabergoline.

A preferred process for manufacturing matrix multiparticulates is the rotary granulation process. For this process cabergoline and excipients such as microcrystalline cellulose are placed in a rotor bow in a fluid bed processor. The drug and excipient are fluidized, while spraying a solution that binds the drug and excipients together in granules or multiparticulates. The solution sprayed into the fluid bed can be water or aqueous solutions or suspensions of binding agents such as polyvinylpyrrolidone or hydroxypropylmethylcellulose. A preferred composition for this method can comprise, by weight, 10 to 80% cabergoline, 10 to 60% microcrystalline cellulose, and 0 to 25% binding agent.

A further preferred process for manufacturing matrix multiparticulates involves coating cabergoline, matrix-forming excipients and if desired release-modifying or solubilizing excipients onto seed cores such as sugar seed cores known as non-pareils. Such coatings can be applied by many methods known in the pharmaceutical industry, such as spray-coating in a fluid bed coater, spray-drying, and granulation methods such as fluid bed or

rotary granulation. Coatings can be applied from aqueous, organic or melt solutions or suspensions.

A further preferred process for manufacturing matrix multiparticulates is the preparation of wax granules. In this process, a desired amount of cabergoline is stirred with
5 liquid wax to form a homogeneous mixture, cooled and then forced through a screen to form granules. Preferred matrix materials are waxy substances. Especially preferred are hydrogenated castor oil and carnauba wax and stearyl alcohol.

A further preferred process for manufacturing matrix multiparticulates involves using an organic solvent to aid mixing of the cabergoline with the matrix material. This technique
10 can be used when it is desired to utilize a matrix material with an unsuitably high melting point that, if the material were employed in a molten state, would cause decomposition of the drug or of the matrix material, or would result in an unacceptable melt viscosity, thereby preventing mixing of cabergoline with the matrix material. Cabergoline and matrix material can be combined with a modest amount of solvent to form a paste, and then forced through a screen
15 to form granules from which the solvent is then removed. Alternatively, cabergoline and matrix material can be combined with enough solvent to completely dissolve the matrix material and the resulting solution (which may contain solid drug particles) spray dried to form the particulate dosage-form. This technique is preferred when the matrix material is a high-molecular weight synthetic polymer such as a cellulose ether or cellulose ester. Solvents
20 typically employed for the process include acetone, ethanol, isopropanol, ethyl acetate, and mixtures of two or more.

A further process for manufacturing matrix multiparticulates contemplated by the present invention involves using an aqueous solution or suspension of cabergoline and matrix forming materials. The solution or suspension can be spray dried or sprayed or dripped into a
25 quench bath or through a light chamber to initiate crosslinking of matrix materials and solidify the droplets. In this manner matrices can be made from latexes (e.g. dispersed ethylcellulose with a plasticizer such as oleic acid or with a volatile water miscible solvent such as acetone or ethanol) by spray-drying techniques. Matrices can also be made in this manner by crosslinking a water soluble polymer or gum. For example, sodium alginate can be
30 crosslinked by spraying into a solution containing soluble calcium salts, polyvinyl alcohol can be crosslinked by spraying into a solution containing gluteraldehyde, and di- and tri-acrylates can be crosslinked by UV irradiation.

Processes for manufacturing multiparticulates are also discussed in further detail herein.

35 Once formed, cabergoline matrix multiparticulates can be blended with compressible excipients such as lactose, microcrystalline cellulose, dicalcium phosphate, and the like and

the blend compressed to form a tablet. Disintegrants such as sodium starch glycolate or crosslinked poly(vinyl pyrrolidone) are also usefully employed. Tablets prepared by this method disintegrate when placed in an aqueous medium (such as the GI tract); thereby exposing the multiparticulates which release cabergoline therefrom. Cabergoline matrix
5 multiparticulates can also be filled into capsules, such as hard gelatin capsules.

A further embodiment of a matrix system has the form of a hydrophilic matrix tablet that eventually dissolves or disperses in water containing cabergoline and an amount of hydrophilic polymer sufficient to provide a useful degree of control over the release of cabergoline. Cabergoline can be released from such matrices by diffusion, erosion or
10 dissolution of the matrix, or a combination of these mechanisms. Hydrophilic polymers useful for forming a hydrophilic matrix include HPMC, HPC, hydroxy ethyl cellulose (HEC), PEO, PVA, xanthan gum; carbomer, carrageenan, and zooglan. A preferred material is HPMC. Other similar hydrophilic polymers can also be employed. In use, the hydrophilic material is swollen by, and eventually dissolves or disperses in, water. The cabergoline release rate
15 from hydrophilic matrix formulations can be controlled by the amount and molecular weight of hydrophilic polymer employed. In general, using a greater amount of the hydrophilic polymer decreases the release rate, as does using a higher molecular weight polymer. Using a lower molecular weight polymer increases the release rate. The release rate can also be controlled by the use of water-soluble additives such as sugars, salts, or soluble polymers. Examples of
20 these additives are sugars such as lactose, sucrose, or mannitol, salts such as NaCl, KCl, NaHCO₃, and water soluble polymers such as PVP, low molecular weight HPC or HPMC or methyl cellulose. In general increasing the fraction of soluble material in the formulation increases the release rate. In addition any of the solubilizing acid excipients previously mentioned can be incorporated into matrix tablets to increase the release rate of cabergoline,
25 increase the total quantity of cabergoline released, and potentially increase absorption and consequently the bioavailability of cabergoline, particularly from matrix formulations that release cabergoline over a period of six hours or longer. A hydrophilic matrix tablet typically comprises about 10 to 90% by weight of cabergoline and about 10 to 80% by weight of polymer.

30 A preferred hydrophilic matrix tablet comprises, by weight, about 30% to about 80% cabergoline, about 5% to about 35% HPMC, 0% to about 35% lactose, 0% to about 15% PVP, 0% to about 20% microcrystalline cellulose, and about 0.25% to about 2% magnesium stearate.

Mixtures of polymers and/or gums can also be utilized to make hydrophilic matrix
35 systems. For example, homopolysaccharide gums such as galactomannans (e.g. locust bean gum or guar gum) mixed with heteropolyoaccharide gums (e.g. xanthan gum or its

derivatives) can provide a synergistic effect at in operation provides faster forming and more rigid matrices for the release of active agent (as disclosed in U.S. Patent Numbers. 5,455,046 and 5,512,297). Optionally, crosslinking agents such as calcium salts can be added to improve matrix properties.

5 Hydrophilic matrix formulations that eventually dissolve or disperse can also comprise multiparticulates. Hydrophilic matrix multiparticulates can be manufactured by the techniques described previously for non-eroding matrix multiparticulates. Preferred methods of manufacture are layering cabergoline, a hydrophilic matrix material, and if desired release modifying agents onto sugar seed cores (e.g. non-pareils) via a spray-coating process or to
10 form multiparticulates by granulation, such as in a rotary granulation of cabergoline, hydrophilic matrix material, and if desired release modifying agents.

 The matrix systems as a class often exhibit non-constant release of the drug from the matrix. This result may be a consequence of the diffusive mechanism of drug release, and modifications to the geometry of the dosage form and/or coating or partially coating the
15 dosage form can be used to advantage to make the release rate of the drug more constant as detailed below.

 In a further embodiment, a cabergoline matrix tablet is coated with an impermeable coating, and an orifice (for example, a circular hole or a rectangular opening) is provided by which the content of the tablet is exposed to the aqueous GI tract. These embodiments are
20 along the lines of those presented in U.S. Pat. No. 4,792,448 to Ranade, and as described by Hansson et al., J. Pharm. Sci. 77 (1988) 322-324 herein incorporated by reference. The opening is typically of a size such that the area of the exposed underlying cabergoline composition constitutes less than about 40% of the surface area of the device, preferably less than about 15%.

25 In another embodiment, a cabergoline matrix tablet is coated with an impermeable material on part of its surface, e.g. on one or both tablet faces, or on the tablet radial surface. The impermeable material impedes the release of cabergoline.

 In another embodiment, a cabergoline matrix tablet is coated with an impermeable material and an opening for drug transport produced by drilling a hole through the coating.
30 The hole may be through the coating only, or may extend as a passageway into the tablet.

 In another embodiment, a cabergoline matrix tablet is coated with an impermeable material and a passageway for drug transport produced by drilling a passageway through the entire tablet.

 In another embodiment, a cabergoline matrix tablet is coated with an impermeable
35 material and one or more passageways for drug transport are produced by removing one or

more strips from the impermeable coating or by cutting one or more slits through the coating, preferably on the radial surface or land of the tablet.

In another embodiment, a cabergoline matrix tablet is shaped in the form of a cone and completely coated with an impermeable material. A passageway for drug transport is produced by cutting off the tip of the cone.

In another embodiment, a cabergoline matrix tablet is shaped in the form of a hemisphere and completely coated with an impermeable material. A passageway for drug transport is produced by drilling a hole in the center of the flat face of the hemisphere. In another embodiment, a cabergoline matrix tablet is shaped in the form of a half-cylinder and completely coated with an impermeable material. A passageway for drug transport is produced by cutting a slit through (or removing a strip from) the impermeable coating along the axis of the half-cylinder along the centerline of the flat face of the half-cylinder.

By "impermeable material" is meant a material having sufficient thickness and impermeability to cabergoline such that the majority of cabergoline is released through the passageway rather than the "impermeable material" during the time scale of the intended drug release (i.e., several hours to about a day). A coating made of such a material can be obtained by selecting a coating material with a sufficiently low diffusion coefficient for cabergoline and applying it sufficiently thickly. Materials for forming the impermeable coating of these embodiments include substantially all materials in which the diffusion coefficient of cabergoline is less than about 10^{-7} cm² /s. It is noted that the preceding diffusion coefficient can be amply sufficient to allow release of cabergoline from a matrix device, as discussed above. However, for a device of the type now under discussion which has been provided with a macroscopic opening or passageway, a material with this diffusion coefficient is effectively impermeable to cabergoline relative to cabergoline transport through the passageway. Preferred coating materials include film-forming polymers and waxes. Especially preferred are thermoplastic polymers, such as poly(ethylene-co-vinyl acetate), poly(vinyl chloride), ethylcellulose, and cellulose acetate. These materials exhibit the desired low permeation rate of cabergoline when applied as coatings of thickness greater than about 100 μ m.

In another embodiment, a cabergoline matrix tablet or particulate is coated with a permeable coating, where "permeable coating" refers to a coating on a tablet or particulate that act as a barrier to drug leaving a tablet or to water contacting the drug. Such coatings include enteric coatings which become permeable as the pH increases when a dosage form exits the stomach. Examples of such coatings include Eudragits® sold by Rohm GmbH Pharma Polymers (Darmstadt, Germany) and cellulose acetate hydrogen phthalate (CAP) sold by Eastman Chemical (Kingsport, Tenn.). One group of such coated sustained release systems includes osmotic systems, such as described in WO 01/47498, incorporated by

reference herein. Such dosage forms involve a semi-permeable membrane surrounding a drug core containing sufficient osmotic pressure to drive water across the membrane in the GI system. The osmotic pressure can then force the drug out of the core through preformed or in situ produced holes or pores in the coating. Such systems often involve the addition of agents (osmagents) designed to increase the osmotic pressure in the core. A review describing such systems is found in G. Santus and R. W. Baker, J. Control. Rel., 1995, 35, 1-21, incorporated by reference herein.

Those skilled in the art will appreciate that the geometric modifications to the embodiments described above can be equivalently produced by more than one method. For example, cutting or drilling to make a passageway for drug transport can be achieved by other operations such as by a technique which produces the desired partial coating directly.

A second class of cabergoline sustained-release dosage forms of this invention includes membrane-moderated or reservoir systems such as membrane-coated diffusion-based capsule, tablet, or systems comprising multiparticulates. Capsules, tablets and systems comprising multiparticulates can all be reservoir systems, such as membrane-coated diffusion-based. In this class, a reservoir of cabergoline is surrounded by a rate-limiting membrane. The cabergoline traverses the membrane by mass transport mechanisms well known in the art, including but not limited to dissolution in the membrane followed by diffusion across the membrane or diffusion through liquid-filled pores within the membrane. These individual reservoir system dosage forms can be large, as in the case of a tablet containing a single large reservoir, or a system comprising a multiparticulate, as in the case of a capsule containing a plurality of reservoir particles, each individually coated with a membrane. The coating can be non-porous, yet permeable to cabergoline (for example cabergoline may diffuse directly through the membrane), or it can be porous.

Sustained release coatings as known in the art can be employed to fabricate the membrane, especially polymer coatings, such as a cellulose ester or ether, an acrylic polymer, or a mixture of polymers. Preferred materials include ethyl cellulose, cellulose acetate and cellulose acetate butyrate. The polymer can be applied as a solution in an organic solvent or as an aqueous dispersion or latex. The coating operation can be conducted in standard equipment such as a fluid bed coater, a Wurster coater, or a rotary bed coater.

If desired, the permeability of the coating can be adjusted by blending of two or more materials. A particularly useful process for tailoring the porosity of the coating comprises adding a pre-determined amount of a finely-divided water-soluble material, such as sugars or salts or water-soluble polymers to a solution or dispersion (e.g., an aqueous latex) of the membrane-forming polymer to be used. When the dosage form is ingested into the aqueous

medium of the GI tract, these water soluble membrane additives are leached out of the membrane, leaving pores which facilitate release of the drug. The membrane coating can also be modified by the addition of plasticizers, as known in the art.

5 A particularly useful variation of the process for applying a membrane coating comprises dissolving the coating polymer in a mixture of solvents chosen such that as the coating dries, a phase inversion takes place in the applied coating solution, resulting in a membrane with a porous structure. Numerous examples of this type of coating system are given in European Patent Specification 0 357 369 B1, published Mar. 7, 1990, herein incorporated by reference.

10 The morphology of the membrane is not of critical importance so long as the permeability characteristics enumerated herein are met. However, specific membrane designs will have membrane morphology constraints in order to achieve the desired permeability. The membrane can be amorphous or crystalline. It can have any category of morphology produced by any particular process and can be, for example, an interfacially-
15 polymerized membrane (which comprises a thin rate-limiting skin on a porous support), a porous hydrophilic membrane, a porous hydrophobic membrane, a hydrogel membrane, an ionic membrane, and other such membrane designs which are characterized by controlled permeability to cabergoline.

A useful reservoir system embodiment is a capsule having a shell comprising the
20 material of the rate-limiting membrane, including any of the membrane materials previously discussed, and filled with a cabergoline drug composition. A particular advantage of this configuration is that the capsule can be prepared independently of the drug composition, thus process conditions that would adversely affect the drug can be used to prepare the capsule. A preferred embodiment is a capsule having a shell made of a porous or a permeable
25 polymer made by a thermal forming process. An especially preferred embodiment is a capsule shell in the form of an asymmetric membrane; i.e., a membrane that has a thin dense region on one surface and most of whose thickness is constituted of a highly permeable porous material. A preferred process for preparation of asymmetric membrane capsules comprises a solvent exchange phase inversion, wherein a solution of polymer, coated on a
30 capsule-shaped mold, is induced to phase by exchanging the solvent with a miscible non-solvent. Examples of asymmetric membranes useful in this invention are disclosed in the aforementioned European Patent Specification 0 357 369 B1. The material made also be made porous by a phase separation process during the coating operation as described in U.S. Pat. Nos. 5,612,059 and 5,698,220, the contents of which are incorporated herein by
35 reference.

Tablets can also be reservoir systems. Tablet cores containing cabergoline can be made by a variety of techniques standard in the pharmaceutical industry. These cores can be coated with a rate-controlling coating which allows the cabergoline in the reservoir, or tablet core, to diffuse out through the coating at the desired rate.

5 Another embodiment of reservoir systems is a dosage form that comprises a multiparticulate wherein each particle is coated with a polymer designed to yield sustained release of cabergoline. The multiparticulate particles each comprise cabergoline and one or more excipients as needed for fabrication and performance. The size of individual particles, as previously mentioned, is generally between about 40 micrometer and about 5 mm,
10 preferably between about 50 micrometer and about 3 mm, although particles, such as beads, of a size outside this-range may also be useful. In general, the beads comprise cabergoline and one or more binders. As it is generally desirable to produce dosage forms which are small and easy to ingest, beads which contain a high fraction of cabergoline relative to excipients are preferred. Binders useful in fabrication of these beads include microcrystalline
15 cellulose (e.g., Avicel.RTM., FMC Corp.), HPC, HPMC, and related materials or combinations thereof. In general, binders which are useful in granulation and tableting, such as starch, pregelatinized starch, and PVP can also be used to form multiparticulates.

Reservoir system cabergoline multiparticulates can be prepared using techniques known to those skilled in the art, including, but not limited to, the techniques of extrusion and
20 spheronization, wet granulation, fluid bed granulation, and rotary bed granulation. In addition, beads can also be prepared by building the cabergoline composition (drug plus excipients) up on a seed core (such as a non-pareil seed) by a drug-layering technique such as powder coating or by applying the cabergoline composition by spraying a solution or dispersion of cabergoline in an appropriate binder solution onto seed cores in a fluidized bed such as a
25 Wurster coater or a rotary processor. An example of a suitable composition and method is to spray a dispersion of a cabergoline/hydroxypropylcellulose composition in water. Advantageously, cabergoline can be loaded in the aqueous composition beyond its solubility limit in water.

A preferred method for manufacturing multiparticulate cores of this embodiment is the
30 extrusion/spheronization process, as also discussed herein for matrix multiparticulates. A preferred process and composition for this method involves using water to wet-mass a blend of about 5 to 75% by weight of microcrystalline cellulose with correspondingly about 25 to 95% by weight cabergoline. Especially preferred is the use of about 5-30% by weight microcrystalline cellulose with correspondingly about 70-95% by weight cabergoline.

35 A preferred process for making multiparticulate cores of this embodiment is the rotary-granulation process, as previously discussed for matrix multiparticulates.

A preferred process for making multiparticulate cores of this embodiment is the process of coating seed cores with cabergoline and optionally other excipients, as previously discussed for matrix multiparticulates.

5 A sustained release coating as known in the art, especially polymer coatings, can be employed to fabricate the membrane, as previously discussed for reservoir systems. Suitable and preferred polymer coating materials, equipment, and coating methods also include those previously discussed.

The rate of cabergoline release from the coated multiparticulates can also be controlled by factors such as the composition and binder content of the drug-containing core, the thickness and permeability of the coating, and the surface-to-volume ratio of the multiparticulates. It will be appreciated by those skilled in the art that increasing the thickness of the coating will decrease the release rate, whereas increasing the permeability of the coating or the surface-to-volume ratio of the multiparticulates will increase the release rate. If desired, the permeability of the coating can be adjusted by blending of two or more materials.

15 A useful series of coatings comprises mixtures of water-insoluble and water-soluble polymers, for example, ethylcellulose and hydroxypropyl methylcellulose, respectively. A particularly useful modification to the coating is the addition of finely-divided water-soluble material, such as sugars or salts. When placed in an aqueous medium, these water soluble membrane additives are leached out of the membrane, leaving pores which facilitate delivery of the drug.

20 The membrane coating can also be modified by the addition of plasticizers, as is known to those skilled in the art. A particularly useful variation of the membrane coating utilizes a mixture of solvents chosen such that as the coating dries, a phase inversion takes place in the applied coating solution, resulting in a membrane with a porous structure.

A preferred embodiment is a multiparticulate with cores comprising, by weight, about 25 50 to 95% cabergoline and 5 to 50% of one or more of the following: microcrystalline cellulose, PVP, HPC and HPMC. The individual cores are coated with either an aqueous dispersion of ethyl cellulose, which dries to form a continuous film, or a film of cellulose acetate containing PEG, sorbitol or glycerol as a release-modifying agent.

In another embodiment, the dosage form is a dosage form in the form of a powder or 30 granules comprising multiparticulates and other excipients, that is then suspended in a liquid dosing vehicle, including an aqueous dosing vehicle, prior to dosing. Such dosage forms may be prepared by several methods. In one method, the powder is placed into a container and an amount of a liquid, such as water, is added to the container. The container is then mixed, stirred, or shaken to suspend the dosage form in the water. In another method, the 35 multiparticulates and dosing vehicle excipients are supplied in two or more separate packages. The dosing vehicle excipients are first dissolved or suspended in a liquid, such as

water, and then the multiparticulates are added to the liquid vehicle solution. Alternatively, the dosing vehicle excipients and multiparticulates, in two or more individual packages, can be added to the container first, water added to the container, and the container mixed or stirred to form a suspension.

5 Preferred processes for forming multiparticulates include thermal-based processes, such as melt- and spray-congealing; liquid-based processes, such as extrusion spheronization, wet granulation, spray-coating, and spray-drying; and other granulation processes such as dry granulation and melt granulation. Processes for forming multiparticulates are further disclosed herein.

10 Examples of carriers suitable for use in the multiparticulates of the present invention include waxes, such as synthetic wax, microcrystalline wax, paraffin wax, carnauba wax, and beeswax; glycerides, such as glyceryl monooleate, glyceryl monostearate, glyceryl palmitostearate, polyethoxylated castor oil derivatives, hydrogenated vegetable oils, glyceryl mono-, di- or tribehenates, glyceryl tristearate, glyceryl tripalmitate; long-chain alcohols, such as stearyl alcohol, cetyl alcohol, and polyethylene glycol; and mixtures thereof.

15 The multiparticulates may optionally include a dissolution enhancer. Dissolution enhancers increase the rate of dissolution of the drug from the carrier. In general, dissolution enhancers are amphiphilic compounds and are generally more hydrophilic than the carrier. Dissolution enhancers will generally make up about 0.1 to about 30 wt% of the total mass of the multiparticulate. Exemplary dissolution enhancers include alcohols such as stearyl alcohol, cetyl alcohol, and polyethylene glycol; surfactants, such as poloxamers (such as poloxamer 188, poloxamer 237, poloxamer 338, and poloxamer 407), docusate salts, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polysorbates, polyoxyethylene alkyl esters, sodium lauryl sulfate, and sorbitan monoesters; sugars such as glucose, sucrose, xylitol, sorbitol, and maltitol; salts such as sodium chloride, potassium chloride, lithium chloride, calcium chloride, magnesium chloride, sodium sulfate, potassium sulfate, sodium carbonate, magnesium sulfate, and potassium phosphate; amino acids such as alanine and glycine; and mixtures thereof. Preferably, the dissolution enhancer is at least one surfactant, and most preferably, the dissolution enhancer is at least one poloxamer.

30 Agents that inhibit or delay the release of cabergoline from the multiparticulates can also be included in the carrier. Such dissolution-inhibiting agents are generally hydrophobic. Examples of dissolution-inhibiting agents include: hydrocarbon waxes, such as microcrystalline and paraffin wax; and polyethylene glycols having molecular weights greater than about 20,000 daltons.

35 Another useful class of excipients that may optionally be included in the multiparticulates include materials that are used to adjust the viscosity of the molten feed

used to form the multiparticulates, for example, by a melt-congeal process. Such viscosity-adjusting excipients will generally make up 0 to 25 wt% of the multiparticulate, based on the total mass of the multiparticulate. The viscosity of the molten feed is a key variable in obtaining multiparticulates with a narrow particle size distribution. For example, when a spinning-disc atomizer is employed, it is preferred that the viscosity of the molten mixture be at least about 1 cp and less than about 10,000 cp, more preferably at least 50 cp and less than about 1000 cp. If the molten mixture has a viscosity outside these preferred ranges, a viscosity-adjusting carrier can be added to obtain a molten mixture within the preferred viscosity range. Examples of viscosity-reducing excipients include stearyl alcohol, cetyl alcohol, low molecular weight polyethylene glycol (e.g., less than about 1000 daltons), isopropyl alcohol, and water. Examples of viscosity-increasing excipients include microcrystalline wax, paraffin wax, synthetic wax, high molecular weight polyethylene glycols (e.g., greater than about 5000 daltons), ethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, methyl cellulose, silicon dioxide, microcrystalline cellulose, magnesium silicate, sugars, and salts.

The multiparticulates may be in the form of a non-disintegrating matrix. By "non-disintegrating matrix" is meant that at least a portion of the carrier does not dissolve or disintegrate after introduction of the multiparticulates to an aqueous use environment. In such cases, the cabergoline and optionally a portion of one or more of the carriers or optional excipients, for example, a dissolution-enhancer, are removed from the multiparticulate by dissolution. At least a portion of the carrier does not dissolve or disintegrate and is excreted when the use environment is in vivo, or remains suspended in a test solution when the use environment is in vitro. In this aspect, it is preferred that at least a portion of the carrier have a low solubility in the aqueous use environment. Preferably, the solubility of at least a portion of the carrier in the aqueous use environment is less than about 1 mg/mL, more preferably less than about 0.1 mg/mL, and most preferably less than about 0.01 mg/mL. Examples of suitable low-solubility carriers include waxes, such as synthetic wax, microcrystalline wax, paraffin wax, carnauba wax, and beeswax; glycerides, such as glyceryl monooleate, glyceryl monostearate, glyceryl palmitostearate, glyceryl mono-, di- or tribehenates, glyceryl tristearate, glyceryl tripalmitate; and mixtures thereof.

In one embodiment, the multiparticulate comprises (i) about 20 to about 75 wt% cabergoline, (ii) about 25 to about 80 wt% of a carrier, and (iii) about 0.1 to about 30 wt% of a dissolution enhancer based on the total mass of the multiparticulate.

In a more preferred embodiment, the multiparticulate comprises about (i) 35 wt% to about 55 wt% cabergoline; (ii) about 40 wt% to about 65 wt% of an excipient selected from waxes, such as synthetic wax, microcrystalline wax, paraffin wax, carnauba wax, and

beeswax; glycerides, such as glyceryl monooleate, glyceryl monostearate, glyceryl palmitostearate, polyethoxylated castor oil derivatives, hydrogenated vegetable oils, glyceryl mono-, di- or tribehenates, glyceryl tristearate, glyceryl tripalmitate and mixtures thereof; and (iii) about 0.1 wt% to about 15 wt% of a dissolution enhancer selected from surfactants, such as poloxamers, polyoxyethylene alkyl ethers, polyethylene glycol, polysorbates, polyoxyethylene alkyl esters, sodium lauryl sulfate, and sorbitan monoesters; alcohols, such as stearyl alcohol, cetyl alcohol and polyethylene glycol; sugars, such as glucose, sucrose, xylitol, sorbitol and maltitol; salts, such as sodium chloride, potassium chloride, lithium chloride, calcium chloride, magnesium chloride, sodium sulfate, potassium sulfate, sodium carbonate, magnesium sulfate and potassium phosphate; amino acids, such as alanine and glycine; and mixtures thereof.

In another embodiment, the multiparticulates comprise (i) cabergoline; (ii) a glyceride carrier having at least one alkylate substituent of 16 or more carbon atoms; and (iii) a poloxamer. At least 70 wt% of the drug in the multiparticulate is crystalline. The choice of these particular carrier excipients allows for precise control of the release rate of the cabergoline over a wide range of release rates. Small changes in the relative amounts of the glyceride carrier and the poloxamer result in large changes in the release rate of the drug.

The multiparticulates may comprise, for example, about 45 to about 55 % by weight cabergoline, from about 43 to about 50 % by weight glyceryl behenate, and from about 2 to about 5 % by weight poloxamer.

The multiparticulates may be made by a melt-congeal process comprising the steps of (a) forming a molten mixture comprising cabergoline and a pharmaceutically acceptable carrier; (b) delivering the molten mixture of step (a) to an atomizing means to form droplets from the molten mixture; and (c) congealing the droplets from step (b) to form the multiparticulates.

The cabergoline in the molten mixture may be dissolved in the molten mixture, may be a suspension of crystalline cabergoline distributed in the molten mixture, or any combination of such states or those states that are in between. Preferably, the molten mixture comprises a homogeneous suspension of crystalline cabergoline in the molten carrier where the fraction of cabergoline that melts or dissolves in the molten carrier is kept relatively low. Preferably less than about 30 wt% of the total cabergoline melts or dissolves in the molten carrier.

Thus, by "molten mixture" is meant that the mixture of cabergoline and carrier are heated sufficiently that the mixture becomes sufficiently fluid that the mixture may be formed into droplets or atomized. Atomization of the molten mixture may be carried out using any of the atomization methods described below. Generally, the mixture is molten in the sense that

it will flow when subjected to one or more forces such as pressure, shear, and centrifugal force, such as that exerted by a centrifugal or spinning-disk atomizer. Thus, the cabergoline/carrier mixture may be considered "molten" when the mixture, as a whole, is sufficiently fluid that it may be atomized. Generally, a mixture is sufficiently fluid for atomization when the viscosity of the molten mixture is less than about 20,000 cp, preferably less than about 15,000 cp, more preferably less than about 10,000 cp. Often, the mixture becomes molten when the mixture is heated above the melting point of one or more of the carrier components, in cases where the carrier is sufficiently crystalline to have a relatively sharp melting point; or, when the carrier components are amorphous, above the softening point of one or more of the carrier components. Thus, the molten mixture is often a suspension of solid particles in a fluid matrix. In one preferred embodiment, the molten mixture comprises a mixture of substantially crystalline cabergoline particles suspended in a carrier that is substantially fluid. In such cases, a portion of the cabergoline may be dissolved in the fluid carrier and a portion of the carrier may remain solid.

Although the term "melt" may refer specifically to the transition of a crystalline material from its crystalline to its liquid state, which occurs at its melting point, and the term "molten" may refer to such a crystalline material in its liquid state, as used herein, the terms may be used more broadly, referring in the case of "melt" to the heating of any material or mixture of materials sufficiently that it becomes fluid in the sense that it may be pumped or atomized in a manner similar to a crystalline material in the liquid state. Likewise "molten" may refer to any material or mixture of materials that is in such a fluid state.

Virtually any process can be used to form the molten mixture. One method involves melting the carrier in a tank, adding the cabergoline to the molten carrier, and then mixing the mixture to ensure the cabergoline is uniformly distributed therein. Alternatively, both the cabergoline and carrier may be added to the tank and the mixture heated and mixed to form the molten mixture. When the carrier comprises more than one material, the molten mixture may be prepared using two tanks, melting a first carrier in one tank and a second in another. The cabergoline is added to one of these tanks and mixed as described above. In another method, a continuously stirred tank system may be used, wherein the cabergoline and carrier are continuously added to a heated tank equipped with means for continuous mixing, while the molten mixture is continuously removed from the tank.

The molten mixture may also be formed using a continuous mill, such as a Dyno® Mill. The cabergoline and carrier are typically fed to the continuous mill in solid form, entering a grinding chamber containing grinding media, such as beads 0.25 to 5 mm in diameter. The grinding chamber typically is jacketed so heating or cooling fluid may be circulated around the

chamber to control its temperature. The molten mixture is formed in the grinding chamber, and exits the chamber through a separator to remove the grinding media.

An especially preferred method of forming the molten mixture is by an extruder. By "extruder" is meant a device or collection of devices that creates a molten extrudate by heat and/or shear forces and/or produces a uniformly mixed extrudate from a solid and/or liquid (e.g., molten) feed. Such devices include, but are not limited to single-screw extruders; twin-screw extruders, including co-rotating, counter-rotating, intermeshing, and non-intermeshing extruders; multiple screw extruders; ram extruders, consisting of a heated cylinder and a piston for extruding the molten feed; gear-pump extruders, consisting of a heated gear pump, generally counter-rotating, that simultaneously heats and pumps the molten feed; and conveyer extruders. Conveyer extruders comprise a conveyer means for transporting solid and/or powdered feeds, such as a screw conveyer or pneumatic conveyer, and a pump. At least a portion of the conveyer means is heated to a sufficiently high temperature to produce the molten mixture. The molten mixture may optionally be directed to an accumulation tank, before being directed to a pump, which directs the molten mixture to an atomizer. Optionally, an in-line mixer may be used before or after the pump to ensure the molten mixture is substantially homogeneous. In each of these extruders the molten mixture is mixed to form a uniformly mixed extrudate. Such mixing may be accomplished by various mechanical and processing means, including mixing elements, kneading elements, and shear mixing by backflow. Thus, in such devices, the composition is fed to the extruder, which produces a molten mixture that can be directed to the atomizer.

Once the molten mixture has been formed, it is delivered to an atomizer that breaks the molten mixture into small droplets. Virtually any method can be used to deliver the molten mixture to the atomizer, including the use of pumps and various types of pneumatic devices such as pressurized vessels or piston pots. When an extruder is used to form the molten mixture, the extruder itself can be used to deliver the molten mixture to the atomizer. Typically, the molten mixture is maintained at an elevated temperature while delivering the mixture to the atomizer to prevent solidification of the mixture and to keep the molten mixture flowing.

Generally, atomization occurs in one of several ways, including (1) by "pressure" or single-fluid nozzles; (2) by two-fluid nozzles; (3) by centrifugal or spinning-disk atomizers; (4) by ultrasonic nozzles; and (5) by mechanical vibrating nozzles. Detailed descriptions of atomization processes can be found in Lefebvre, *Atomization and Sprays* (1989) or in Perry's *Chemical Engineers' Handbook* (7th Ed. 1997). In a preferred embodiment, the atomizer is a centrifugal or spinning-disk atomizer, such as the FX1 100-mm rotary atomizer manufactured by Niro A/S of Soeborg, Denmark.

Once the molten mixture has been atomized, the droplets are congealed, typically by contact with a gas or liquid at a temperature below the solidification temperature of the droplets. Typically, it is desirable that the droplets are congealed in less than about 60 seconds, preferably in less than about 10 seconds, more preferably in less than about 1 second. Often, congealing at ambient temperature results in sufficiently rapid solidification of the droplets. However, the congealing step often occurs in an enclosed space to simplify collection of the multiparticulates. In such cases, the temperature of the congealing medium (either gas or liquid) will increase over time as the droplets are introduced into the enclosed space. Thus, a cooling gas or liquid is often circulated through the enclosed space to maintain a constant congealing temperature. When the carrier used is reactive with cabergoline and the time the cabergoline is exposed to the molten carrier must be limited, the cooling gas or liquid can be cooled to below ambient temperature to promote rapid congealing.

A third class of cabergoline sustained-release dosage forms includes the osmotic delivery devices or "osmotic pumps" as they are known in the art. Osmotic pumps comprise a core containing an osmotically effective composition surrounded by a semipermeable membrane. The term "semipermeable" in this context means that water can pass through the membrane, but solutes dissolved in water permeate through the membrane at a rate significantly slower than water. In use, when placed in an aqueous environment, the device imbibes water due to the osmotic activity of the core composition. Owing to the semipermeable nature of the surrounding membrane, the contents of the device (including the drug and any excipients) cannot pass through the non-porous regions of the membrane and are driven by osmotic pressure to leave the device through an opening or passageway pre-manufactured into the dosage form or, alternatively, formed in situ in the GI tract as by the bursting of intentionally-incorporated weak points in the coating under the influence of osmotic pressure, or alternatively, formed in situ in the GI tract by dissolution and removal of water-soluble porosigens incorporated in the coating. The osmotically effective composition includes water-soluble species, which generate a colloidal osmotic pressure, and water-swellaable polymers. The drug itself (if highly water-soluble) can be an osmotically effective component of the mixture. Materials useful for forming the semipermeable membrane include polyamides, polyesters, and cellulose derivatives. Preferred are cellulose ethers and esters. Especially preferred are cellulose acetate, cellulose acetate butyrate, and ethyl cellulose. Especially useful materials include those which spontaneously form one or more exit passageways, either during manufacturing or when placed in an environment of use. These preferred materials comprise porous polymers, the pores of which are formed by phase

inversion during manufacturing, as described below, or by dissolution of a water-soluble component present in the membrane.

A class of materials which have particular utility for forming semipermeable membranes for use in osmotic delivery devices is that of porous hydrophobic polymers or vapor-permeable films, as disclosed by commonly assigned U.S. application Serial No. 08/096,144, filed Jul. 22, 1993, now abandoned, herein incorporated by reference. These materials are highly permeable-to water, but highly impermeable to solutes dissolved in water. These materials owe their high water permeability to the presence of numerous microscopic pores (i.e., pores which are much larger than molecular dimensions). Despite their porosity, these materials are impermeable to molecules in aqueous solution because liquid water does not wet the pores. Water in the vapor phase is easily able to pass across membranes made from these materials. Such membranes are also known as vapor permeable membranes.

A preferred embodiment of this class of osmotic delivery devices consists of a coated bi-layer tablet. The coating of such a tablet comprises a membrane permeable to water but substantially impermeable to cabergoline and excipients contained within. The coating contains one or more exit passageways in communication with the cabergoline-containing layer for delivering the drug composition. The tablet core consists of two layers: one layer containing the cabergoline composition (including optional osmagents and hydrophilic water-soluble polymers) and another layer consisting of an expandable hydrogel, with or without additional osmotic agents.

When placed in an aqueous medium, the tablet imbibes water through the membrane, causing the cabergoline composition to form a dispensible aqueous composition, and causing the hydrogel layer to expand and push against the cabergoline composition, forcing the cabergoline composition out of the exit passageway. The cabergoline composition can swell aiding in forcing the cabergoline out the passageway. Cabergoline can be delivered from this type of delivery system either dissolved or dispersed in the composition forced out of the exit passageway.

The rate of cabergoline delivery is controlled by such factors as the permeability and thickness of the coating, the osmotic pressure of the cabergoline-containing layer, the water activity of the hydrogel layer, and the surface area of the device. Those skilled in the art will appreciate that increasing the thickness of the coating will reduce the release rate, whereas increasing the permeability of the coating or the water activity of the hydrogel layer or the osmotic pressure of the cabergoline-containing layer or the surface area of the device will increase the release rate.

Exemplary materials which are useful to form the cabergoline composition, in addition to the cabergoline itself, include HPMC, PEO, and PVP, and other pharmaceutically-

acceptable carriers. In addition, osmagents such as sugars or salts, especially sucrose, mannitol, or sodium chloride, can be added. Materials which are useful for forming the hydrogel layer include sodium carboxymethyl cellulose, poly (ethylene oxide), poly(acrylic acid), sodium (poly-acrylate) and other high molecular-weight hydrophilic materials. In addition, osmagents such as sugars or salts may be added. Particularly useful are poly (ethylene oxide)s having a molecular weight from about 5,000,000 to about 7,500,000.

Materials which are useful for forming the coating are cellulose esters, cellulose ethers, and cellulose ester-ethers. Preferred are cellulose acetate and ethylcellulose and optionally with PEG included as permeability modifying component.

The exit passageway must be located on the side of the tablet containing the cabergoline composition. There can be more than one such exit passageway. The exit passageway can be produced by mechanical means or by laser drilling, or by creating a difficult-to-coat region on the tablet by use of special tooling during tablet compression or by other means. The rate of cabergoline delivery from the device can be optimized so as to provide a method of delivering cabergoline to a mammal for optimum therapeutic effect.

Osmotic systems can also be made with a homogeneous core surrounded by a semipermeable membrane coating. Cabergoline can be incorporated into a tablet core that also contains other excipients that provide sufficient osmotic driving force and optionally solubilizing excipients such as acids or surfactant-type compounds. A semipermeable membrane coating can be applied via conventional tablet-coating techniques such as using a pan coater. A drug-delivery passageway can then be formed in this coating by drilling a hole in the coating, either by use of a laser or other mechanical means. Alternatively, the passageway can be formed by rupturing a portion of the coating or by creating a region on the tablet that is difficult to coat, as described above.

An embodiment of cabergoline-sustained-release osmotic dosage forms of this invention comprises an osmotic cabergoline containing tablet, which is surrounded by an asymmetric membrane, where said asymmetric membrane possesses one or more thin dense regions in addition to less dense porous regions. This type of membrane, similar to those used-in the reverse-osmosis industry, generally allows higher osmotic fluxes of water than can be obtained with a dense membrane. When applied to a drug formulation, e.g. a tablet, an asymmetric membrane allows high drug fluxes and well-controlled sustained drug release. This asymmetric membrane comprises a semipermeable polymeric material, that is, a material which is permeable to water, and substantially impermeable to salts and organic solutes such as drugs like cabergoline.

Materials useful for forming the semipermeable membrane include polyamides, polyesters, and cellulose derivatives. Preferred are cellulose ethers and esters. Especially

preferred are cellulose acetate, cellulose acetate butyrate and ethyl cellulose. Especially useful materials include those which spontaneously form one or more exit passageways, either during manufacturing or when placed in an environment of use. These preferred materials comprise porous polymers, the pores of which are formed by phase inversion during
5 manufacturing, as described above, or by dissolution of a water-soluble component present in the membrane.

The asymmetric membrane is formed by a phase-inversion process. The coating polymer, e.g. ethylcellulose or cellulose acetate, is dissolved in a mixed solvent system comprising a mixture of solvents (e.g. acetone) and non-solvents (e.g. water) for the
10 ethylcellulose or cellulose acetates. The components of the mixed solvent are chosen such that the solvent (e.g. acetone) is more volatile than the non-solvent (e.g. water). When a tablet is dipped into such a solution, removed and dried, the solvent component of the solvent mixture evaporates more quickly than the non-solvent. This change in solvent composition during drying causes a phase-inversion, resulting in precipitation of the polymer on the tablet
15 as a porous solid with a thin dense outer region. This outer region possesses multiple pores through which drug delivery can occur.

In a preferred embodiment of an asymmetric membrane-coated tablet, the polymer/solvent/non-solvent mixture is sprayed onto a bed of tablets in a tablet-coating apparatus such as a Freund HCT-60 tablet coater. In this process, the tablet is coated with
20 thick porous regions, and with a final outer thin dense region.

In the environment of use, e.g. the GI tract-water is imbibed through the semipermeable asymmetric membrane into the tablet core. As soluble material in the tablet core dissolves, an osmotic pressure gradient across the membrane builds. When the hygrostatic pressure within the membrane enclosed core exceeds the pressure of the
25 environment of use (e.g. the GI lumen), the cabergoline-containing solution is "pumped" out of the dosage form through preformed pores in the semipermeable membrane. The constant osmotic pressure difference across the membrane results in a constant well-controlled delivery of cabergoline to the use environment. A portion of the cabergoline dissolved in the tablet also exits via diffusion.

30 In this asymmetric-membrane-coated cabergoline tablet embodiment, pharmaceutically acceptable salts of cabergoline may be used, including, for example, the hydrochloride, aspartate, acetate and lactate salts. . One or more solubilizing excipients may also be included in this embodiment, such as, for example, ascorbic acid, erythorbic acid, citric acid, glutamic acid, aspartic acid, partial glycerides, glycerides, glycerides derivatives,
35 such as, for example, glyceryl monocaprylate, glyceryl monostearate, glyceryl monolaurate, and C₈-C₁₀ partial glycerides, polyethylene glycol esters, polypropylene glycol esters,

polyhydric alcohol esters, polyoxyethylene ethers, sorbitan esters, polyoxyethylene sorbitan esters, saccharide esters, phospholipids, polyethylene oxide-polypropylene oxide block copolymers, and polyethylene glycols.

Osmotic tablets can also be made with a core tablet containing osmagents and/or solubilizing excipients surrounded first by a drug containing layer and then second a semipermeable coating. The core tablet containing osmagents and/or solubilizing excipients can be made by standard tableting methods known in the pharmaceutical industry. The drug containing layer can be applied around the core by spray-coating methods where a solution or slurry of drug and excipients is coated onto the tablet core. The drug and excipients can also be layered around the tablet core by making a "layered" type of configuration using a tablet press to form a second drug-containing layer around the tablet core. This type of compression coating method can be used to apply a powder coating (without solvents) around a tablet-core. The semipermeable coating can then be applied to the layered core by many processes known in the art such as spray-coating or dip-coating methods described previously in these specifications.

Another embodiment of sustained release cabergoline osmotic dosage forms of this invention consists of cabergoline multiparticulates coated with an asymmetric membrane. Cabergoline-containing multiparticulates are prepared by, for example, extrusion/spheronization or fluid bed granulation, or by coating non-pareil seeds with a mixture of cabergoline and a water-soluble polymer, as described above. Cabergoline-containing multiparticulates are then spray-coated with a solution of a polymer in a mixture of a solvent and a non-solvent, as described above, to form asymmetric-membrane-coated multiparticulates. This spray operation is preferably carried out in a fluid bed coating apparatus, e.g. a Glatt GPCG-5 fluid bed coater.

The polymer used for forming the semipermeable asymmetric membrane is chosen as described above for asymmetric membrane coated tablets. Likewise excipients for the multiparticulate cores can be chosen as described above for asymmetric-membrane coated tablets.

Osmotic capsules can be made using the same or similar components to those described above for osmotic tablets and multiparticulates. The capsule shell or portion of the capsule shell can be semipermeable and made of materials described above. The capsule can then be filled either by a powder or liquid consisting of cabergoline, excipients that provide osmotic potential, and optionally solubilizing excipients. The capsule core can also be made such that it has a bilayer or multilayer composition as to the bilayer tablet described above.

A fourth class of cabergoline sustained release dosage forms of this invention are the forms described in EP 378404A2, herein incorporated by reference. Coated swellable tablets comprise a tablet core comprising cabergoline and a swelling material, preferably a hydrophilic polymer, coated with a membrane which contains holes or pores through which, in the aqueous use environment, the hydrophilic polymer can extrude and carry out the cabergoline. Alternatively, the membrane can contain polymeric or low molecular weight water soluble porosigens which dissolve in the aqueous use environment, providing pores through which the hydrophilic polymer and cabergoline can extrude. Examples of porosigens are water-soluble polymers such as hydroxypropylmethylcellulose (HPMC), and low molecular weight compounds like glycerol, sucrose, glucose, and sodium chloride. In addition, pores can be formed in the coating by drilling holes in the coating using a laser or other mechanical means. In this fourth class of cabergoline sustained release dosage forms, the membrane material can comprise any film-forming polymer, including polymers which are water permeable or impermeable, providing that the membrane deposited on the tablet core is porous or contains water-soluble porosigens or possesses a macroscopic hole for water ingress and cabergoline release. Multiparticulates (or beads) can be similarly prepared, with a cabergoline/swellable material core, coated by a porous or porosigen-containing membrane. Embodiments of this fourth class of cabergoline sustained release dosage forms can also be multilayered, as described in EP 378 404 A2.

Sustained release formulations can also be prepared with a small portion of the dose released initially rapidly, followed by sustained release of the remaining majority portion of the dose. The combined cabergoline release profile in this case is within the scope of sustained release dosage forms of this invention. For example, cabergoline may be released at a rate less than about 10 mgA/hr, provided said dosage form (1) releases not more than about 70% of the cabergoline contained therein within the first hour following entry into a use environment and (2) releases cabergoline at a rate of at least 0.01 mgA/hr, such as, for example, at least about 1 mgA/hr.

When formulating cabergoline, it is advantageous to employ a high solubility salt, a formulation which otherwise increases cabergoline solubility, or a combination of both collectively known as a "high solubility form". The following is a discussion of the reasons and advantages accruing, from a formulations standpoint, from the use of high solubility forms of cabergoline. Whether due to the salt form employed or the particular excipients employed in the dosage form, the high solubility form should effect a cabergoline solubility of at least 10 mgA/ml.

Salts of cabergoline or excipients that, in combination with cabergoline, aid in solubilizing cabergoline can be beneficial to almost all types of sustained-release dosage

forms. Solubilized cabergoline can enhance release from the dosage form by increasing the concentration gradient for diffusive based systems such as matrix dosage forms and reservoir dosage forms. Solubilized cabergoline can also enhance delivery from osmotic dosage forms in that a more soluble cabergoline can increase the osmotic pressure in the core and increase the cabergoline concentration in the fluid that is pumped or extruded out of the dosage form. In addition, solubilized-cabergoline can benefit sustained-release formulations by aiding absorption of drug from the G.I. tract. For example, higher concentrations of drug in the colon can increase absorption due to a higher concentration gradient across the colonic wall.

Preferred embodiments of sustained release formulations are osmotic systems comprising a core containing cabergoline or a cabergoline salt, an acid such as ascorbic, erythorbic, citric, glutamic, or aspartic acid, and if needed, a soluble sugar as an osmogen, binder material such as microcrystalline cellulose, swellable hydrophilic polymers, and a lubricant such as magnesium stearate. More preferred embodiments incorporate cabergoline in crystalline form II.

Another preferred embodiment of sustained release formulations are osmotic systems comprising a core containing cabergoline or a cabergoline salt, an acid such as ascorbic, erythorbic, citric, glutamic, or aspartic acid, a surfactant-like material such as partial glycerides, glycerides, sorbitan esters, phospholipids, polyethylene oxide-polypropylene oxide block co-polymers, and polyethylene glycols, and if needed, a soluble sugar to increase the osmotic pressure within the core, swellable hydrophilic polymers, binder material such as microcrystalline cellulose, and a lubricant such as magnesium stearate.

Another preferred embodiment of sustained release formulations are osmotic systems comprising a core containing cabergoline-lactate or cabergoline-acetate, a surfactant-like material such as partial glycerides, glycerides, sorbitan esters, phospholipids, polyethylene oxide-polypropylene oxide block co-polymers, and polyethylene glycols, a soluble sugar to increase the osmotic pressure within the core, and if needed, swellable hydrophilic polymers, binder material such as microcrystalline cellulose, and a lubricant such as magnesium stearate.

Preferred embodiments of sustained release formulations are osmotic systems such as any of the three osmotic systems discussed immediately above, and further coated with an asymmetric membrane coating made by a phase-inversion process. For use in these membrane systems cabergoline in crystalline form II is especially preferred.

Preferred embodiments of sustained release formulations are osmotic systems comprising a core containing cabergoline lactate or cabergoline acetate or cabergoline aspartate, an acid such as ascorbic, erythorbic, citric, glutamic, or aspartic acid, and if needed, a soluble sugar as an osmogen, binder material such as microcrystalline cellulose,

swellable hydrophilic polymers, and a lubricant such as magnesium stearate. More preferred embodiments incorporate cabergoline in crystalline form II.

Preferred embodiments of sustained release formulations are osmotic systems such as any of the osmotic systems discussed immediately above, and further coated with an asymmetric membrane coating made by a phase-inversion process. For use in these membrane systems cabergoline in crystalline form II is especially preferred.

A wide variety of conditions or diseases may be treated using the dosage form of the invention. In one embodiment, this invention provides a method for treating Parkinson's disease, comprising orally administering to a mammal in need of such treatment, including a human patient, a therapeutically effective amount of cabergoline in a sustained-release dosage form comprising cabergoline or a pharmaceutically acceptable salt thereof, such as an oral dosage form which releases the cabergoline according to the release rate described above, such as, for example, from about 0.01 mgA/hr to about 5 mgA/hr in a use environment as described herein, such as an in vivo gastrointestinal fluid.

In a further embodiment, this invention provides a method for treating Progressive Supranuclear Palsy, comprising orally administering to a mammal in need of such treatment, including a human patient, a therapeutically effective amount of cabergoline in a sustained-release dosage form comprising cabergoline or a pharmaceutically acceptable salt thereof, such as an oral dosage form which releases the cabergoline according to the release rate described above, such as, for example, from about 0.01 mgA/hr to about 5 mgA/hr in a use environment as described herein, such as an in vivo gastrointestinal fluid.

In a further embodiment, this invention provides a method for treating Multisystemic Atrophy, comprising orally administering to a mammal in need of such treatment, including a human patient, a therapeutically effective amount of cabergoline in a sustained-release dosage form comprising cabergoline or a pharmaceutically acceptable salt thereof, such as an oral dosage form which releases the cabergoline according to the release rate described above, such as, for example, from about 0.01 mgA/hr to about 5 mgA/hr in a use environment as described herein, such as an in vivo gastrointestinal fluid.

In a further embodiment, this invention provides a method for treating Restless Legs Syndrome, comprising orally administering to a mammal in need of such treatment, including a human patient, a therapeutically effective amount of cabergoline in a sustained-release dosage form comprising cabergoline or a pharmaceutically acceptable salt thereof, such as an oral dosage form which releases the cabergoline according to the release rate described above, such as, for example, from about 0.01 mgA/hr to about 5 mgA/hr in a use environment as described herein, such as an in vivo gastrointestinal fluid.

In a further embodiment, this invention provides a method for treating Fibromyalgia, comprising orally administering to a mammal in need of such treatment, including a human patient, a therapeutically effective amount of cabergoline in a sustained-release dosage form comprising cabergoline or a pharmaceutically acceptable salt thereof, such as an oral dosage
5 form which releases the cabergoline according to the release rate described above, such as, for example, from about 0.01 mgA/hr to about 5 mgA/hr in a use environment as described herein, such as an in vivo gastrointestinal fluid.

In a further embodiment, this invention provides a method for treating Chronic Fatigue Syndrome comprising orally administering to a mammal in need of such treatment, including a
10 human patient, a therapeutically effective amount of cabergoline in a sustained-release dosage form comprising cabergoline or a pharmaceutically acceptable salt thereof, such as an oral dosage form which releases the cabergoline according to the release rate described above, such as, for example, from about 0.01 mgA/hr to about 5 mgA/hr in a use environment as described herein, such as an in vivo gastrointestinal fluid.

In a further embodiment, this invention provides a method for treating other nervous system disorders, particularly addictive disorders, comprising orally administering to a mammal in need of such treatment, including a human patient, a therapeutically effective amount of cabergoline in a sustained-release dosage form comprising cabergoline or a pharmaceutically acceptable salt thereof, such as an oral dosage form which releases the
15 cabergoline according to the release rate described above, such as, for example, from about 0.01 mgA/hr to about 5 mgA/hr in a use environment as described herein, such as an in vivo gastrointestinal fluid.

Typically, a preferred range of dosages is about .25 mgA of cabergoline per day and can be as high as about 10 mgA of cabergoline per day for average adult subjects having a
25 body weight of about 70 kg. For example, the dosage may range from about .25 mgA to about 6 mgA, about .5 mgA to about 6 mgA, about .5 mgA to about 2 mgA, or within other ranges comprised between .25 mgA and 10 mgA. The preferred dosage amount will depend upon the dosage form in which cabergoline or cabergoline salt is administered as well as other factors which will be readily apparent to a person skilled in the art, such as a physician.

30 The invention will now be illustrated by the following examples, which are not to be taken as limiting.

EXAMPLES

Example 1 (Multiparticulates)

Multiparticulates are made comprising 50 wt% cabergoline, 47 wt% COMPRITOL 888
35 ATO (a mixture of glyceryl mono-, di- and tri-behenates from Gattefossé Corporation of Paramus, New Jersey), and 3 wt% LUTROL F127 (pharmaceutical grade poloxamer 407 with

an average molecular weight of 9800 to 14,600 daltons from BASF Corporation of Mt. Olive, New Jersey) using the following process. First, 5000 g cabergoline, 4700 g of the COMPRITOL 888 ATO and 300 g of the LUTROL F127 are blended in a twinshell blender for 20 minutes. This blend is de-lumped using a Fitzpatrick L1A mill at 3000 rpm, knives forward
5 using a 0.065-inch screen. The mixture is blended again in a twinshell blender for 20 minutes, forming a preblend feed. The preblend feed is delivered to a B&P 19-mm twin-screw extruder (MP19-TC with a 25 L/D ratio purchased from B & P Process Equipment and Systems, LLC, Saginaw, MI) at a rate of 140 g/min. The extruder produced a molten mixture consisting of a suspension of the cabergoline in the COMPRITOL 888 ATO/ LUTROL F127 at
10 a temperature of about 90°C. The feed suspension is delivered to the center of a spinning-disk atomizer. The spinning disk atomizer, which is custom made, consists of a bowl-shaped stainless steel disk of 10.1 cm (4 inches) in diameter. The surface of the disk is heated with a thin film heater beneath the disk to about 90°C. That disk is mounted on a motor that drives the disk of up to approximately 10,000 RPM. The entire assembly is enclosed in a plastic bag
15 of approximately 8 feet in diameter to allow congealing and to capture microparticulates formed by the atomizer. Air is introduced from a port underneath the disk to provide cooling of the multiparticulates upon congealing and to inflate the bag to its extended size and shape. The surface of the spinning disk atomizer is maintained at 90 °C and the disk is rotated at 5500 rpm while forming the cabergoline multiparticulates. The formed multiparticulates have
20 a diameter of about 180 µm. The resulting multiparticulates can be loaded into appropriate capsules, compressed into tablets, or formed into sachets for oral administration

Example 2 (Matrix)

HPMC K4M (45.000 g) and 50.575g of calcium phosphate dibasic are Turbula blended in a bottle for 10 min. Approximately 10 g of this blend is combined with 3.425 g of
25 cabergoline and Turbula blended for 10 min. The remaining powder from the first mix is then added to drug containing blend and the combination is Turbula blended for 20 min. Magnesium stearate (1.000 g) is added and the combination blended for an additional 3 min. Tablets are prepared using a Manesty™ F-Press (single-punch tablet machine available from Manesty Corporation, Liverpool, UK) using ¼" SRC tooling.

Example 3 (Matrix - 2)

HPMC K100 LV (45.000 g) and 50.575g of calcium phosphate dibasic are Turbula blended in a bottle for 10 min. Approximately 10 g of this blend is combined with 3.425 g of
cabergoline and Turbula blended for 10 min. The remaining powder from the first mix is then added to drug containing blend and the combination is Turbula blended for 20 min.
35 Magnesium stearate (1.000 g) is added and the combination blended for an additional 3 min.

Tablets are prepared using a Manesty™ F-Press (single-punch tablet machine available from Manesty Corporation, Liverpool, UK) using ¼" SRC tooling.

Example 4 (Matrix - 3)

A mixture of 0.86 g of cabergoline and 42.25 g of mannitol is passed through a #30 screen and Turbula blended for 2 min. Carnuba wax (6.04 g) and stearic acid (0.61 g) are added to a beaker and melted using a water bath at 90°C. While mixing, the mannitol and drug blend are added to the melted wax and stearic acid mixture. The warm material is screened through a #20 mesh screen and allowed to cool overnight. The material is combined with 0.09g of silicon dioxide and Turbula blended for 2 min. Magnesium stearate (0.17g) is added followed by an additional 0.5 min. of Turbula blending. Tablets are prepared using 5/16" SRC tooling using an F-Press.

Example 5 (Multiparticulates)

In general, various functional layers are prepared as aqueous dispersions and applied to sugar spheres in a Glatt model GPCG-120 fluid bed processor fitted with a 32 inch Wurster column. Cabergoline is milled to reduce the particle size and to distribute it uniformly throughout the resulting mixture. Spray nozzles located at the base of the Wurster column apply dispersions to spheres as they move through the column, entrained in a high velocity air stream. The spheres exit the top of the column, where they dry as they return under the influence of gravity to the base of the column to become eventually re-entrained in the high velocity air stream. The re-circulating motion of the spheres continued until the desired amount of dispersion is applied. Prior to discharge, the coated spheres are dried for approximately 1 hour with approximately 2,450 cubic feet per minute airflow at 70°C. The dried beads are passed through a screen to remove unwanted aggregates. The bead composition is provided in Table 1 below. Ninety mg of the resulting beads are loaded into 2 mg hard gelatin capsules (or 180 mg of beads into 4 mg capsules) to form test articles.

Table 1. Bead Composition for Example 5.

Component	Dry Weight
Core	
Sugar sphere (Surelease)	73.3
First Layer	
Surelease® E-7-19010 Clear	11.9 ¹
Purified Water	
Second Layer	
Cabergoline	2.2
HPMC 2910	1.7 ¹
Purified Water	

Component	Dry Weight
Third Layer	
Surelease® E-7-19010 Clear	8.5
HPMC 2910	1.4 ¹
Purified Water	
Fourth Layer	
Purified Water	See Footnote 1

¹ Water removed during processing to a residual level of 6% loss on drying or less, typically 1%

Example 6 (Coated Matrix)

Microcrystalline cellulose (1,050 g) and 3,340 g of calcium phosphate dibasic is
5 mixed in a 16 quart V-blender for 20 min. To an 8 quart V-blender is added 2,450 g of
mannitol and 71.8 g of cabergoline. The mixture is mixed for 30 minutes. The material
containing the drug is added to the 16 quart V-blender (still containing the microcrystalline
cellulose/calcium phosphate dibasic blend) and the mixture blended for 30 minutes.
10 Magnesium stearate (52.5 g) is added to the V-blender and the mixture blended for 5
minutes. The mixture is roller compacted using a TF-Mini roller compactor with DSP rollers,
using a roll pressure of 30 kg/cm², a roll speed of 4.0 rpm and an auger speed of 15 rpm
resulting in ribbons with 0.06 to 0.08" thickness. The ribbons are milled using an M5A mill
(available from Fitzpatrick Corp., Elmhurst, Ill.) with an 18 mesh Conidur rasping screen at
300 rpm. The powder is placed back in the V-blender and another 35 g of magnesium
15 stearate is added, followed by an additional 5 minutes of blending.

The granulation is tableted using a Kilian T100 tablet press using 9/32" (11 mm) SRC
tooling. The precompression force is 1.2 kN, the main compression force is 8 kN, running at
74 rpm with a feed paddle speed of 20 rpm.

The tablets are coated by first preparing a coating solution consisting of 4,095 g of
20 cellulose acetate and 405 g of PEG in 30.6 kg of acetone and 9.9 kg of water. Coating is
carried out using an HCT-60 Hicoater (available from Vector Corp., Marion, Iowa). A spray
rate of 180 g/min is maintained with an outlet temperature of 27 °C until the target coating
weight of 13% weight gain is achieved. The tablets are tray dried in an oven at 40 °C for 16
hours.

What is claimed is:

1. A sustained-release dosage form suitable for oral administration to a mammal, comprising cabergoline, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, which dosage form releases cabergoline into a use
5 environment at a rate not exceeding about 5 mgA/hr, provided said dosage form (1) releases not more than about 70% by weight of the cabergoline contained therein within the first hour following entry into said use environment and (2) releases cabergoline at a rate of at least about 0.01 mgA/hr.
2. A dosage form as defined in claim 1 wherein said cabergoline is present as
10 crystalline form II.
3. A dosage form as defined in claim 1, wherein the acetate buffer contains trypsin in a concentration of 0.1 mg/ml.
4. A sustained release dosage form suitable for oral administration to a mammal, comprising cabergoline or a pharmaceutically acceptable salt thereof and a
15 pharmaceutically acceptable carrier, which dosage form releases cabergoline at a rate less than about 10 mgA/hr in vitro when dissolution tested in an USP-2 apparatus containing 900 ml of an acetate buffer at pH 4.0, and containing NaCl in a concentration of 0.075 M at 37°C, wherein: (1) if said dosage form is a sustained release tablet or a non-disintegrating sustained release capsule, said USP-2 apparatus is equipped with a paddle stirring at 50 rpm; (2) if said
20 dosage form is a multiparticulate comprises multiparticulates and is not a tablet, said USP-2 apparatus is equipped with a paddle stirring at 100 rpm; provided said dosage form (a) releases not more than about 70% by weight of the cabergoline contained therein within the first hour following initiation of the dissolution test and (b) releases cabergoline at a rate of at least about 0.01 mgA/hr.
- 25 5. A dosage form as defined in claim 4 wherein said cabergoline is present as cabergoline free base, cabergoline hydrochloride, cabergoline aspartate, cabergoline acetate or cabergoline lactate.
6. A dosage form as defined in claim 4 wherein said cabergoline is present as crystalline form II.
- 30 7. A sustained release dosage form suitable for oral administration to a mammal, said dosage form having an initial delay period prior to the onset of sustained release, comprising cabergoline or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, which dosage form releases cabergoline into 900 ml of 0.1 N HCl at a rate less than about 0.001 mgA/hr for at least about 1 hour at 37° C in vitro
35 when dissolution tested in an USP-2 apparatus and wherein said dosage form thereafter releases cabergoline into 900 ml of a phosphate buffer at a pH of 6.8 and containing 1% by

weight of polysorbate 80 at 37° C, at a rate of from about 0.01mgA/hr to about 10 mgA/hr, provided said dosage form releases not more than about 70% by weight of the cabergoline within the first hour following the initial delay period, wherein: (1) if said dosage form is a sustained release tablet or a non-disintegrating sustained release capsule, said USP-2 apparatus is equipped with a paddle stirring at 50 rpm; (2) if said dosage form is a multiparticulate comprises multiparticulates and is not a tablet, said USP-2 apparatus is equipped with a paddle stirring at 100 rpm.

8. The dosage form as defined in claim 7, wherein the dosage form is coated with a polymer that prevents release of cabergoline at the pH of the stomach of a mammal, but which is permeable to cabergoline at the pH of the duodenum of the mammal.

9. The dosage form as defined in claim 7, wherein the phosphate buffer at pH 6.8 and containing 1% by weight polysorbate 80 also contains an enzyme suitable for triggering the onset of said sustained release.

10. A sustained release dosage form suitable for oral administration to a mammal, comprising cabergoline or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, which dosage form, following ingestion by said mammal, releases cabergoline into said mammal's stomach at a rate less than about 0.01 mgA/hr, and which, after having passed into said mammals' duodenum; releases cabergoline at a rate of from about 0.01 mgA/hr to about 10 mgA/hr, provided said dosage form releases not more than about 70% by weight of the cabergoline contained therein within the first hour after passing into said mammal's duodenum.

11. A sustained release dosage form suitable for oral administration to a mammal, comprising cabergoline, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, which dosage form, when orally administered to said mammal, results in a maximum cabergoline plasma concentration, C_{max} , which is less than about 80% of the C_{max} determined when an equal dose of cabergoline is orally administered in the form of an immediate release bolus, provided said sustained release dosage form (1) releases not more than about 70% by weight of the cabergoline contained therein within the first hour following ingestion and (2) releases cabergoline at a rate of at least about 0.01 mgA/hr.

12. A sustained release dosage according to claim 11, wherein the sustained release dosage form provides an AUC higher than 65% than the AUC provided by the immediate release bolus.

13. A dosage form as defined in claim 1, which provides a sustained release dosage form of cabergoline suitable for oral administration to a mammal, which results in a maximum cabergoline plasma concentration, C_{max} , of about 1 to 100 picograms/ml.

14. A dosage form as defined in claim 1, which results in a maximum cabergoline plasma concentration, C_{max} , of about 50 to 100 picograms/ml, wherein plasma levels in the 12–24 hour period following administration are about 1 to 100 picograms/ml.

5 15. A method for treating a disease or disorder selected from the group consisting of Parkinson's disease, Progressive Supranuclear Palsy, Multisystemic Atrophy, Restless Legs Syndrome, Fibromyalgia, Chronic Fatigue Syndrome, nervous system disorders, stroke, and addictive disorders, comprising orally administering to a mammal in need of such treatment, a therapeutically effective amount of cabergoline in a sustained-release dosage form according to claim 1.