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[54] **DUAL CONTROL SUSTAINED RELEASE DRUG DELIVERY SYSTEMS AND METHODS FOR PREPARING SAME**

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Related U.S. Application Data

[63] Continuation of Ser. No. 275,198, Jul. 14, 1994, abandoned, which is a continuation of Ser. No. 875,846, Apr. 29, 1992, abandoned.

[51] **Int. Cl.**[6] **A61K 9/24**

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[58] **Field of Search** 424/473, 472, 424/474, 481, 482, 440

[56] **References Cited**

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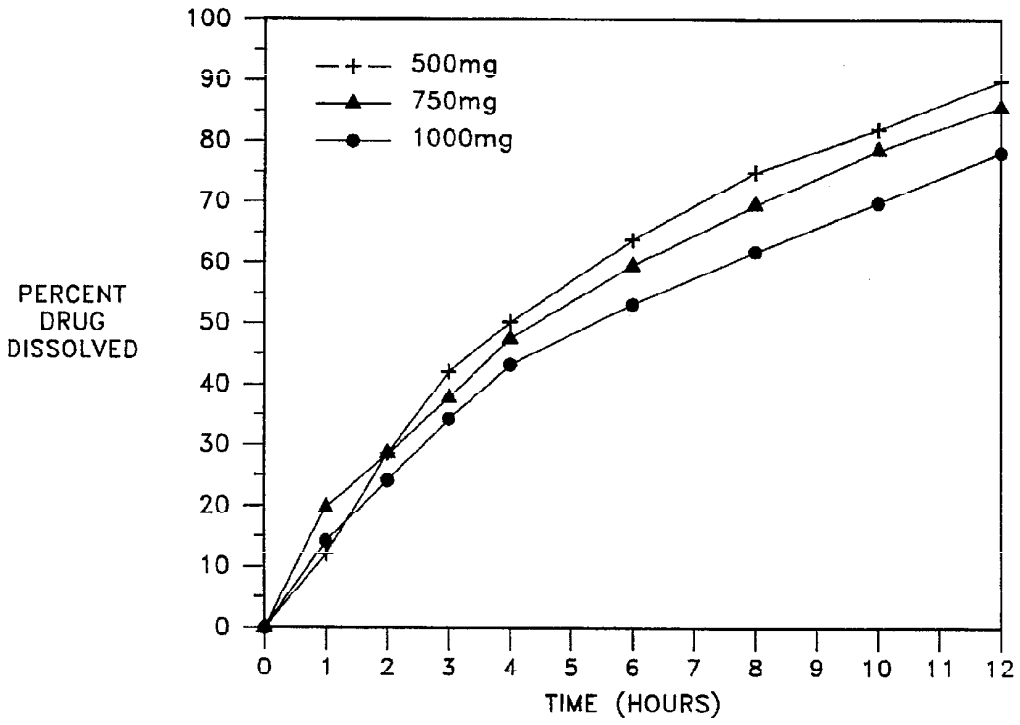
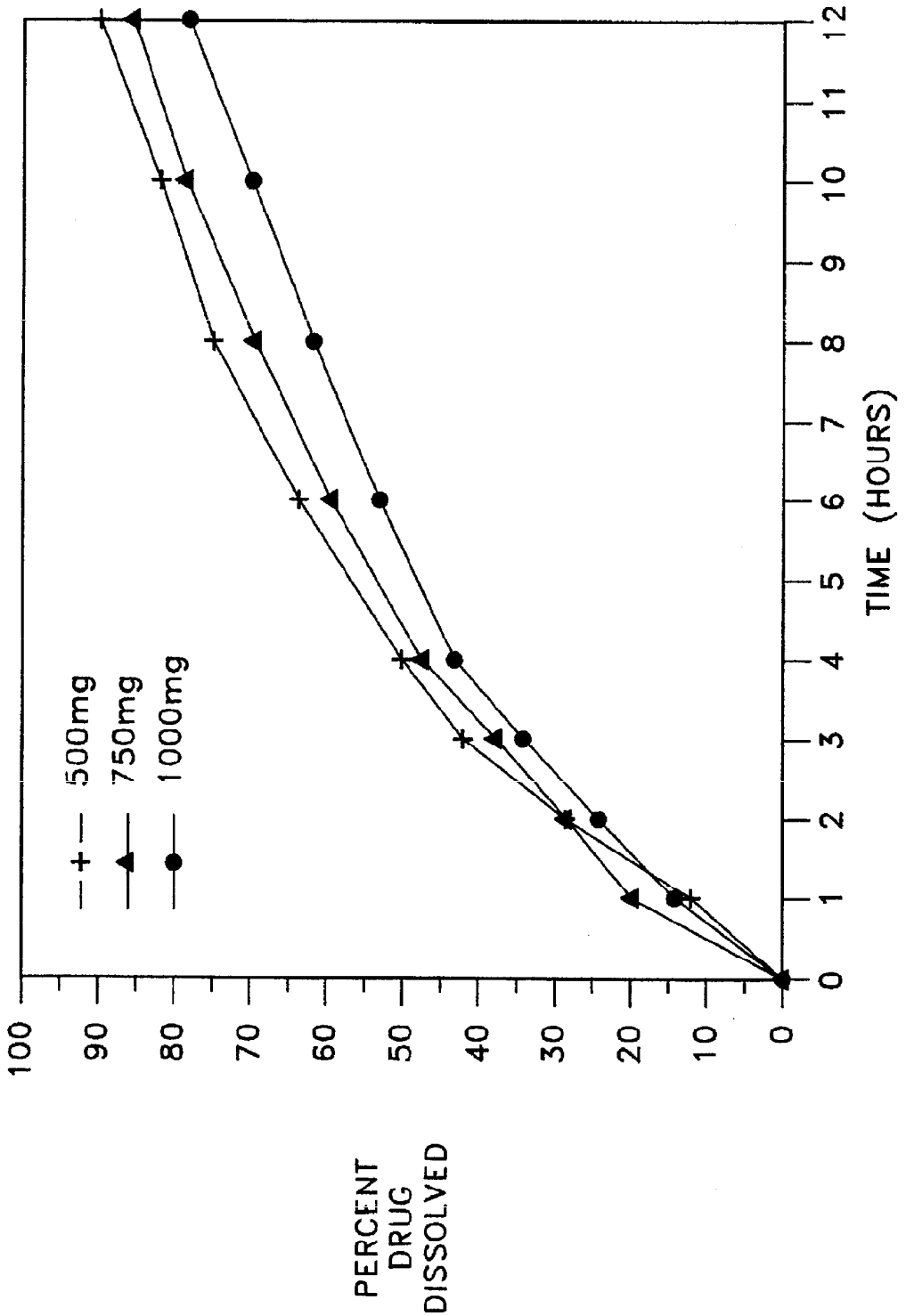
[57] **ABSTRACT**

The present invention pertains to a dual control sustained release drug delivery system which comprises a core and a porous coating layer over the core, wherein the coated core comprises (A) a core comprising in percentages by weight of the core composition (a) a medicament present in an amount from about 60% to about 90%; (b) an edible material having a melting point from about 25° C. to about 100° C. selected from the group consisting of (i) fatty acids having an iodine value from about 1 to about 10, (ii) natural waxes, (iii) synthetic waxes, and (iv) mixtures thereof, present in an amount from about 5% to about 40%; and (B) a porous coating layer over the core comprising in percentages by weight of the coating layer composition (a) a pH-independent water-insoluble polymer present in an amount from about 40% to about 80%; and (b) a water-soluble film forming polymer present in an amount from about 20% to about 60%.

15 Claims, 1 Drawing Sheet





DUAL CONTROL SUSTAINED RELEASE DRUG DELIVERY SYSTEMS AND METHODS FOR PREPARING SAME

This is a continuation of prior application Ser. No. 08/275,198 as originally filed on Jul. 14, 1994, now abandoned which was a continuation of U.S. Ser. No. 07/875,846 filed Apr. 29, 1992, now abandoned.

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention pertains to dual control sustained release drug delivery systems. The novel drug delivery systems contain a core comprising a medicament and a waxy material and a coating layer over the core comprising a pH-independent water-insoluble polymer and a water-soluble polymer. Therapeutically effective amounts of the drug delivery systems may be utilized in a wide variety of pharmaceutically acceptable carriers to prepare medicated sustained release compositions. This invention also relates to methods for preparing these drug delivery systems and the medicated sustained release compositions in which they may be used.

2. Description of the Background

Sustained release compositions for the sequential or timed release of medicaments are well known in the art. Generally such compositions contain medicament particles, normally administered in divided doses two or more times daily, mixed with or covered by a coating material which is resistant to degradation or disintegration in the stomach and/or in the intestine for a selected period of time. Release of the medicament may occur by leaching, erosion, rupture, diffusion or similar actions, depending upon the nature and thickness of the coating material.

A frequently encountered problem in the field of sustained release compositions is that many water-miscible drugs have a tendency to be dumped or surged into the body during the first hour or two after an oral dosage form is ingested. This problem is particularly acute when the sustained release compositions are administered with food.

U.S. Pat. No. 4,789,549, issued to Khan et al. and assigned to Warner-Lambert Company, discloses a sustained release composition comprising a medicament in a water-soluble polymer matrix coated with a semi-permeable membrane coating layer consisting of hydroxypropyl cellulose and cellulose acetate phthalate with polyoxypropylene polyoxyethylene block copolymer and acetylated monoglycerides. The water-soluble polymer matrix is preferably hydroxypropyl methylcellulose.

U.S. Pat. No. 4,816,264, issued to Phillips et al. and assigned to Warner-Lambert Company, discloses a sustained release drug delivery system containing a core comprising a medicament and a cellulosic gelling polymer such as hydroxyethyl cellulose coated with a semi-permeable membrane coating layer comprising a water-soluble cellulosic polymer such as hydroxypropyl cellulose and a water-insoluble acrylic polymer such as Eudragit E30D.

U.S. Pat. No. 4,851,233, issued to Khan et al. and assigned to Warner-Lambert Company, discloses a compressed table binder system consisting essentially of procainamide hydrochloride or sodium meclofenamate, type "H" hydroxyethyl cellulose, and microcrystalline cellulose coated with hydroxyethyl cellulose.

While the above sustained release compositions provide some degree of improved sustained release activity, none of the above compositions are entirely satisfactory. All of the above sustained release compositions have a tendency to rapidly release water-miscible drugs into the body when the sustained release compositions are administered with food. Thus it would be advantageous to prepare a sustained release composition having release properties which are unaffected by the consumption of food. The present invention provides such improved sustained release drug delivery systems without the disadvantages characteristic of previously known products. The present invention also provides methods for preparing these improved sustained release drug delivery systems and the medicated sustained release compositions in which they may be employed.

SUMMARY OF THE INVENTION

The present invention pertains to a dual control sustained release drug delivery system which comprises a core and a porous coating layer over the core, wherein the coated core comprises:

(A) a core comprising in percentages by weight of the core composition:

(a) a medicament present in an amount from about 60% to about 90%;

(b) an edible material having a melting point from about 25° C. to about 100° C. selected from the group consisting of (i) fatty acids having an iodine value from about 1 to about 10, (ii) natural waxes, (iii) synthetic waxes, and (iv) mixtures thereof, present in an amount from about 5% to about 40%; and

(B) a porous coating layer over the core comprising in percentages by weight of the coating layer composition:

(a) a pH-independent water-insoluble polymer present in an amount from about 40% to about 80%; and

(b) a water-soluble film forming polymer present in an amount from about 20% to about 60%.

BRIEF DESCRIPTION OF THE FIGURE

FIG. 1 is a graph showing the in vitro dissolution profile of a procainamide hydrochloride prolonged release tablet over a 12 hour period prepared according to the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention pertains to a sustained release drug delivery systems having a dual control mechanism. The drug delivery system contains a core comprising a medicament and a waxy material and a porous coating layer over the core comprising a pH-independent water-insoluble polymer and a water-soluble film forming polymer. Applicants have found that conventional sustained release compositions containing a water-soluble polymer matrix in the core have a tendency to either dump or delay the release of a medicament when administered with a high fat meal. Applicants have discovered that sustained release compositions containing the combination of a core having a medicament and a waxy material and a semi-permeable coating layer are essentially unaffected by food consumption. The dual control mechanism is achieved by employing a fatty acid or waxy material in the core and a specific combination of polymeric materials in the porous coating layer. The improved dual control sustained release drug delivery systems prolong the release of medicaments for up to 12 hours or more.

The dual control sustained release drug delivery systems may be utilized in a wide variety of pharmaceutically

acceptable carriers and confectionery bulking agents to prepare medicated sustained release compositions. This invention also relates to methods for preparing these dual control sustained release drug delivery systems and the medicated sustained release compositions in which they may be employed.

As set out above, the dual control sustained release drug delivery systems contain a core comprising a medicament and an edible material having a melting point from about 25° C. to about 100° C. selected from the group consisting of (i) fatty acids having an iodine value from about 1 to about 10, (ii) natural waxes, (iii) synthetic waxes, and (iv) mixtures thereof.

The medicaments (drugs, pharmaceuticals) present in the core of the drug delivery system of the present invention may be selected from a wide variety of water-soluble and water-insoluble drugs and their acid addition or metallic salts. Both organic and inorganic salts may be used provided the drug maintains its medicament value. Exemplary acid addition salts include hydrochloride, hydrobromide, orthophosphate, benzoate, maleate, tartrate, succinate, citrate, salicylate, sulfate and acetate. Exemplary metallic salts include sodium, potassium, calcium, and magnesium.

The medicament may be selected from a wide range of therapeutic agents and mixtures of therapeutic agents which may be administered in sustained release or prolonged action form. Nonlimiting illustrative categories and specific examples of such medicaments include:

(a) Analgesics, such as acetylsalicylic acid, acetaminophen, ibuprofen, phenacetin, phenylbutazone, salicylamide, sodium salicylate, and meclofenamic acid;

(b) Anthelmintics, such as dithiazanine iodide and gardona;

(c) Antiasmatics, such as aminophylline, metaproterenol, epinephrine, theophylline, and oxtriphylline;

(d) Antiarrhythmics, such as procainamide hydrochloride and pirminol;

(e) Anticholesterolemic and antilipid agents, such as gemfibrozil, HMG reductase inhibitors, and ACAT inhibitors;

(f) Antiemetics, such as prochloroperazine dimaleate;

(g) Antiepileptic drugs, such as sodium phenytoin;

(h) Antihistamines, such as chlorpheniramine maleate, brompheniramine maleate, phenindamine tartrate, pyrilamine maleate, methapyrilene fumarate, doxylamine succinate, phenyltoloxamine citrate, diphenylhydramine hydrochloride, promethazine, terfenedine and triprolidine;

(i) Antihypertensives, such as methyldopa;

(j) Anti-inflammatory agents, such as isoxicam, meclofenamic acid, sodium meclofenamate, and naproxen;

(k) Antinauseants, such as dimenhydrinate and meclizine;

(l) Antipyretics, such as N-acetyl-p-aminophenol;

(m) Antitussives, such as dextromethorphan, dextromethorphan hydrobromide, noscapine, carbetapentane citrate, chlophedianol hydrochloride, codeine and diphenhydramine hydrochloride;

(n) Anxiety agents, such as buspirone hydrochloride and N-methylglucamine;

(o) Appetite suppressants, such as phenylpropanolamine hydrochloride and caffeine;

(p) Cathartics, such as castor oil;

(q) Central nervous system stimulants, such as nicotine and caffeine;

(r) Cardiovascular preparations, such as angiotensin converting enzyme inhibitors (ACE inhibitors), including enalapril maleate and catopril; calcium channel blockers, including verapamil hydrochloride;

(s) Cognition activators such as tactine;

(t) Decongestants, such as phenylephrine hydrochloride, phenylpropanolamine hydrochloride, pseudoephedrine hydrochloride, pseudoephedrine hydrobromide, pseudoephedrine sulfate and ephedrine;

(u) Expectorants, such as guaifenesin and glycerol guaiacolate;

(v) Laxatives, such as phenolphthalein, danthron, pamabrom and bisocadyl;

(w) Nutritional supplements, including vitamins and minerals, such as ascorbic acid, niacin, pantothenic acid, vitamin B6, thiamine hydrochloride, riboflavin, potassium iodide, potassium chloride, cupric sulfate and ferrous sulfate; and

(x) Various alkaloids, such as codeine phosphate, codeine sulfate and morphine.

Preferred drugs to be employed include sparingly soluble drugs such as sodium meclofenamate, meclofenamic acid, methyldopa, sodium phenytoin, and the like, and freely soluble drugs such as diphenhydramine hydrochloride, pseudoephedrine hydrochloride, procainamide hydrochloride, and oxtriphylline. In a preferred embodiment, the medicament is selected from the group consisting of sodium meclofenamate and procainamide hydrochloride. In a more preferred embodiment, the medicament is procainamide hydrochloride.

The medicament of the present invention may be used in many distinct physical forms well known in the pharmaceutical art to provide an initial dosage of the medicament and/or a further time-release form of the medicament. Without being limited thereto, such physical forms include free forms and encapsulated forms, and mixtures thereof.

The amount of medicament drug or its acid addition salt used in the present invention may vary depending upon the therapeutic dosage recommended or permitted for the particular medicament. In general, the amount of medicament present is the ordinary dosage required to obtain the desired result. Such dosages are known to the skilled practitioner in the medical arts and are not a part of the present invention. In a preferred embodiment, the medicament in the core of the drug delivery system is present in an amount from about 60% to about 90%, preferably from about 70% to about 90%, and more preferably from about 75% to about 85%, by weight of the core composition.

The edible material present in the core of the drug delivery system of the present invention is a material which has a melting point in the range from about 25° C. to about 100° C., preferably from about 35° C. to about 100° C., and more preferably from about 45° C. to about 100° C. The melting point of the edible material should be within the recited range because the sustained release properties of the final drug delivery system will be greatly affected by the fat or wax constituent.

The edible materials useful in the core are selected from the group consisting of fatty acids, natural waxes, synthetic waxes, and the like, and mixtures thereof. Fatty acids are carboxylic acids derived from or contained in an animal or vegetable fat or oil. Fatty acids are composed of a chain of alkyl groups containing from 4 to 22 carbon atoms and are characterized by a terminal carboxyl group. Waxes are low-melting organic mixtures or compounds having a high

molecular weight, are solid at room temperature and generally are similar in composition to fats and oils except that waxes contain no glycerides. Waxes may be hydrocarbons or esters of fatty acids and alcohols. Fatty acids and waxes are both classified as lipids.

The fatty acids useful in the present invention are acids which have an iodine value from about 1 to about 10. The iodine value is a means of determining the degree of unsaturation in a fat or oil. The measurement of iodine values is determined by known titrating methods and is reported in terms of centigrams of iodine absorbed per gram of fat or oil sample titrated. (See "Bailey's Industrial Oil and Fat Products," Vol. 2, 4th Ed., Swern, Daniel ed., pp. 436–438 (1982)). Hence the fatty acids useful in the present invention have an iodine value from about 1 centigram to about 10 centigrams.

Fatty acids useful in the present invention are selected from the group consisting of hydrogenated palm oil, hydrogenated palm kernel oil, hydrogenated peanut oil, hydrogenated rapeseed oil, hydrogenated rice bran oil, hydrogenated soybean oil, hydrogenated cottonseed oil, hydrogenated sunflower oil, hydrogenated castor oil, and the like, and mixtures thereof. Other fatty acids include, for example, decenoic acid, docosanoic acid, stearic acid, palmitic acid, lauric acid, myristic acid, and the like, and mixtures thereof. The preferred fatty acids are selected from the group consisting of hydrogenated palm oil, hydrogenated castor oil, hydrogenated cottonseed oil, stearic acid, palmitic acid, and mixtures thereof. The most preferred fatty acid is stearic acid.

Waxes useful in the present invention include natural waxes, such as animal waxes, vegetable waxes, and petroleum waxes (i.e., paraffin waxes, microcrystalline waxes, petrolatum waxes, mineral waxes), and synthetic waxes which are edible and have a melting point within the range from about 25° C. to about 100° C. Specific examples of useful waxes are spermaceti wax, carnauba wax, Japan wax, bayberry wax, flax wax, beeswax, Chinese wax, shellac wax, lanolin wax, sugarcane wax, candelilla wax, paraffin wax, microcrystalline wax, petrolatum wax, carbowax, and the like, and mixtures thereof. Mixtures of these waxes with the fatty acids set out above may also be used. The preferred waxes are selected from the group consisting of carnauba wax, bees wax, glyceryl tristearate, glyceryl monostearate, paraffin wax, microcrystalline wax, glyceryl distearate, and mixtures thereof. The most preferred waxes are carnauba wax, bees wax, glyceryl tristearate, glyceryl monostearate, and paraffin wax.

The wax may also be an ester of a fatty acid having from about 12 to about 31 carbon atoms and a fatty alcohol having from about 12 to about 31 carbon atoms, the ester having a carbon atom content from about 24 to about 62 carbon atoms. Examples of such fatty, acid esters are myricyl palmitate, ceryl palmitate, ceryl cerotate, myricyl melissate, stearyl palmitate, stearyl myristate, lauryl laurate, and the like, and mixtures thereof. The preferred fatty acid esters are selected from the group consisting of stearyl palmitate, stearyl myristate, and mixtures thereof.

The wax may also be a monoglyceryl ester, diglyceryl ester, or triglyceryl ester (glycerides) which is an ester formed from a fatty acid having from about 10 to about 22 carbon atoms and glycerol, wherein one or more of the hydroxyl groups of glycerol is substituted by a fatty acid. Examples of useful glycerides include glyceryl monostearate, glyceryl distearate, glyceryl tristearate, glyceryl dipalmitate, glyceryl tripalmitate, glyceryl monopalmitate, glyceryl dilaurate, glyceryl trilaurate, glyceryl monolaurate, glyceryl didocosanoate, glyceryl tridocosanoate, glyceryl monodocosanoate, glyceryl monocaproate, glyceryl dicaproate, glyceryl tricaproate, glyceryl monomyristate, glyceryl dimyristate, glyceryl trimyristate, glyceryl monodecenoate, glyceryl didecenoate, glyceryl tridecenoate, and the like, and mixtures thereof. The preferred glycerides are selected from the group consisting of glyceryl monostearate, glyceryl distearate, glyceryl tristearate, and mixtures thereof.

In a preferred embodiment, the edible material is selected from the group consisting of carnauba wax, hydrogenated vegetable oils, and stearic acid. More preferably, the edible material is carnauba wax.

The amount of edible material used in the core may vary depending upon the medicament employed and the degree of sustained release desired. In general, the fatty acid or waxy edible material will be present in the core in an amount from about 5% to about 40%, preferably from about 5% to about 30%, and more preferably from about 5% to about 15%, by weight of the core composition.

The core of the drug delivery system of the present invention may also contain conventional excipients and additives which function to facilitate processing or storage. Thus coloring agents, flavoring agents, perfumes, sweetening agents, surface active agents, lubricants, softeners, glidants, stabilizing agents, and the like, and mixtures thereof, may be employed.

As set out above, the cores in the drug delivery systems are coated with a porous coating layer comprising a pH-independent water-insoluble polymer present and a water-soluble film forming polymer.

The pH-independent water-insoluble polymers in the coating layer of the drug delivery system of the present invention are preferably acrylic polymers. Suitable water-insoluble polymers in the present invention include aqueous acrylic resin dispersions such as polyacrylamide, polyacryldextran, polyalkyl cyanoacrylate, polymethyl methacrylate, methacrylic resin copolymer, and the like, and mixtures thereof. Preferred resins are the Eudragits™ (methacrylic resin copolymer), made by Rohm Pharma. Eudragit NE30D™ is highly preferred.

The amount of pH-independent water-insoluble polymer used in the present invention may vary depending upon the medicament employed and the degree of sustained release desired. The pH-independent water-insoluble polymer in the coating layer is preferably present in an amount from about 40% to about 80%, more preferably from about 50% to about 75%, and most preferably from about 55% to about 70%, by weight of the coating layer composition.

The water-soluble film forming polymers in the coating layer of the drug delivery system of the present invention include cellulose derivatives such as hydroxypropylcellulose, hydroxypropyl-methylcellulose, hydroxypropylmethylcellulose phthalate, sodium carboxymethylcellulose, and the like, and mixtures thereof. In a preferred embodiment, the film forming polymer is hydroxypropylcellulose.

The amount of water-soluble film forming polymer used in the present invention may vary depending upon the medicament employed and the degree of sustained release desired. The water-soluble film forming polymer in the coating layer is preferably present in an amount from about 20% to about 60%, more preferably from about 25% to about 50%, and most preferably from about 30% to about 45%, by weight of the coating layer composition.

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