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(54) Title: CONTROLLED-RELEASE CLOZAPINE COMPOSITIONS

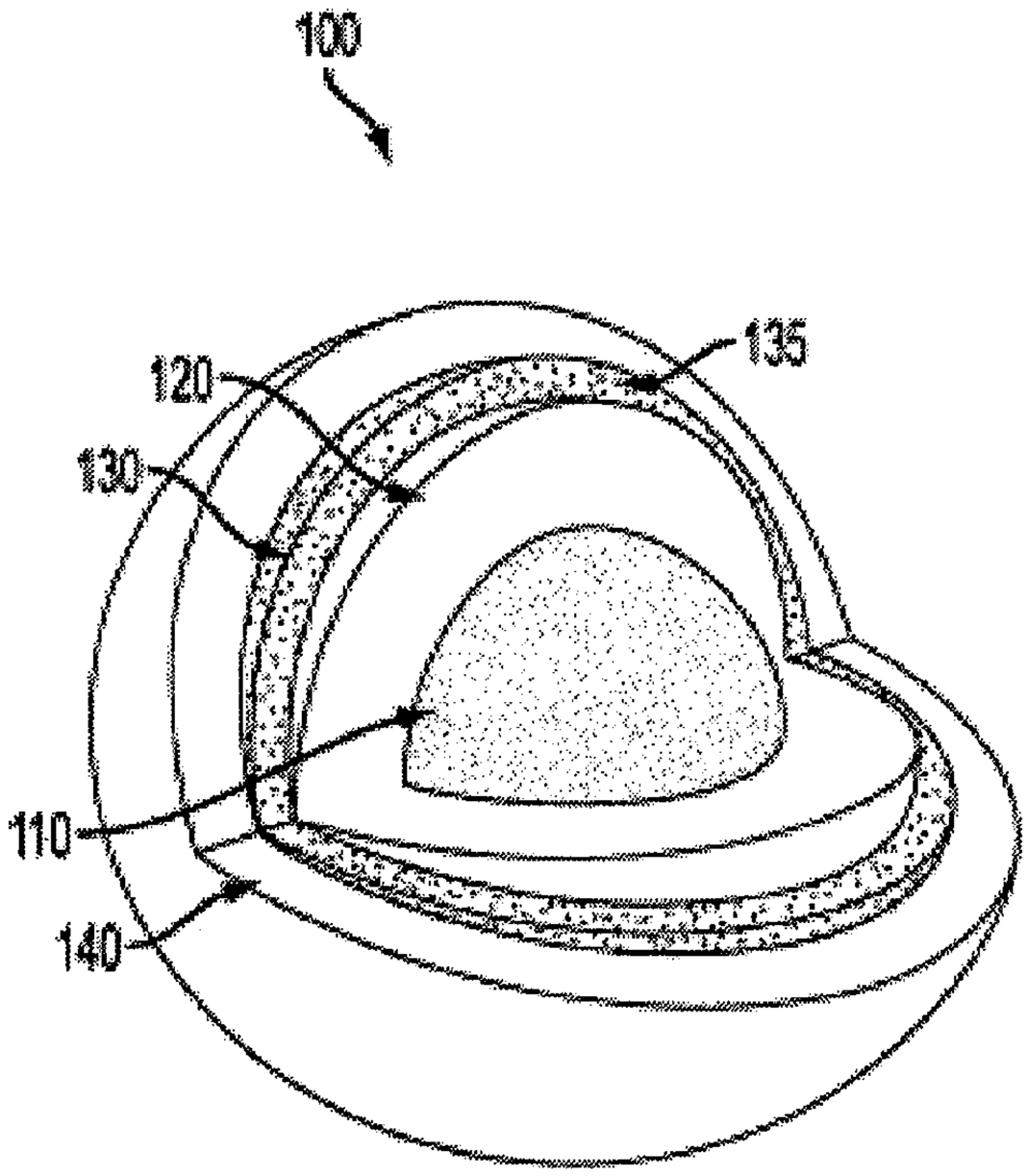

FIG. 1

(57) Abrégé/Abstract:
A composition for delivery of a drug is disclosed. The composition has a semipermeable coating, particles of clozapine having an effective average particle size of less than or about 2 μm and at least one surface stabilizer adsorbed on the surface of the clozapine particles, and a solubilizing agent.

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[Continued on next page]

(54) Title: CONTROLLED-RELEASE CLOZAPINE COMPOSITIONS

(57) Abstract: A composition for delivery of a drug is disclosed. The composition has a semipermeable coating, particles of clozapine having an effective average particle size of less than or about 2 μm and at least one surface stabilizer adsorbed on the surface of the clozapine particles, and a solubilizing agent.

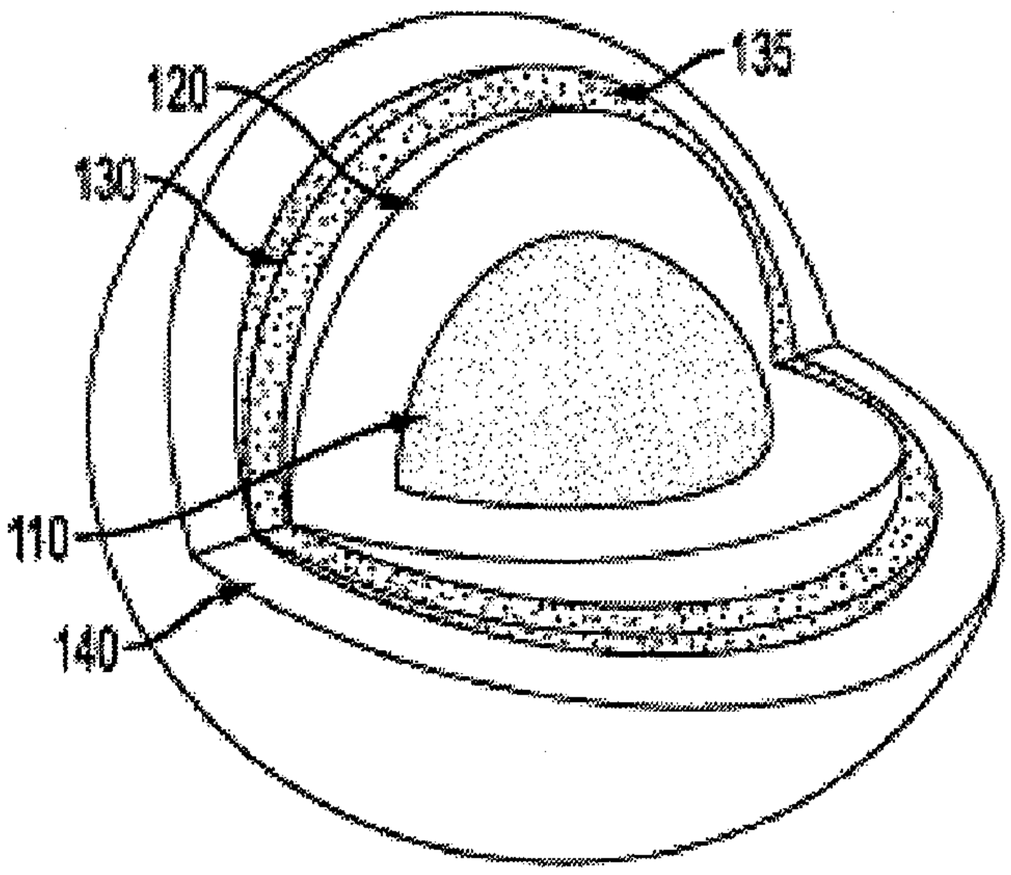

FIG. 1

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CONTROLLED-RELEASE CLOZAPINE COMPOSITIONS

CROSS-REFERENCE TO RELATED APPLICATION

This application claims benefit under 35 U.S.C. § 119(e) of U.S. Provisional Application Number 61/168,040, filed April 9, 2009, the disclosure of which is hereby incorporated by reference herein, in its entirety.

BACKGROUND OF THE INVENTION

Clozapine is used for the management of severely ill schizophrenic patients who fail to respond adequately to standard drug treatment for schizophrenia. Clozapine is also used for reducing the risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder who are judged to be at chronic risk for re-experiencing suicidal behavior, based on history and recent clinical state. Clozapine is also used in the treatment of Parkinson related psychosis. Suicidal behavior refers to actions by a patient that put him/herself at risk for death. Clozapine is the preferred treatment for patients with refractory schizophrenia that have had inadequate or no response to other antipsychotic therapy. See, for example, Y. W. Francis Lam et al., "Branded Versus Generic Clozapine: Bioavailability Comparison and Interchangeability Issues," J Clin Psychiatry 2001; 62 (suppl. 5), 18-24, which is incorporated by reference herein in its entirety.

Currently available clozapine formulations are immediate-release products and patients need to be titrated to a steady state using these dosage forms. This is not without difficulty. For example, clozapine patient insert leaflets specify that titration should be at no more than 25 to 50 mg per day. A patient can take 10 or more days to receive a therapeutic dose, such as a dose of 400 mg or more, and reaching the desired therapeutic dose can take weeks. See, for example, Iqbal et al., "Clozapine: A Clinical Review of Adverse Effects and Management"; Annals of 10 Clinical Psychiatry, Vol. 15, No. I, pages 33-48, March 2003, which is incorporated by reference herein in its entirety.

Clozapine is typically prescribed for refractory patients, i.e., patients who have not responded to other antipsychotic drugs, such as RESPERDAL or ZYPREXA. A

large percentage of patients that will be administered clozapine are also in an institutional setting. Once these patients are titrated to a dose, it is necessary to administer the immediate-release forms of clozapine multiple times. This is inconvenient for the patient and institution caring for the patient. What is needed is a formulation of clozapine that releases the drug over a 24 hour period.

U.S. Patent No. 6,210,712 to Alza Corporation is an attempt at an extended release dosage form of a drug composition. This dosage form includes a drug and a pharmaceutically acceptable carrier, a first ethyl cellulose and hydroxyalkycellulose coat that surrounds the drug composition, and a second coat that surrounds the first coat. The second coat is one of a cellulose acylate, cellulose diacylate or cellulose triacylate. The drug composition is permeable to fluid but impermeable to the passage of drug. In order for the drug to leave the dosage form, an exit passageway is laser drilled or mechanically drilled through the coats to contact the drug layer to allow the release of the drug. Accordingly, there is still a need in the art for a formulation of clozapine that releases the drug over a 24 hour period.

SUMMARY OF THE INVENTION

A composition comprising a semipermeable coating, particles of clozapine having an effective average particle size of less than or about 2 μm, a surface stabilizer adsorbed on the surface of the clozapine particles, and a solubilizing agent is discussed.

Also discussed is a method of treating a patient inflicted with schizophrenia comprising administering to the patient a pharmaceutical dosage form of clozapine having a therapeutic effect for up to 24 hours, the dosage form comprising a semipermeable coating, particles of clozapine having an effective average particle size of less than or about 2 μm and a surface stabilizer adsorbed on the surface of the clozapine particles, and a pH-modulating agent.

Further discussed is a method of reducing the risk of recurrent suicidal behavior in a patient with schizophrenia or schizoaffective disorder comprising administering a single dose over a 24 hour period of a composition comprising a semipermeable coating, particles of clozapine having an effective average particle size of less than or about 2 μm and a surface stabilizer adsorbed on the surface of the clozapine particles, and a pH-modulating agent.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention is best understood from the following detailed description when read in connection with the accompanying drawing. It is emphasized that, according to common practice, the various features of the drawing are not to scale. On the contrary, the dimensions of the various features are arbitrarily expanded or reduced for clarity. Included in the drawing are the following figures:

Fig. 1 is an illustration of a bead, an exemplary dosage form of the controlled-release clozapine composition of the present invention;

Fig. 2 is an illustration of the principle of operation of the bead depicted in Fig. 1;

Fig. 3 is a plot of the % of 200-mg dose of clozapine dissolved over time in various pH environments;

Fig. 4 is a plot of the of 200-mg dose of clozapine dissolved over time when formulated with different pH-modulating agents;

Fig. 5 is a plot of the % of 200-mg dose of clozapine dissolved over time when formulated with differing amounts of the pH-modulating agent, tartaric acid;

Fig. 6 is a plot of dissolution profiles of exemplary clozapine compositions of the invention compared to a Clozapine, USP tablet formulation; and

Fig. 7 is a plot of mean PK profiles in patients following steady-state dosing of an exemplary embodiment of the invention compared to steady-state dosing of FazaClo® BID.

DETAILED DESCRIPTION OF THE INVENTION

"About" will be understood by persons of ordinary skill in the art and will vary to some extent on the context in which it is used. If there are uses of the term which are not clear to persons of ordinary skill in the art given the context in which it is used, "about" will mean up to plus or minus 10% of the particular term.

“Effective average particle size” means that for a given particle size value, x, 50% of the particles in the population are of a size less than x, and 50% of the particles in the population are of a size greater than x, when measured on a weight

or volume basis. For example, a composition comprising particles of clozapine having an "effective average particle size of 2000 nm" means that 50% of the clozapine particles are smaller than 2000 nm and 50% of the clozapine particles are larger than 2000 nm, when measured on a weight or volume basis.

"Nanoparticle/nanoparticulate clozapine" refers to clozapine in the form of solid particles having finite mass, the population of particles being characterized by an effective average particle size of less than or about 2000 nm. Nanoparticle/nanoparticulate clozapine is prepared either from non-nanoparticulate clozapine that has been subjected to a size reduction process (a so-called "top down" process), or by a molecular deposition of clozapine (a so-called "bottom up" process). Alternatively, nanoparticle/nanoparticulate clozapine is one that is manufactured using a technique intended to result in nanoparticulates. Examples of such techniques are described in more detail below. Nanoparticle/nanoparticulate clozapine is distinguished from non-nanoparticulate clozapine, which typically does not have a reduced particle size.

According to an embodiment, non-nanoparticulate clozapine is processed to reduce its particle size to nanoparticulate clozapine. In an embodiment, the size reduction process is a milling process. The resulting milled nanoparticulate clozapine is typically characterized as having a particle size distribution characterized according to their size as a list of values or as a mathematical function that defines the relative amounts of particles present, sorted according to size. The particle size distribution of nanoparticulate clozapine may be measured by any conventional particle size measuring technique well known to those skilled in the art. Such techniques include, for example, sedimentation field flow fractionation, photon correlation spectroscopy, light scattering, and disk centrifugation. An exemplary instrument utilizing light scattering measurement techniques is the Horiba LA-950 Laser Scattering Particle Size Distribution Analyzer manufactured by Horiba, Ltd. of Minami-ku Kyoto, Japan. The resulting measured particle size distribution is typically reported using the Weibull distribution or Rosin Rammler distribution as would be understood by one of ordinary skill in the art. These reporting techniques are useful for characterizing particle size distributions of materials generated by grinding, milling, precipitation, and crushing operations.

The nomenclature "D" followed by a number indicates the numbered percentile of the particle size distribution, e.g., D_{50}, is the particle size below which

50% of the particles in a particle size distribution are smaller and above which 50% of the particles are larger, when measured on a weight or volume basis. In another example, the D_{90} of a particle size distribution is the particle size below which 90% of particles reside, and above which only 10% of the particles reside, when measured on a weight or volume basis.

"Solubility" refers to a quantity of clozapine dissolved in a given quantity of environmental fluid. In the case where the addition of clozapine to the environmental fluid results in no net change in the quantity of clozapine dissolved, the clozapine and the environmental fluid exist in a state of "equilibrium." The resulting solubility of clozapine in the environmental fluid is defined by its "equilibrium solubility."

"Native solubility" is the equilibrium solubility of clozapine in a specific fluid environment in the absence of a solubilization aid.

"Supersaturation" refers to the solubility state of clozapine in excess of its equilibrium solubility, characterized by a solubility that is greater than that defined by the native solubility of clozapine in a given fluid environment.

"Environment of use" or "environmental fluid" or "fluid environment" is used herein to describe the physiologic or local environmental conditions to which a typical, orally administered dosage form is exposed. An environmental fluid may consist of the stomach fluids. Exemplary physiologic conditions of the stomach include a pH value typically reported between 1 and 2 in the fasted state. Another environmental fluid may be the fluids of the small intestine. The pH values of the small intestine range from about 4.7 to 7.3. The pH of the duodenum has been reported to range from about 4.7 to 6.5, that of the upper jejunum to range from about 6.2 to 6.7, and that of the lower jejunum to range from about 6.2 to 7.3.

"Therapeutically effective amount" means the drug dosage that provides the specific pharmacological response for which the drug is administered in a significant number of subjects in need of such treatment. It is emphasized that a therapeutically effective amount of a drug that is administered to a particular subject in a particular instance will not always be effective in treating the conditions/diseases described herein, even though such dosage is deemed to be a therapeutically effective amount by those of skill in the art.

The controlled-release clozapine composition of the invention comprises a solubilizing agent, particles of clozapine, and a semipermeable coating. The controlled-release clozapine composition is intended to provide rapid solubilization of clozapine particles within the interior of the controlled-release clozapine composition and enable dissolved clozapine to exit the composition by osmotically facilitated convection and/or passive diffusion.

It is believed that both the particle size of clozapine and the ability of the solubilizing agent to enhance the solubility of clozapine in the environmental fluid that penetrates the controlled-release clozapine composition serve to influence the rate of clozapine delivery from the composition. Without wishing to be bound to a particular theory, it is believed that the transport mechanism is an osmotically facilitated convection and/or passive diffusion gradient.

Fig. 1 illustrates an exemplary embodiment of the controlled-release clozapine composition in a bead form. In this embodiment, the controlled-release clozapine composition **100** is a multilayered bead. It would be understood by one skilled in the art that numerous beads would be placed into a capsule to create the final dosage form, a multiparticulate capsule. At the center of the bead is inert substrate **110**. Surrounding inert substrate **110** is a layer of solubilizing agent **120**. As shown in this embodiment, the outermost layer of the bead is semipermeable coating **140**. Disposed between the layer of solubilizing agent **120** and semipermeable coating **140** is nanoparticulate clozapine layer **130**. Clozapine particles **135** are represented by a stippling pattern for illustration purposes only.

Fig. 2 is an illustration of the theoretical principle of operation of the bead depicted in **Fig. 1**. Without wishing to be bound to a particular theory, it is believed that the fluid **210** of the environment of use penetrates semipermeable coating **140** through pores **142**. Fluid **210** passes through nanoparticulate clozapine layer **130** without substantially dissolving the clozapine particles **135**, and contacts solubilizing agent layer **120**. Solubilizing agent layer **120** is dissolved in fluid **210**. The dissolved solubilizing agent assists and/or provides a mechanism for dissolving the (previously insoluble) clozapine particles **135** in the fluid **210** that has penetrated composition **100**. The now-solubilized clozapine with solubilizing agent **220** exits the controlled-release clozapine composition **100** driven by osmotically facilitated convection and/or passive diffusion, as shown by the arrows **225**.

The controlled-release clozapine composition of the present invention may be formulated into a variety of oral dosage forms. Suitable oral dosage forms include, but are not limited to, beads or pellets dispensed into capsules, granules, pills, suspensions, all tablets, or wafers. Reference to non-limiting definitions of the foregoing dosage forms may be found in the CDER Data Standards Manual (2006). According to a preferred embodiment, the present invention is a capsule containing beads or pellets.

According to the bead embodiment, the composition comprises an inert substrate, a solubilizing agent, particles of clozapine, a semipermeable coating, and optionally, a controlled-release or enteric layer.

In the embodiment of a bead, the center of the bead comprises an inert substrate. By "inert" it is meant that the substrate does not chemically react with clozapine in the controlled-release composition. The inert substrate provides support for the solubilizing agent layer. The inert substrate may also contribute to the osmotic pressure gradient that is established across the semipermeable coating. The substrate is made from a carrier material or combinations of carrier materials. The carrier material is any soluble or insoluble, biologically acceptable material, such as sucrose or starch. Exemplary carrier materials are NON-PAREIL® seeds such as Sugar Spheres NF having a uniform diameter such as those manufactured by JRS Pharma LP, of Patterson, NY.

In an alternative embodiment to the bead, the inert substrate is replaced by the solubilizing agent, a combination of the solubilizing agent admixed with a binder or carrier, clozapine particles, or a combination of the clozapine particles admixed with a binder or carrier.

In other dosage form embodiments, for example, the inert substrate may be eliminated altogether, for example in a compressed or matrix tablet.

The controlled-release clozapine composition comprises a solubilizing agent. The solubilizing agent is of a type and present in an amount sufficient to dissolve the clozapine particles in the fluid of the environment of use. As described previously, the solubilizing agent dissolves in the fluid that has penetrated the controlled-release clozapine composition. The presence of the dissolved solubilizing agent provides a mechanism for dissolving the clozapine particles (which are poorly soluble or have low native solubility in the environmental fluid).

According to various dosage form embodiments, the solubilizing agent is admixed with a binder and forms part of the core of a bead, is a layer that is adjacent to and disposed about the inert substrate (e.g., the sugar sphere core), is a layer that is disposed between the drug layer and the semipermeable membrane, or is admixed with the other components of the composition when the dosage form is a compressed tablet or matrix tablet.

In the embodiments where the solubilizing agent is a layer that surrounds or is disposed about another layer of a bead, it is envisaged that the solubilizing agent layer may have slight defects, gaps, cracks, crevices, or holes and that there does not have to be a complete and utter surrounding.

In certain embodiments, the solubilizing agent is a surface-active agent or a pH-modulating agent.

In embodiments where the solubilizing agent is a surface-active agent, it is theorized that the mechanisms by which it dissolves clozapine is by enhancing the dissolution of the clozapine particles, formation of micelles, or though formation of colloidal self-association structures. By providing a mechanism to dissolve clozapine in fluids in which clozapine would otherwise have low native solubility, the controlled-release clozapine composition of the invention delivers to an environment of use a solution of clozapine having a higher concentration than that defined by the native solubility of clozapine in the fluid environment.

Micelles are water-soluble aggregates of molecules with hydrophobic and hydrophilic portions (so-called amphiphilic molecules) which associate spontaneously. Such micelles can be in the form of small spheres, ellipsoids or long cylinders, and can also consist of bilayers with two parallel layers of amphiphilic molecules. Such bilayered micelles usually take the shape of spherical vesicles with an internal aqueous compartment. The particular surface-active agent is chosen, in part, based upon its micellular uptake ratio, which is the amount of surfactant required to dissolve a fixed amount of clozapine.

Exemplary surface-active agents include, but are not limited to, ionic (e.g., anionic, cationic, and zwitterionic) and nonionic surface-active agents. Exemplary anionic (based on sulfate, sulfonate or carboxylate anions) surface-active agents include sodium dodecyl sulfate (SDS), ammonium lauryl sulfate, sodium lauryl sulfate (SLS) and other alkyl sulfate salts, sodium laureth sulfate, also known as sodium lauryl ether sulfate (SLES), alkyl benzene sulfonate, various soaps, and fatty

acid salts. Exemplary cationic (based on quaternary ammonium cations) surface-active agents include cetyl trimethylammonium bromide (CTAB) a.k.a. hexadecyl trimethyl ammonium bromide, and other alkyltrimethylammonium salts, cetylpyridinium chloride (CPC), polyethoxylated tallow amine (POEA), benzalkonium chloride (BAC), and benzethonium chloride (BZT). Exemplary zwitterionic (amphoteric) surface-active agents include dodecyl betaine, dodecyl dimethylamine oxide, cocamidopropyl betaine, and coco ampho glycinate. Exemplary nonionic surface-active agents include alkyl poly(ethylene oxide), copolymers of poly(ethylene oxide) and poly(propylene oxide) [commercially called Poloxamers or Poloxamines], alkyl polyglucosides, including octyl glucoside, and decyl maltoside, fatty alcohols, including cetyl alcohol, and oleyl alcohol, cocamide MEA, cocamide DEA and polysorbates (commercially sold under the trade name Tween® by ICI Americas).

Selection of the appropriate surface-active agent is made based on a consideration of clozapine's physicochemical properties such as the presence and type of ionizable functional groups, pKa values, solubility and pH-solubility profile, salt forming characteristics, hydrophobicity, molecular size, complex formation characteristics, chemical stability, and the dose and delivery environment of clozapine. If a surface-active agent is used as the solubilizing agent then the surface-active agent is chosen based on the hydrophobicity and molecular size of clozapine and the ability of the surface-active agent to solubilize clozapine by micellization, molecular inclusion, hydrotropy, complexation or molecular-association. Because clozapine contains two weakly basic ionizable functional groups, additional considerations in the selection of the surface-active agent include its pH-charge-solubility profile and any charge carried by the surface-active agent. Identification of the appropriate surface-active agent can be determined using in vitro screening techniques for clozapine solubility and chemical stability, which techniques are known by one of ordinary skill in the art.

The surface-active agent is present in the composition in an amount sufficient to enhance the solubility of clozapine in the environmental fluid which penetrates the composition. The surface-active agent is present in an amount from about 1%, 3%, 5%, 7%, 10%, 12%, 14%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, 30%, 32%, 34%, 36%, 38%, 40%, 43%, 46%, 49%, 50% 55%, 60%, 65%, 70%, 75%, 80%, 85%, and 90% by weight of the composition. The amount of surface-active agent in the composition may also be expressed as a range between any of the above-listed individual percentages.

In embodiments were the solubilizing agent is a pH-modulating agent, it is theorized that the mechanism for dissolving the clozapine particles is by modifying the pH environment of the fluid within the controlled-release clozapine composition. The pH-modulating agent modifies the pH of the fluid that has entered the controlled-release clozapine composition to favor the ionized form of clozapine thereby allowing clozapine (which would otherwise have low native solubility in the fluid) to dissolve. The dissolved clozapine exits the dosage form, passing through the pores of the semipermeable coating, to the environment of use in a pre-dissolved form.

Preferably, the pH-modulating agent is a pharmaceutically acceptable organic or inorganic weak acid.

In the embodiment were the pH-modulating agent is an acid, at least one organic acid, possibly two or more, are present as the pH-modulating agent. Depending on the desired delivery profile of the controlled-release clozapine composition, more than three pH-modulating agents are envisaged. Types of organic acids which are exemplary pH-modulating agents include, but are not limited to, adipic acid, ascorbic acid, citric acid, fumaric acid, gallic acid, glutaric acid, lactic acid, malic acid, maleic acid, succinic acid, tartaric acid, and other organic acids suitable for use in pharmaceutical preparations for oral administration such as described in WO 01/032149, herein incorporated by reference.

A diagnostic formulation model system was established to support the controlled-release clozapine compositions of the invention. This model system encompassed a semipermeable membrane, nanoparticulate clozapine particles and a solubilizing agent. The model system was designed with multiple features to provide flexibility to address a wide variety of formulation variables and different in vitro release experiments that may be required to support the controlled-release clozapine composition of the invention.

Shown in Figure 4 is the effect of different pH-modulating agents, specifically, tartaric, fumaric, malic, and succinic acid, on the percentage of clozapine released over time, obtained using the model system.

Selection of the appropriate pH-modulating agent is made based on a consideration of relevant clozapine physicochemical properties such as the number and type of ionizable functional groups, pKa values of the functional groups, pH-solubility profile, salt forming characteristics, ksp, chemical stability, and the dose and delivery environment for clozapine. Because clozapine contains two weakly basic functional

groups, the pH-modulating agent is typically an organic or inorganic weak acid possessing a pKa value that is preferably at least 1 log unit lower than the pKa values of one or both of the weakly basic clozapine functional groups. If salt formation between clozapine and pH-modulating agent is possible then an agent forming a salt with a high solubility product constant (k_{sp}) is preferred.

The pH-modulating agent is present in the composition in an amount sufficient to enhance the solubility of clozapine in the environmental fluid which penetrates the composition. The pH-modulating agent is present in an amount from about 1%, 3%, 5%, 7%, 10%, 12%, 14%, 17%, 20%, 22%, 25%, 27%, 30%, 31%, 32%, 33%, 34%, 35%, 36%, 37%, 38%, 39%, 40%, 41%, 43%, 46%, 49%, 50% 55%, 60%, 65%, 70%, 75%, 80%, 85%, and 90% by weight of the composition. The amount of pH-modulating agent in the composition may also be expressed as a range between any of the above-listed individual percentages.

Figure 5 shows the effect of the amount of pH-modulating agent, specifically tartaric acid, on the percentage release of clozapine over time, in accordance with the model system in Figure 4. The amounts of pH-modulating agent shown in Figure 5 are expressed as molar ratios relative to the amount of clozapine in the controlled-release composition.

In certain embodiments, the composition delivers to the environment of use a solution of clozapine at a concentration that is higher than that defined by the native solubility of clozapine in the same environment of use. In other words, the controlled-release clozapine composition of the invention enables clozapine to be delivered to the environment in the form of a solution that is effectively supersaturated when compared to the native solubility of clozapine in the same fluid environment.

In another embodiment, an exemplary composition of the invention delivers to the environment of use a solution of clozapine at a higher concentration than would otherwise be achieved using a commercially available immediate-release tablet of clozapine, such as Clozapine, USP tablets.

The controlled-release clozapine composition of the invention delivers dissolved clozapine at a concentration that is 101%, 102%, 103%, 104%, 105%, 106%,107%,108%, 109% 100%, 110%, 120%, 130%, 140%, 150%, 160%, 170%, 180%, 190%, 200%, 210%, 220%, 230%, 240%, 250%, 260%, 270%, 280%, 290%, 300, 310%, 320%, 330%, 340%, 350%, 360%, 370%, 380%, 390%, 400%, 410%, 420%, 430%, 440%, 450%, 460%, 470%, 480%, 490%, 500%, 510%, 520%, 530%,

540%, 550%, 560%, 570%, 580%, 590%, 600%, 700%, 800% or 1000% of the native solubility of clozapine in the environment of use, or of that achieved by a commercially available immediate-release tablet of clozapine tablets, USP.

Alternatively stated, the controlled-release clozapine composition of the invention can deliver the clozapine to the environment of use at a factor of 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 2.75, 3.00, 3.25, 3.50, 3.75, 4.00, 4.25, 4.50, 4.75, 5.00, 5.25, 5.50, 5.75, 6.00, 6.25, 6.50, 6.75, 7.00, 7.25, 7.50, 7.75, 8.00, 8.25, 8.50, 8.75, 9.00, 9.25, 9.50, 9.75, or 10.0 times the native solubility of the clozapine in the environment of use, or that achieved by a commercially available immediate-release tablet of clozapine tablets, USP.

Clozapine, the IUPAC name of which is 8-chloro-11-(4-methylpiperazin-1-yl)-5*H*-dibenzo[*b*,*e*][1,4]diazepine, is an antipsychotic medication used in the treatment of schizophrenia. Clozapine is indicated for the management of severely ill schizophrenic patients who fail to respond adequately to standard drug treatment for schizophrenia. Clozapine is a yellow, crystalline powder, and is very slightly soluble in water. It is a tricylic dibenzodiazepine, classified as an atypical antipsychotic agent. It binds several types of central nervous system receptors, and displays a unique pharmacological profile. Clozapine is a serotonin antagonist, with strong binding to 5-HT 2A/2C receptor subtype. It also displays strong affinity to several dopaminergic receptors, but shows only weak antagonism at the dopamine D2 receptor, a receptor commonly thought to modulate neuroleptic activity.

The amount of clozapine in the composition ranges in an amount from about 10% to about 90% by weight, for example between 20% and 40%. In certain embodiments, the amount of clozapine is 0.1%, 0.5%. 0.75%, 1%, 1.25%, 1.5%, 1.75%, 2%, 3%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, and 90% by weight of the total composition. The amount of clozapine in the composition may also be expressed as a range between any of the above-listed individual percentages.

Exemplary milligram amounts of clozapine in a finished controlled-release dosage form include 1200, 600, 400, 200, 175, 150, 125, 120, 100, 80, 75, 60, 50, 40, 30, 25, 20, 12.5, or 10 mg.

In the exemplary embodiment dosage form of a capsule comprising beads, the beads may also include one or more isolation layers. The isolation layer serves to protect the clozapine layer from the other component layers. Exemplary

isolation layer components include the aqueous film coating systems sold under the Opadry® trade name by Colorcon, Inc. of West Point, PA.

The clozapine particles of the present invention have at least one surface stabilizer adsorbed on the surface thereof. Surface stabilizers useful herein physically adhere to or associate with the surface of the nanoparticulate clozapine, but do not chemically react with the clozapine particles. The surface stabilizers are present in an amount sufficient to substantially prevent aggregation or agglomeration of clozapine particles during formation and/or upon redispersion of the clozapine particles in the environment of use. Although certain compounds suitable as surface stabilizers of the invention may also be suitable as solubilizing agents of the invention, amounts of such compounds required to function as surface stabilizers are generally insufficient to achieve substantial dissolution of the clozapine particles in the fluid of the environment of use. Moreover, as defined herein, a surface stabilizer of the invention is adsorbed on the surface of the clozapine particle.

Exemplary surface stabilizers include, but are not limited to, known organic and inorganic pharmaceutical excipients, as well as peptides and proteins. Such excipients include various polymers, low molecular weight oligomers, natural products, and surfactants. Useful surface stabilizers include nonionic surface stabilizers, anionic surface stabilizers, cationic surface stabilizers, and zwitterionic surface stabilizers. Combinations of more than one surface stabilizer can be used in the invention.

Representative examples of surface stabilizers include, but are not limited to, foregoing alone or in combination: hydroxypropyl methylcellulose (HPMC); dioctyl sodium sulfosuccinate (DOSS); sodium lauryl sulfate (SLS) a.k.a. sodium dodecyl sulfate (SDS); hydroxypropyl cellulose grade HPC-SL (viscosity of 2.0 to 2.9 mPa.s, aqueous 2% W/V solution, 20 DEG C, Nippon Soda Co., Ltd.); polyvinylpyrrolidone (PVP) such as Kollidone® K12 sold by BASF a.k.a. Plasdone® C-12 sold by ISP Technologies, Inc. (USA), Kollidone® K17 sold by BASF a.k.a. Plasdone® C-17 sold by ISP Technologies, Inc. (USA), Kollidone® K29/32 sold by BASF a.k.a. Plasdone® C-29/32 sold by ISP Technologies, Inc. (USA); sodium deoxycholate; block copolymers based on ethylene oxide and propylene oxide commonly known as poloxamers which are sold under the Pluronic® name by BASF (sold under the trade name Lutrol® in EU) and include Pluronic® F 68 a.k.a. poloxamer 188, Pluronic® F 108, a.k.a. poloxamer 338, Pluronic® F 127 a.k.a

poloxamer 407; benzalkonium chloride a.k.a. alkyldimethylbenzylammonium chloride; copolymers of vinylpyrrolidone and vinyl acetate commonly known as copovidone sold under the tradename Plasdone® S-630 by ISP Technologies, Inc. (USA); lecithin; polyoxyethylene sorbitan fatty acid esters commonly known as polyoxyethylene 20 sorbitan monolaurate a.k.a. "polysorbate 20", polyoxyethylene 20 sorbitan monopalmitate a.k.a. "polysorbate 40," polyoxyethylene 20 sorbitan monooleate a.k.a. "polysorbate 80" sold under the trade names Tween® 20, Tween® 40 and Tween® 80, respectively, by ICI Americas; albumin; lysozyme; gelatin; macrogol 15 hydroxystearate sold as Solutol® 15 by BASF; tyloxapol, and polyethoxylated castor oils sold under the trade name Cremophor® EL by BASF.

Other surface stabilizers include, but are not limited to, hydroxypropylcellulose, random copolymers of vinyl pyrrolidone and vinyl acetate, casein, dextran, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers (e.g., macrogol ethers such as cetomacrogol 1000); polyethylene glycols (e.g., Carbowaxes 3550® and 934® (Union Carbide)), polyoxyethylene stearates, colloidal silicon dioxide, phosphates, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol (PVA), 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde (also known as tyloxapol, superione, and triton); poloxamines (e.g., Tetronic 908®, also known as Poloxamine 908®, which is a tetrafunctional block copolymer derived from sequential addition of propylene oxide and ethylene oxide to ethylenediamine (BASF Wyandotte Corporation, Parsippany, N.J.); Tetronic 1508® (T-1508) (BASF Wyandotte Corporation), Tritons X-200®, which is an alkyl aryl polyether sulfonate (Dow); Crodestas F-110®, which is a mixture of sucrose stearate and sucrose distearate (Croda Inc.); p-isononylphenoxypoly-(glyc- idol), also known as Olin-10G® or Surfactant 10-G® (Olin Chemicals, Stamford, Conn.); Crodestas SL-40® (Croda, Inc.); and SA_9OHCO, which is $C_{18}H_{37}CH_2C(O)N(CH_3)--CH_2(CHOH)_4(CH_20H)_2$ (Eastman Kodak Co.); decanoyl-N-methylglucamide; n-decyl β-D-glucopyranoside; n-decyl β-D-maltopyranoside; n-dodecyl β-D-glucopyranoside; n-dodecyl β-D-maltoside; heptanoyl-N-methylglucamide; n-heptyl-β-D-glucopyranoside; n-heptyl β-D-thioglucoside; n-hexyl β-D-glucopyranoside; nonanoyl-N-methylglucamide; n-noyl β-D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl-β-D-glucopyranoside; octyl β-

D-thioglucopyranoside; PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, PEG-vitamin E, and the like.

Additional examples of useful surface stabilizers include, but are not limited to, polymers, biopolymers, polysaccharides, cellulosics, alginates, phospholipids, poly-n-methylpyridinium chloride, anthryul pyridinium chloride, cationic phospholipids, chitosan, polylysine, polyvinylimidazole, polybrene, polymethylmethacrylate trimethylammonium bromide (PMMTMABr), hexyldecyltrimethylammonium bromide (HDMAB), and polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate.

Still further examples of useful stabilizers include, but are not limited to, cationic lipids, sulfonium, phosphonium, and quarternary ammonium compounds, stearyltrimethylammonium chloride, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride or bromide, coconut methyl dihydroxyethyl ammonium chloride or bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride or bromide, C_{12-15}dimethyl hydroxyethyl ammonium chloride or bromide, coconut dimethyl hydroxyethyl ammonium chloride or bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride or bromide, lauryl dimethyl (ethenoxy)4 ammonium chloride or bromide, N-alkyl (C_{12-18})dimethylbenzyl ammonium chloride, N-alkyl (C_{14-18})dimethyl-benzyl ammonium chloride, N-tetradecylidmethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C_{12-14}) dimethyl 1-napthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts and dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt and/or an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C_{12-14}) dimethyl 1-naphthylmethyl ammonium chloride and dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C_{12}, C_{15}, C_{17} trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride (sold under the ALIQUAT® 336 trade name of the Henkel Corporation), Polyquaternium-10,

tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters (such as choline esters of fatty acids), benzalkonium chloride, stearalkonium chloride compounds (such as stearyltrimonium chloride and Di-stearyldimonium chloride), cetyl pyridinium bromide or chloride, halide salts of quatemized polyoxyethylalkylamines, alkyl pyridinium salts; amines, such as alkylamines, dialkylamines, alkanolamines, polyethylenepolyamines, N,N-dialkylaminoalkyl acrylates, and vinyl pyridine, amine salts, such as lauryl amine acetate, stearyl amine acetate, alkylpyridinium salt, and alkylimidazolium salt, and amine oxides; imide azolinium salts; protonated quaternary acrylamides; methylated quaternary polymers, such as poly[diallyl dimethylammonium chloride] and poly-[N-methyl vinyl pyridinium chloride]; and cationic guar.

Additional exemplary surface stabilizers are described in detail in the *Handbook of Pharmaceutical Excipients*, published jointly by the American Pharmaceutical Association and The Pharmaceutical Society of Great Britain, the Pharmaceutical Press, 2005. The surface stabilizers are commercially available and/or can be prepared by techniques known in the art. Presentations of exemplary surface stabilizers are given in McCutcheon, *Detergents and Emulsifiers*, Allied Publishing Co., New Jersey, 2004 and Van Os, Haak and Rupert, *Physico-chemical Properties of Selected Anionic, Cationic and Nonionic Surfactants*, Elsevier, Amsterdam, 1993; *Analytical and Biological Evaluation* (Marcel Dekker, 1994); P. and D. Rubingh (Editor), *Cationic Surfactants: Physical Chemistry* (Marcel Dekker, 1991); and J. Richmond, *Cationic Surfactants: Organic Chemistry*, (Marcel Dekker, 1990); all of which are incorporated by reference.

Exemplary methods of making nanoparticles are described in U.S. Pat. No. 5,145,684, the entire content of which is incorporated by reference herein. The desired effective average particle size of the invention can be obtained by controlling the process of particle size reduction, such as controlling the milling time and the amount of surface stabilizer added. Crystal growth and particle aggregation can be minimized by milling or precipitating the composition under colder temperatures, milling in the presence of or adding a surface stabilizer after size reduction, and by storing the final composition at colder temperatures.

Milling clozapine in an aqueous solution to obtain a nanoparticulate dispersion comprises dispersing clozapine in water, followed by applying mechanical means in the presence of grinding media to reduce the particle size of the compound to the desired effective average particle size. Clozapine can be effectively reduced in size

in the presence of surface stabilizers. Alternatively, clozapine can be contacted with two or more surface stabilizers after attrition. Other compounds, such as a bulking agent, can be added to the clozapine/surface stabilizer mixture during the size reduction process. Dispersions can be manufactured continuously or in a batch mode. The resultant nanoparticulate clozapine dispersion can be sprayed dried and formulated into the desired dosage from.

Exemplary useful mills include low energy mills, such as a roller mill, attrition mill, vibratory mill and ball mill, and high energy mills, such as Dyno mills, Netzsch mills, DC mills, and Planetary mills. Media mills include sand mills and bead mills. In media milling, clozapine is placed into a reservoir along with a dispersion medium (for example, water) and at least two surface stabilizers. The mixture is recirculated through a chamber containing media and a rotating shaft/impeller. The rotating shaft agitates the media which subjects the compound to impacting and sheer forces, thereby reducing particle size.

Exemplary grinding media comprises media that are substantially spherical in shape, such as beads, consisting essentially of polymeric resin. In another embodiment, the grinding media comprises a core having a coating of a polymeric resin adhered thereon. Other examples of grinding media comprise essentially spherical particles comprising glass, metal oxide, or ceramic.

In general, suitable polymeric resins are chemically and physically inert, substantially free of metals, solvent, and monomers, and of sufficient hardness and friability to enable them to avoid being chipped or crushed during grinding. Suitable polymeric resins include, without limitation: crosslinked polystyrenes, such as polystyrene crosslinked with divinylbenzene; styrene copolymers, for example, PolyMill® milling media (Elan Pharma International Ltd.); polycarbonates; polyacetals, for example, Delrin® milling media (E.I. du Pont de Nemours and Co.); vinyl chloride polymers and copolymers; polyurethanes; polyamides; poly(tetrafluoroethylenes), for example, Teflon® polymers (E.I. du Pont de Nemours and Co.), and other fluoropolymers; high density polyethylenes; polypropylenes; cellulose ethers and esters such as cellulose acetate; polyhydroxymethacrylate; polyhydroxyethyl acrylate; and silicone-containing polymers such as polysiloxanes. The polymer can be biodegradable. Exemplary biodegradable polymers include poly(lactides), poly(glycolide) copolymers of lactides and glycolide, polyanhydrides, poly(hydroxyethyl methacylate), poly(imino carbonates), poly(N-acylhydroxyproline)esters, poly(N-

palmitoyl hydroxyproline) esters, ethylene-vinyl acetate copolymers, poly(orthoesters), poly(caprolactones), and poly(phosphazenes). For biodegradable polymers, contamination from the media itself advantageously can metabolize in vivo into biologically acceptable products that can be eliminated from the body.

The grinding media preferably ranges in size from about 10 μm to about 3 mm. For fine grinding, exemplary grinding media is from about 20 μm to about 2 mm. In another embodiment, exemplary grinding media is from about 30 μm to about 1 mm in size. In another embodiment, the grinding media is about 500 μm in size. The polymeric resin can have a density from about 0.8 to about 3.0 g/ml.

Another method of forming the desired nanoparticulate clozapine is by microprecipitation. This is a method of preparing stable dispersions of clozapine in the presence of surface stabilizers and one or more colloid stability enhancing agents free of any trace toxic solvents or solubilized heavy metal impurities. An exemplary method comprises: (1) dissolving the compound in a suitable solvent; (2) adding the formulation from step (1) to a solution comprising at surface stabilizer to form a clear solution; and (3) precipitating the formulation from step (2) using an appropriate non-solvent. The method can be followed by removal of any formed salt, if present, by dialysis or diafiltration and concentration of the dispersion by conventional means. The resultant nanoparticulate clozapine dispersion can be sprayed dried and formulated into the desired dosage from.

Another method of forming the desired nanoparticulate clozapine is by homogenization. Like precipitation, this technique does not use milling media. Instead, clozapine, surface stabilizer(s) and a carrier--the "mixture" (or, in an alternative embodiment, clozapine and carrier with the surface stabilizer added following reduction in particle size) constitute a process stream propelled into a process zone, which in a Microfluidizer® spray (Microfluidics Corp.) is called the Interaction Chamber. The mixture to be treated is inducted into the pump and then forced out. The priming valve of the Microfluidizer® purges air out of the pump. Once the pump is filled with the mixture, the priming valve is closed and the mixture is forced through the Interaction Chamber. The geometry of the Interaction Chamber produces powerful forces of sheer, impact and cavitation which reduce particle size. Inside the Interaction Chamber, the pressurized mixture is split into two streams and accelerated to extremely high velocities. The formed jets are then directed toward each other and

collide in the interaction zone. The resulting product has very fine and uniform particle size.

The distribution of clozapine particles formed by any of the above exemplary techniques has an effective average particle size of less than or about 2000 nm (2 μm), 1900 nm, 1800 nm, 1700 nm, 1600 nm, 1500 nm, 1400 nm, 1300 nm, 1200 nm, 1100 nm, 1000 nm (1 μm), 900 nm, 800 nm, 700 nm, 600 nm, 500 nm, 400 nm, 300 nm, 200 nm, 150 nm, 100 nm, 75 nm, and 50 nm (nm = nanometers or 10^{-9} m).

The distribution of clozapine particles is also characterized by a D_{90}. The D_{90} of the distribution of clozapine particles according to an embodiment of the invention is less than or about 5000 nm, 4900 nm, 4800 nm, 4700 nm, 4600 nm, 4500 nm, 4400 nm, 4300 nm, 4200 nm, 4100 nm, 3000 nm, 3900 nm, 3800 nm, 3700 nm, 3600 nm, 3500 nm, 3400 nm, 3300 nm, 3200 nm, 3100 nm, 3000 nm 2900 nm, 2800 nm, 2700 nm, 2600 nm, 2500 nm, 2400 nm, 2300 nm, 2200 nm, 2150 nm, 2100 nm, 2075 nm, 2000 nm (2 μm), 1900 nm, 1800 nm, 1700 nm, 1600 nm, 1500 nm, 1400 nm, 1300 nm, 1200 nm, 1100 nm, 1000 nm (1 μm), 900 nm, 800 nm, 700 nm, 600 nm, 500 nm, 400 nm, 300 nm, 200 nm, 150 nm, 100 nm, 75 nm, and 50 nm.

The controlled-release clozapine composition comprises one or more semipermeable coatings that does not adversely affect the drug, animal body, or host. The semipermeable coating substantially prevents the passage of clozapine particles out of the controlled-release clozapine composition, but allows dissolved clozapine to be release from within the composition. In an embodiment, the semipermeable coating is the outermost layer of the composition.

The semipermeable coating is present in the controlled-release clozapine composition in an amount that ranges from 1% to 50%, and an amount in between, for example, 1%, 3%, 5%, 7%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 22%, 25%, 30%, 35%, 40%, and 50% based upon the total weight of the controlled-release clozapine composition. The amount of semipermeable coating in the composition may also be expressed as a range between any of the above-listed individual percentages.

In certain embodiments, the semipermeable coating is a controlled-porosity microporous coating, one or more water-swellable polymers, or a combination thereof.

The controlled-porosity microporous coating comprises: (1) a polymer that is insoluble in the environment of use, (2) a pore forming additive soluble in the environment of use and dispersed throughout the microporous coating, and optionally, (3) other excipients. Suitable exemplary, controlled-porosity microporous coatings are described in WO/2001/032149 herein incorporated by reference.

The controlled-porosity microporous coating visually appears as a sponge-like structure composed of numerous open and closed cells that form a discontinuous interwoven network of void spaces when viewed with a scanning electron microscope. The physical characteristics of the controlled-porosity microporous coating, i.e., the network of open and closed cells, serve as both an entry point for environmental fluid and as an exit for dissolved clozapine. The pores can be continuous pores that have an opening on both faces of the controlled-porosity microporous coating (i.e., the inner surface facing the center of the controlled-release clozapine composition and the exterior surface facing the environment of use). The pores may be interconnected through tortuous paths of regular and irregular shapes including curved, curved-linear, randomly oriented continuous pores, hindered connected pores and other porous paths discernible by microscopic examination. Generally, the controlled-porosity microporous coating is defined by the pore size, the number of pores, the tortuosity of the microporous path and the porosity which relates to the size and number of pores. The pore size of the controlled-porosity microporous coating is easily ascertained by measuring the observed pore diameter at the surface of the material under the electron microscope. Generally, materials possessing from about 5% to about 95% pores and having a pore size from about 10 angstroms to about 100 microns can be used. The controlled-porosity microporous coating, as constituted in the environment of use, has a small solute reflection coefficient, σ, and displays poor semipermeable characteristics when placed in a standard osmosis cell.

Exemplary polymers that are insoluble in the environment of use and comprise the controlled-porosity microporous coating include cellulosic polymers, methacrylates and pthalates.

More specifically, exemplary polymers include cellulose acetates having a degree of substitution, D.S., meaning the average number of hydroxyl groups on the anhydroglucose unit of the polymer replaced by a substituting group, up to 1 and acetyl content up to 21%; cellulose diacetate having a D.S. of 1 to 2 and an acetyl content of 21 to 35%; cellulose triacetate having a D. S. of 2 to 3 and an acetyl

content of 35 and 44.8%; cellulose propionate having an acetyl content of 1.5 to 7% and a propionyl content of 39.2 and 45% and hydroxyl content of 2.8 to 5.4%; cellulose acetate butyrate having a D.S. of 1. 8, an acetyl content of 13 to 15% and a butyryl content of 34 to 39% ; cellulose acetate having an acetyl content of 2 to 99.5%, a butyryl content of 17 to 53%, and a hydroxyl content of 0.5 to 4.7%; cellulose triacetylates having a D. S. of 2. 9 to 3 such as cellulose trivalerate, cellulose trilaurate, cellulose tripalmitate, cellulose trisuccinate, cellulose triheptylate, cellulose tricaprylate, cellulose trioctanoate, and cellulose tripropionate ; cellulose diesters having a lower degree of substitution and prepared by the hydrolysis of the corresponding triester to yield cellulose diacylates having a D.S. of 2.2 to 2.6 such as cellulose dicapyrlate and cellulose dipentanate; and esters prepared from acyl anhydrides or acyl acids in an esterification reaction to yield esters containing different acyl groups attached to the same cellulose polymer such as cellulose acetate valerate, cellulose acetate succinate, cellulose propionate succinate, cellulose acetate octanoate, cellulose valerate palmitate, cellulose acetate palmitate and cellulose acetate heptanoate and the like.

Additional exemplary polymers include cellulose acetate acetoacetate, cellulose acetate chloroacetate, cellulose acetate furoate, dimethoxyethyl cellulose acetate, cellulose acetate carboxymethoxy- propionate, cellulose acetate benzoate, cellulose butyrate napthylate, methylcellulose acetate methylcyanoethyl cellulose, cellulose acetate methoxyacetate, cellulose acetate ethoxyacetate, cellulose acetate dimethylsulfamate, ethylcellulose, ethyl- cellulose dimethylsulfamate, cellulose acetate p-toluene sulfonate, cellulose acetate methylsulfonate, cellulose acetate dipropylsulfamate, cellulose acetate butylsulfonate, cellulose acetate laurate, cellulose stearate, cellulose acetate methylcarbamate, agar acetate, amylose triacetate beta glucan acetate, beta glucan triacetate, acetaldehyde dimethyl acetate, cellulose acetate ethyl carbamate, cellulose acetate phthalate, cellulose acetate dimethyl aminoacetate, cellulose acetate ethyl carbonate, poly (vinyl methyl) ether copolymers, cellulose acetate with acetylated hydroxy-ethyl cellulose hydroxylated ethylenevinylacetate, poly ortho esters, polyacetals, semipermeable polyglycolic or polyactic acid and derivatives thereof, selectively permeable associated polyelectrolytes, polymers of acrylic and methacrylic acid and esters thereof, film forming materials with a water sorption of one to fifty percent by weight at ambient temperatures with a presently preferred water sorption of less than thirty percent, acylated polysaccharides, acylated starches, aromatic nitrogen containing polymeric materials that exhibit permeability to aqueous

fluids, membranes made from polymeric epoxides, copolymers of alkylene oxides and alkyl glycidyl ethers, polyurethanes, and the like. Admixtures of various polymers may also be used.

The polymers described are known to the art or they can be prepared according to the procedures in Encyclopedia of Polvmer Science and Technology, Vol. 3, pages 325 to 354 and 459 and 549, published by Interscience Publishers, Inc., New York, in Handbook of Common Polymers by Scott, J. R. and Roff, W. J., 1971, published by CRC Press, Cleveland, Ohio; and in U. S. Patent Nos. 3,133,132; 3,173,876; 3,276,586; 3,541,055; 3,541,006; and 3,546,142.

The pore forming additive defines the porosity of the controlled-released microporous coating. The porosity of the controlled-release microporous coating may be formed in situ, by the pore forming additive being removed by dissolving or leaching it to form the microporous coating during the operation of the system. The pores may also be formed prior to operation of the system by gas formation within curing polymer solutions which result in voids and pores in the final form of the coating. The pore forming additive can be a solid or a liquid.

An exemplary pore forming additive soluble in the environment of use, according to exemplary embodiments, is the pore forming additive sold under the tradename Opadry® by Colorcon, Inc. of West Point, PA.

According to other embodiments, the pore forming additives include, but are not limited to, HPMC, PVP, polyhydric alcohols, or sugars.

Yet in other embodiments, the pore forming additive is an inorganic or organic compound. The pore forming additives suitable for the invention include a pore forming additives that can be extracted without any chemical change in the polymer. Solid additives include alkali metal salts such as sodium chloride, sodium bromide, potassium chloride, potassium sulfate, potassium phosphate, sodium benzoate, sodium acetate, sodium citrate, potassium nitrate and the like. The alkaline earth metal salts such as calcium chloride, calcium nitrate, and the like. The transition metal salts such as ferric chloride, ferrous sulfate, zinc sulfate, cupric chloride, and the like. Water may be used as the pore-former. These pore forming additives include organic compounds such as saccharides. The saccharides include the sugars sucrose, glucose, fructose, mannose, galactose, aldohexose, altrose, talose, lactose, monosaccharides, disaccharides, and water soluble polysaccharides. Also, sorbitol, manitol, organic aliphatic and aromatic ols, including diols and polyols, as

exemplified by polyhydric alcohols, poly (alkylene glycols), polygylcols, alkylene glycols, poly (a-co) alkylenediols, esters or alkylene glycols poly vinylalcohol, poly vinyl pyrrolidone, and water soluble polymeric materials. Pores may also be formed in the microporous coating by the volatilization of components in a polymer solution or by chemical reactions in a polymer solution which evolves gases prior to application or during application of the solution to the cores mass resulting in the creation of polymer foams serving as the microporous coating of the invention. The pore forming additives are nontoxic, and on their removals, channels form that fill with fluid. In a preferred embodiment, the non-toxic pore forming additives are selected from the group consisting of inorganic and organic salts, carbohydrates, polyalkylene glycols, poly (a-co) alkylenediols, esters of alkylene glycols, and glycols that are used in a biological environment.

Processes for preparing microporous coatings are described in Synthetic Polymer Membranes, by R. E. Kesting, Chapters 4 and 5, 1971, published by McGraw Hill, Inc. ; Chemical Reviews, Ultrafiltration, Vol. 18, pages 373 to 455, 1934 ; Polymer Eng. And Sci., Vol. 11, No. 4, pages 284-288, 1971; J. Appl. Poly. Sci., Vol. 15, pages 811 to 829, 1971; and in U. S. Patent Nos. 3,565,259; 3,615,024 ; 3,751,536; 3,801,692; 3,852,224; and 3,849,528.

The percent by weight of pore forming additive in the controlled-porosity microporous coating is from about 0.5%, 0.75%, 1.0%, 1.3%, 1.5%, 1.7%, 1.9%, 2.0%, 2.5%, 3.0%, 3.5%, 4%, 4.5%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 13%, 15%, 17%, 19%, 21%, 22%, 24%, 26%, 28%, 30%, 32%, 34%, 36%, 38%, 41%, 43%, 45%, 47%, 49%, and 50%. The amount of pore forming additive in the composition may also be expressed as a range between any of the above-listed individual percentages.

In yet another embodiment of the invention, the semipermeable coating comprises one or more water-swellable polymers. The water-swellable polymers form a hydrophillic matrix that substantially prevents release of clozapine particles, while simultaneously allowing passage of dissolved clozapine into the environment of use. These polymers, when in contact with the environment of use, absorb the fluid and swell to form a viscous gel.

Exemplary water-swellable polymers include the Methocel™ methylcellulose and hypromellose systems of water-soluble cellulose ethers sold by The Dow Chemical Company of Midland, Michigan, USA.

In a further embodiment, the controlled-release clozapine composition of the invention includes additional coatings or layers. Such coatings or layers include delayed release polymers or enteric polymers as would be known in the art.

Figure 7 is a plot of mean PK profiles in patients following steady-state dosing of an exemplary controlled-release clozapine formulation (200mg dose) prepared in accordance with Example 1 compared to steady-state dosing of FazaClo® (100 mg clozapine, USP, Azur Pharma, Inc.) BID.

EXAMPLES

The following examples are intended to illustrate various embodiments of the invention.

EXAMPLE 1

Example 1 demonstrates the amount of dissolved drug in the fluid environment using an exemplary controlled-release clozapine composition comprising clozapine and a pH-modulating agent when compared to a clozapine control formulation, i.e., commercially available immediate-release Clozapine, USP tablets.

The established intrinsic solubility of clozapine in water is 0.016 mg/mL. The pKa values for clozapine are 3.98 and 7.62. The theoretically calculated saturation solubility of clozapine at pH 6.8 was estimated at 0.12 mg/mL.

The concentration of clozapine delivered from the controlled-release clozapine composition of the invention to a fluid environment was determined in 0.1M sodium phosphate buffer, pH 6.8 at 37°C, which is representative of the fluid environment of the human small intestine. The formulation of the controlled-release clozapine composition of this Example is described in the table below.

Ingredient	Component
Clozapine	Medicament
Hypromellose	Surface Stabilizer
Docusate Sodium	Surface Stabilizer
Pearlitol® (mannitol)	Dispersing agent
Sodium Lauryl Sulfate	Surface-active agent
Sugar Spheres	Inert core
Tartaric acid	pH-modulating agent
Opadry®	Pore former
Surelease®	Water in-soluble polymer

Three separate quantities of the above composition were studied corresponding to 200mg, 600mg and 1200mg of clozapine. These compositions were placed in 1000mL of 0.1M sodium phosphate, pH 6.8 according to USP <711>, apparatus II (2009), paddles at 75rpm. Control experiments were performed using 200mg, 600mg and 1200mg of clozapine in the form of immediate-release tablets. Comparative dissolution results of the composition of the invention and the control clozapine formulation are set forth in the table below. A graphical representation of this data is expressed in Figure 6. Lines (1), (2) and (3) represent the profiles obtained for the 200mg, 600mg and 1200mg samples of clozapine control tablets. Line (4) represents the profile obtained for nominal 200mg of clozapine. Line (5) represents the profile obtained for nominal 600mg of clozapine, and Line (6) represents the profile obtained for nominal 1200mg of clozapine.

Sample description	Experimentally determined concentration in mg/mL of clozapine at T = 20 hours in pH 6.8, 0.1M sodium phosphate	Experimentally determined concentration as a percentage of the anticipated clozapine saturation solubility at pH 6.8	Ratio of clozapine concentration achieved with composition of the invention to the concentration with equivalent amount of clozapine control formulation
200mg clozapine (control)	0.087	71.3	-
600mg clozapine (control)	0.094	76.9	-
1200mg clozapine (control)	0.102	83.9	-
204mg clozapine*	0.171	140	1.96
624mg clozapine*	0.453	371	4.82
1203mg clozapine*	0.787	645	7.72

*Clozapine was formulated into the controlled-release clozapine composition of the invention.

After 20 hours the measured concentration of the control clozapine formulation in the environmental fluid approached, but did not reach, the anticipated saturation solubility for the 200mg, 600mg, and 1200mg sample sizes. Rather, the 600mg and 1200mg sample sizes of control clozapine formulation achieved values of 0.094mg/mL and 0.102mg/mL, respectively. The concentration of clozapine delivered from the controlled-release clozapine composition of the invention to the pH 6.8 sodium phosphate buffer far exceeded that achieved from the experiments using an equivalent quantity of the control clozapine tablet formulation.

For the nominal 200mg sample the controlled-release clozapine composition of the invention delivered a clozapine concentration of 0.171mg/mL (140% of the theoretical saturation solubility) or a factor of 1.96 times the concentration achieved with an equivalent amount of control clozapine tablet formulation.

For the nominal 600mg sample the controlled-release clozapine composition delivered a concentration of clozapine at 0.453 mg/mL (371% of the

theoretical saturation solubility) or a factor of 4.82 times the concentration achieved with an equivalent amount of the control clozapine tablet formulation.

For the nominal 1200mg sample the controlled-release clozapine composition delivered a concentration of clozapine at 0.787 mg/mL (645% of the anticipated saturation solubility) or a factor of 7.69 times the concentration achieved with an equivalent amount of the control clozapine tablet formulation.

What is Claimed:

1. A composition comprising:

a semipermeable coating;

particles of clozapine having an effective average particle size of less than or about 2 μm and a surface stabilizer adsorbed on the surface of the clozapine particles; and

a solubilizing agent.

2. The composition of claim 1, wherein the semipermeable coating is a controlled-porosity microporous coating.

3. The composition of claim 2, wherein the controlled-porosity microporous coating comprises a polymer that is insoluble in an environment of use and a pore forming additive that is soluble in the environment of use.

4. The composition of claim 3, wherein the polymer is selected from the group consisting of cellulosic polymers, methacrylates and phthalates, and

wherein the pore forming additive is selected from the group consisting of HPMC, PVP, polyhydric alcohols, and sugars.

5. The composition of claim 3, wherein the percent by weight of pore forming additive in the controlled-porosity microporous coating is selected from the group consisting of 0.5%. 1.0%, 1.5%, 2.0%, 2.5%, 3.0%, 3.5%, 4%, 4.5%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 13%, 15%, 17%, 19%, 21%, 22%, 24%, 26%, 28%, 30%, 32%, 34%, 36%, 38%, 41%, 43%, 45%, 47%, 49%, and 50%.

6. The composition of claim 1, wherein the effective average particle size is selected from the group consisting of less than or about 1900 nm, 1800 nm, 1700 nm, 1600 nm, 1500 nm, 1400 nm, 1300 nm, 1200 nm, 1100 nm, 1000 nm (1

μm), 900 nm, 800 nm, 700 nm, 600 nm, 500 nm, 400 nm, 300 nm, 200 nm, 150 nm, 100 nm, 75 nm, and 50 nm.

7. The composition of claim 1, wherein the particles of clozapine have a D_{90} selected from the group consisting of less than or about 5000 nm, 4900 nm, , 4800 nm, 4700 nm, 4600 nm, 4500 nm, 4400 nm, 4300 nm, 4200 nm, 4100 nm, 3000 nm, 3900 nm, 3800 nm, 3700 nm, 3600 nm, 3500 nm, 3400 nm, 3300 nm, 3200 nm, 3100 nm, 3000 nm 2900 nm, 2800 nm, 2700 nm, 2600 nm, 2500 nm, 2400 nm, 2300 nm, 2200 nm, 2150 nm, 2100 nm, 2075 nm, and 2000 nm.

8. The composition of claim 1, wherein the surface stabilizer is selected from the group consisting of hydroxypropyl methylcellulose (HPMC), hypromellose, dioctyl sodium sulfosuccinate (DOSS), sodium lauryl sulfate (SLS), hydroxypropyl cellulose, polyvinylpyrrolidone, sodium deoxycholate, block copolymers based on ethylene oxide and propylene, copolymers of vinylpyrrolidone and vinyl acetate, lecithin, polyoxyethylene sorbitan fatty acid esters, albumin, lysozyme, gelatin, macrogol 15 hydroxystearate, tyloxapol, and polyethoxylated castor oil.

9. The composition of claim 1, wherein the solubilizing agent is of a type and present in an amount sufficient to dissolve the clozapine particles within the composition prior to delivery of clozapine to an environment of use.

10. The composition of claim 9, wherein the solubilizing agent is a surface-active agent or a pH-modulating agent.

11. The composition of claim 10, wherein the surface-active agent is selected from the group consisting of anionic, cationic, zwitterionic and nonionic surface-active agents.

12. The composition of claim 10, wherein the solubilizing agent is a pH-modulating agent and, when exposed to fluid of the environment of use, modifies the pH environment within the composition to favor an ionized form of the clozapine.

13. The composition of claim 12, wherein the pH-modulating agent is a weak acid selected from the group consisting of adipic acid, ascorbic acid, citric acid, fumaric acid, gallic acid, glutaric acid, lactic acid, malic acid, maleic acid, succinic acid, tartaric acid, and mixtures and combinations thereof.

14. The composition of claim 1, wherein the composition delivers to an environment of use a solution of clozapine having a concentration that is higher than that defined by the native solubility of clozapine in the environment of use.

15. The composition of claim 14, wherein the concentration of clozapine dissolved in the fluid of the environment of use is 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% 100%, 110%, 120%, 130%, 140%, 150%, 160%, 170%, 180%, 190%, 200%, 210%, 220%, 230%, 240%, 250%, 260%, 270%, 280%, 290%, 300, 310%, 320%, 330%, 340%, 350%, 360%, 370%, 380%, 390%, 400%, 410%, 420%, 430%, 440%, 450%, 460%, 470%, 480%, 490%, 500%, 510%, 520%, 530%, 540%, 550%, 560%, 570%, 580%, 590%, 600%, 700%, 800% or 1000% higher than that defined by the native solubility of clozapine in the environment of use.

16. A method of treating a patient afflicted with schizophrenia comprising administering to the patient a pharmaceutical dosage form of clozapine having a therapeutic effect for up to 24 hours, the dosage form comprising a semipermeable coating, particles of clozapine having an effective average particle size of less than or about 2 μm and a surface stabilizer adsorbed on the surface of the clozapine particles, and a pH-modulating agent.

17. A method of reducing the risk of recurrent suicidal behavior in a patient with schizophrenia or schizoaffective disorder comprising administering a single dose over a 24 hour period of a composition comprising a semipermeable coating,

particles of clozapine having an effective average particle size of less than or about 2 μm and a surface stabilizer adsorbed on the surface of the clozapine particles, and a pH-modulating agent.

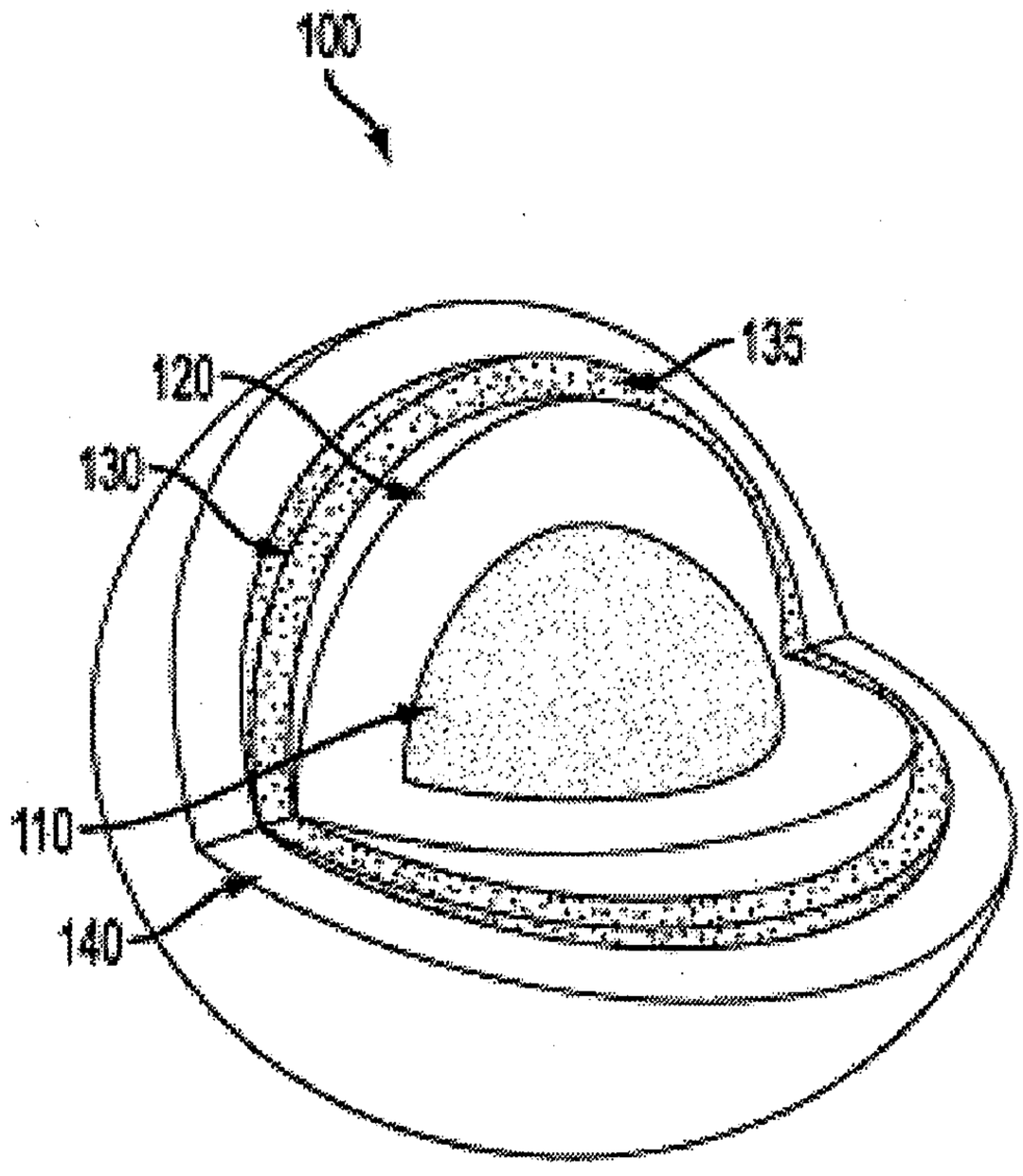

FIG. 1

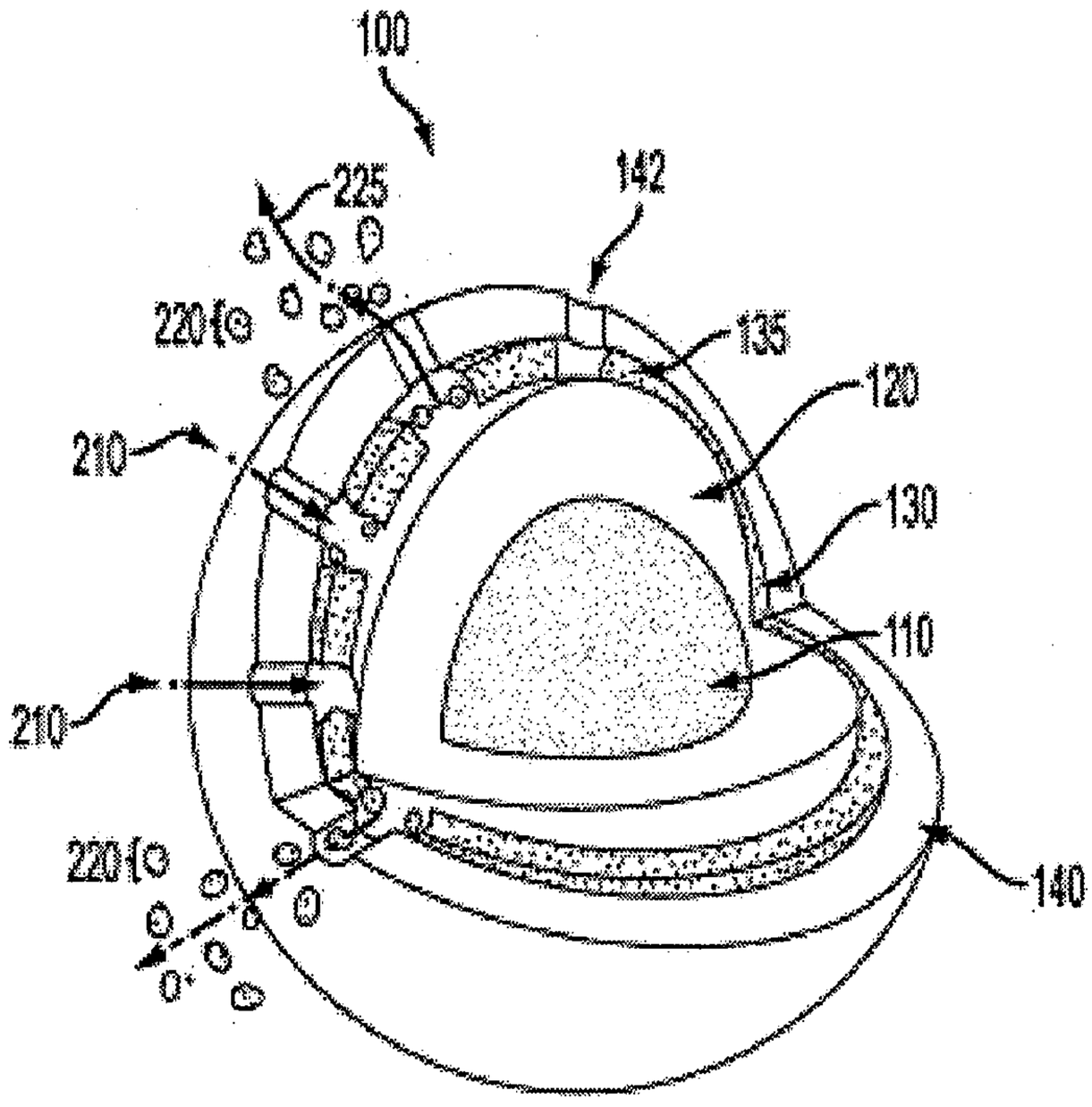

FIG. 2

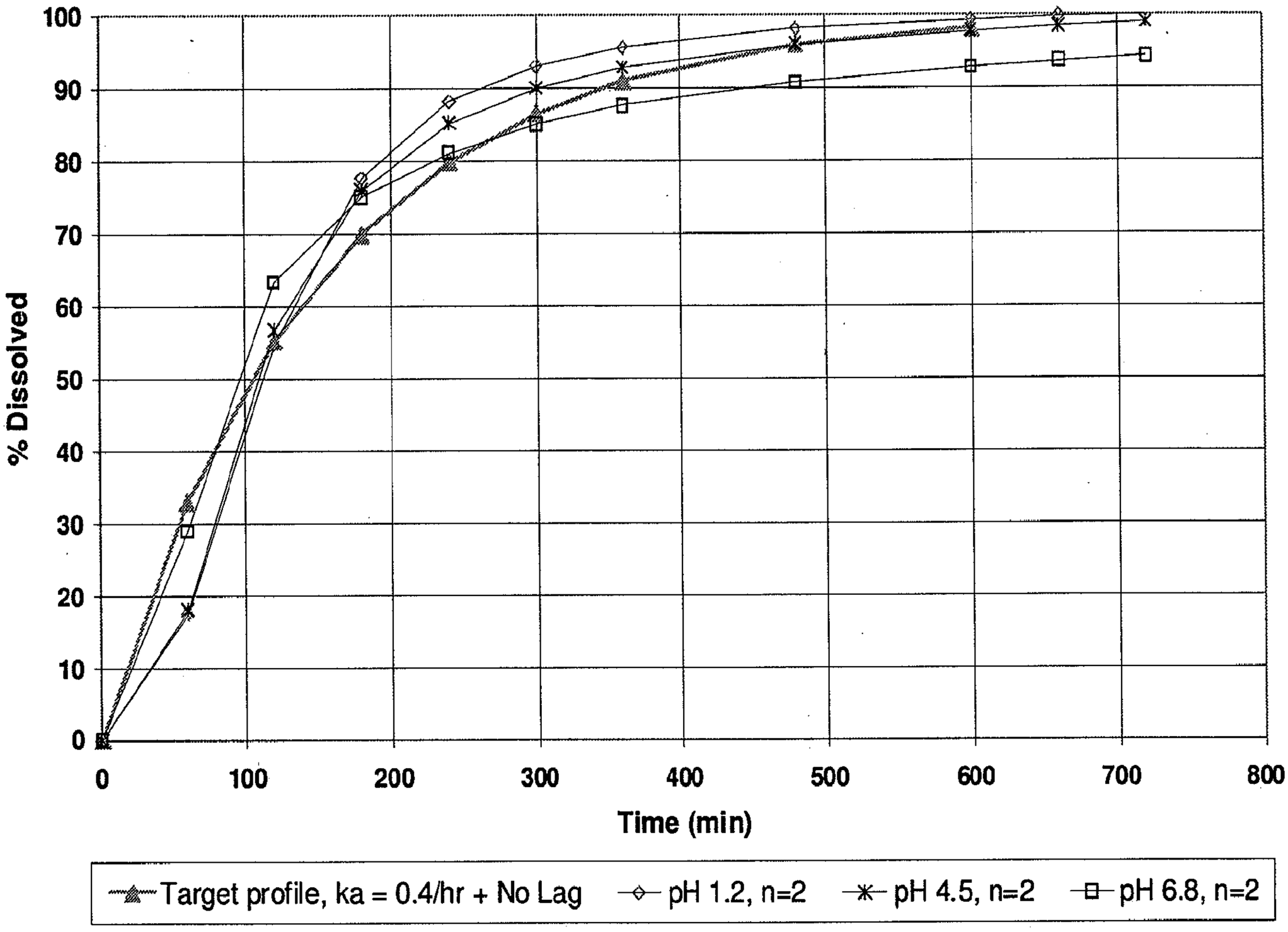
% Dissolved
100
90
80
70
60
50
40
30
20
10
0
0
100
200
300
400
500
600
700
800
Time (min)
Target profile, ka = 0.4/hr + No Lag
pH 1.2, n=2
pH 4.5, n=2
pH 6.8, n=2

FIG. 3

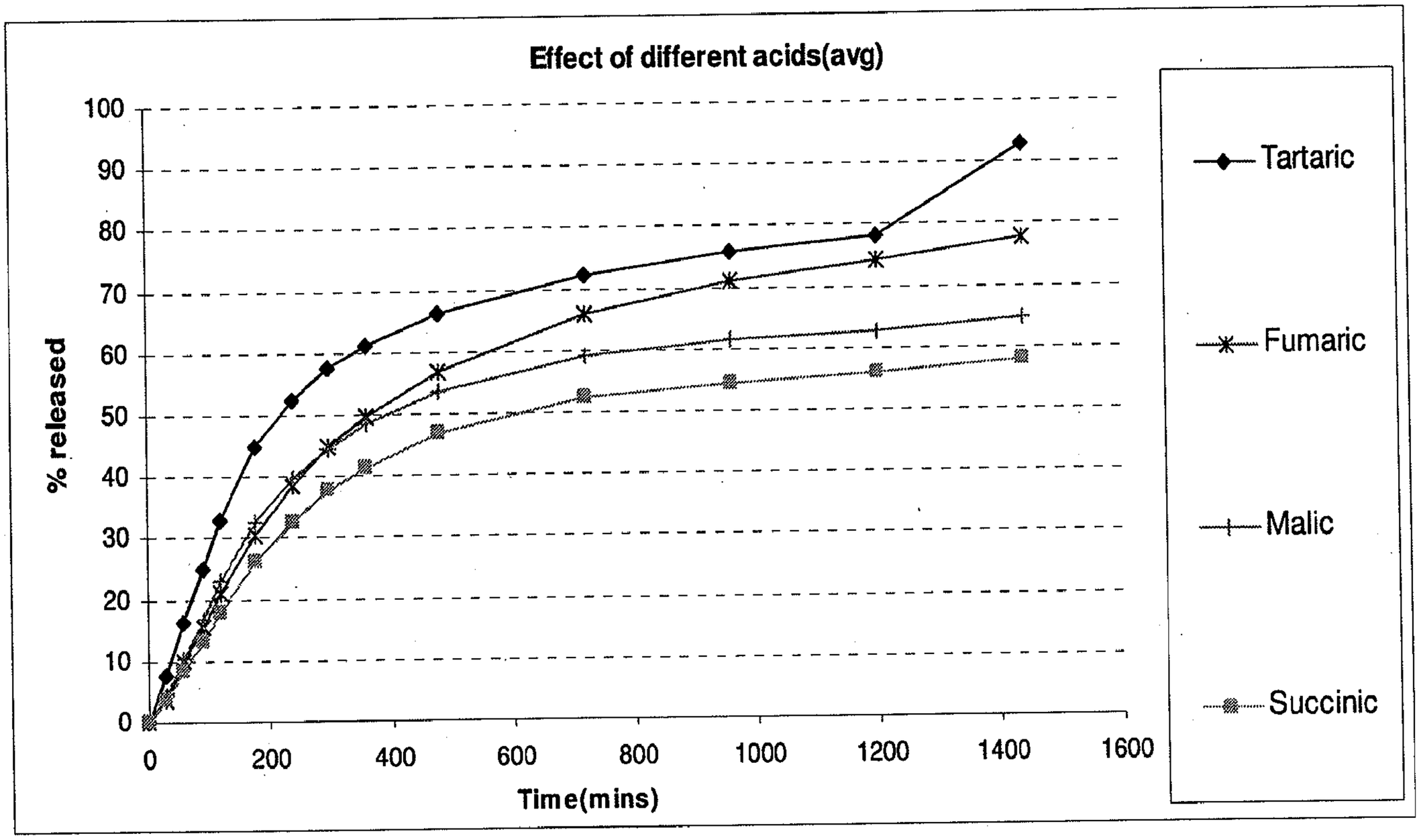
Effect of different acids(avg)
% released
Time(mins)
0
10
20
30
40
50
60
70
80
90
100
0
200
400
600
800
1000
1200
1400
1600
Tartaric
Fumaric
Malic
Succinic

FIG. 4

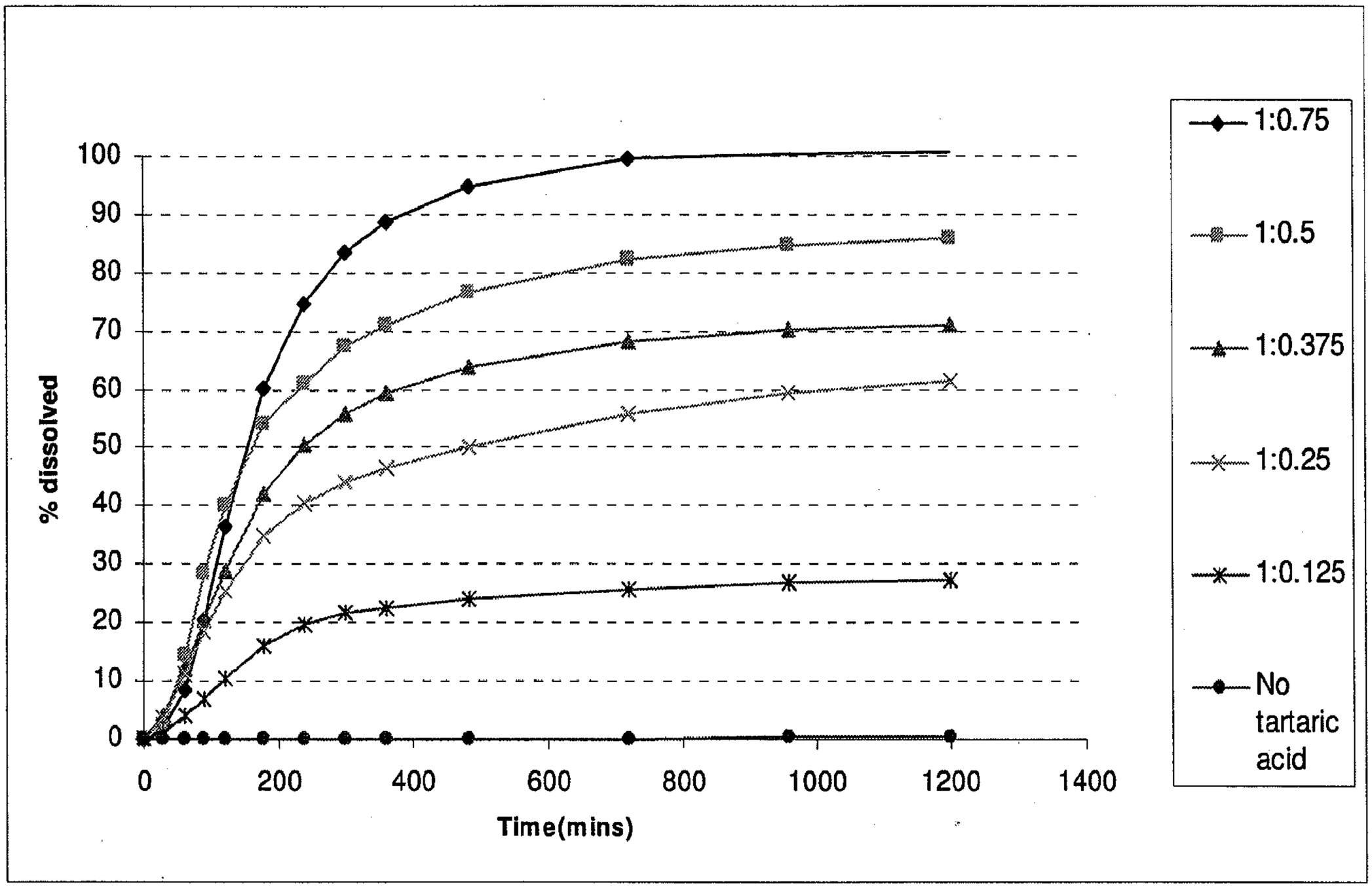
100
90
80
70
60
50
40
30
20
10
0
% dissolved
0
200
400
600
800
1000
1200
1400
Time(mins)
1:0.75
1:0.5
1:0.375
1:0.25
1:0.125
No tartaric acid

FIG. 5

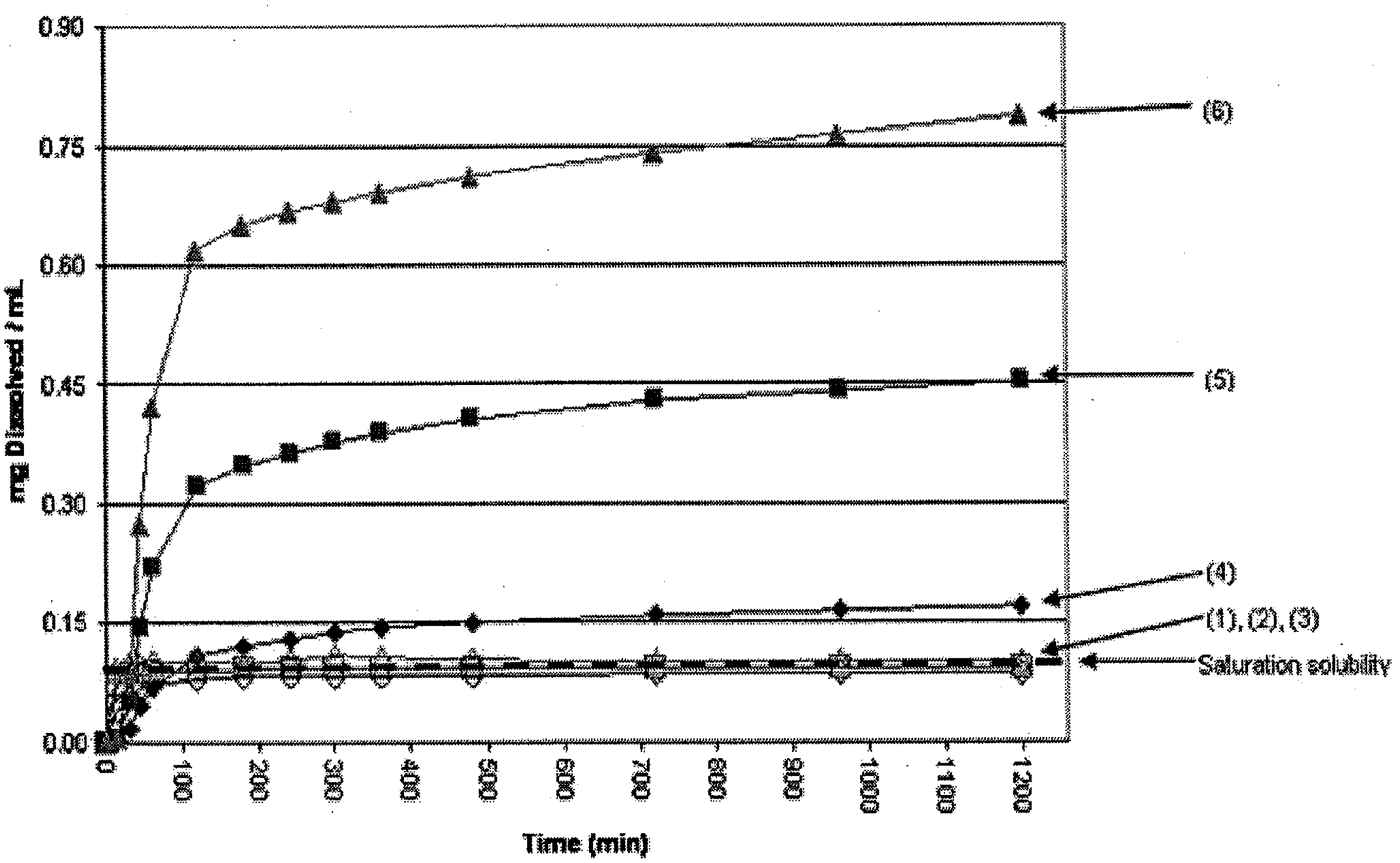
0.90
0.75
0.60
0.45
0.30
0.15
0.00
mg Dissolved / mL
0
100
200
300
400
500
600
700
800
900
1000
1100
1200
Time (min)
(6)
(5)
(4)
(1), (2), (3)
Saturation solubility

FIG. 6

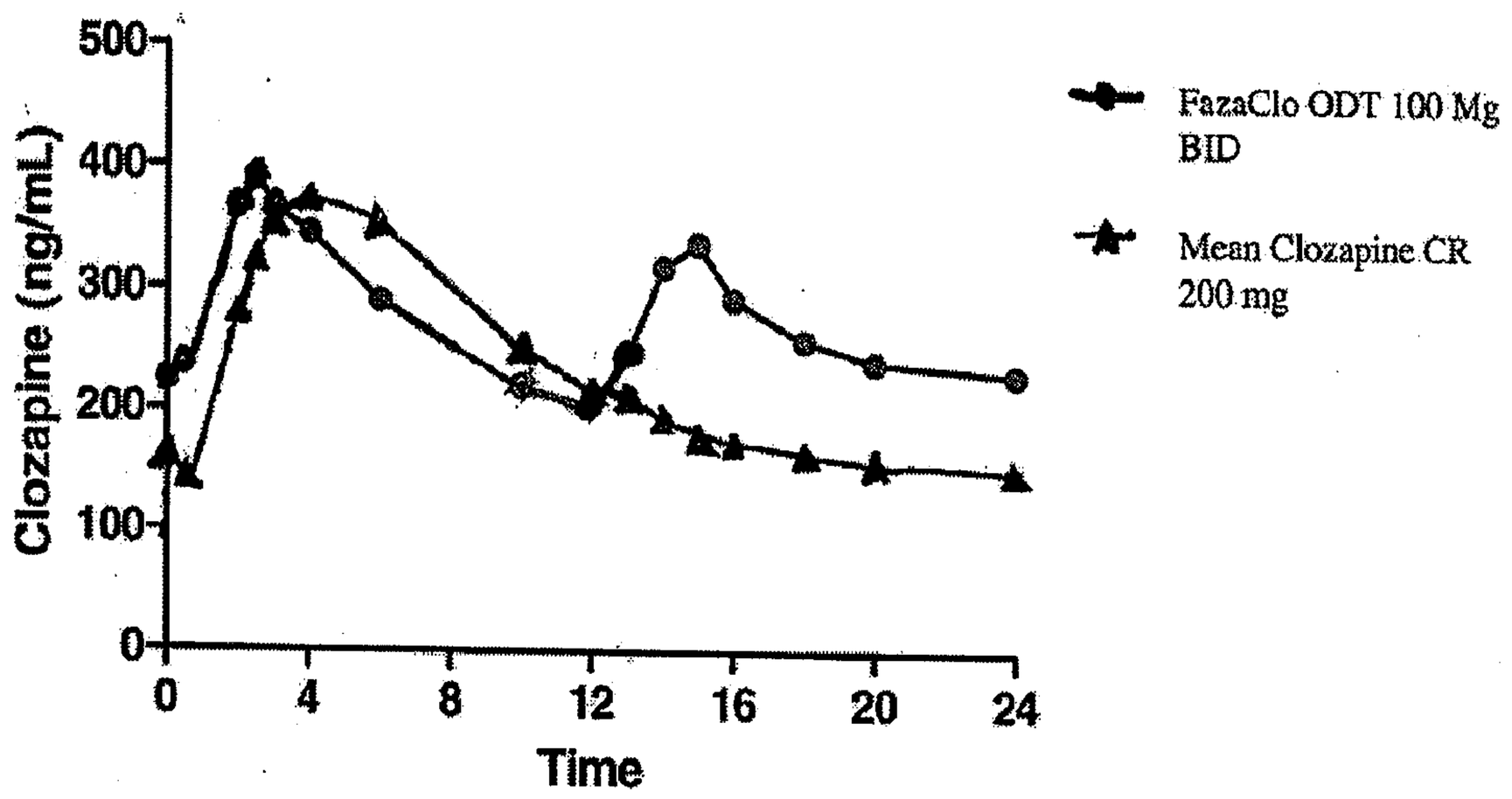
Mean Steady State Clozapine Levels Following FazaClo ODT 100 mg BID vs Clozapine CR 200 mg
Clozapine (ng/mL)
500
400
300
200
100
0
0
4
8
12
16
20
24
Time
FazaClo ODT 100 Mg BID
Mean Clozapine CR 200 mg

FIG. 7

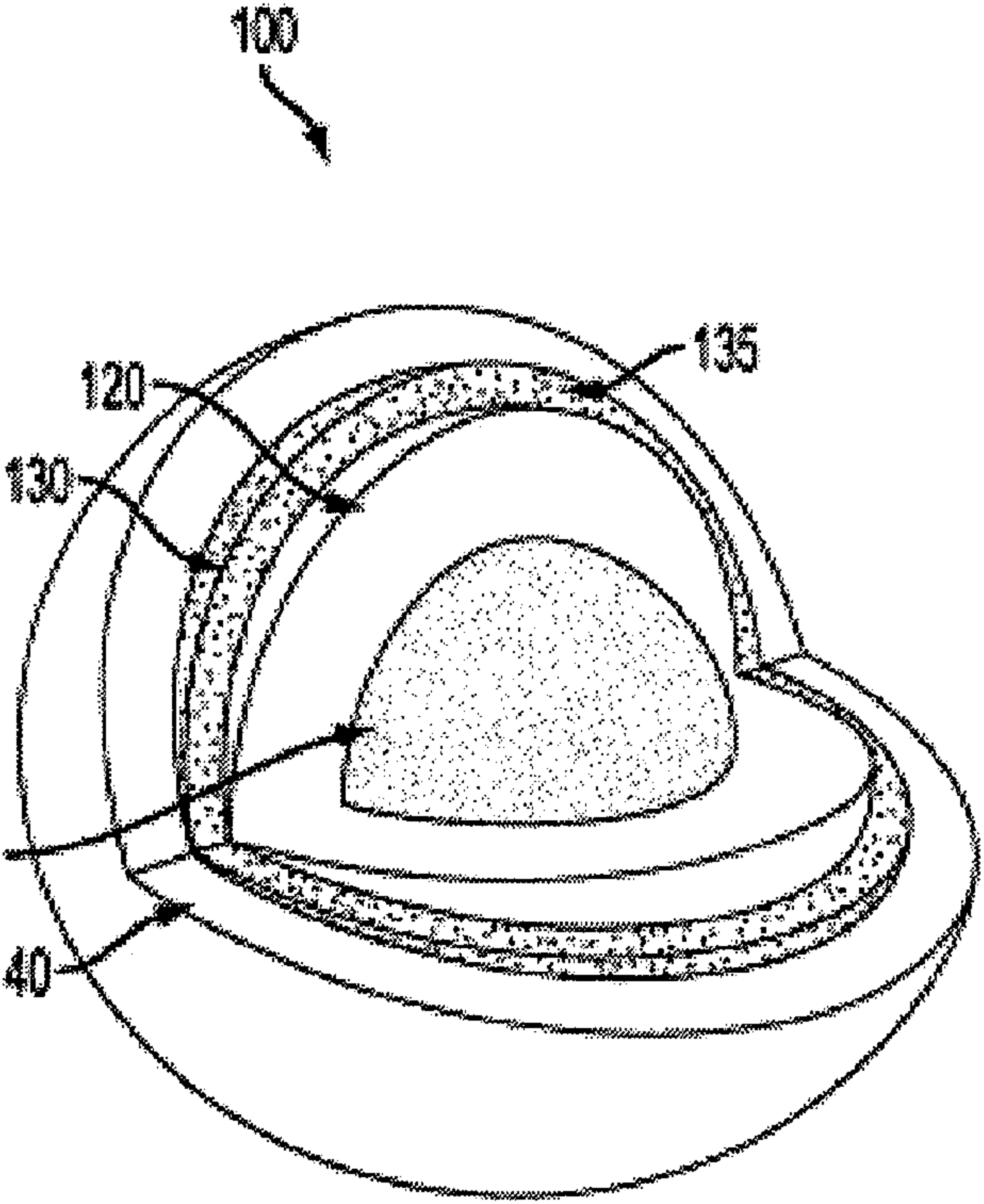

FIG. 1