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Berliner et al.

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[54] **DELIVERY OF DRUGS TO THE LOWER GASTROINTESTINAL TRACT**

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[73] Assignee: **Advanced Polymer Systems, Inc.**, Redwood City, Calif.

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Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 432,619, May 2, 1995, abandoned, which is a continuation-in-part of Ser. No. 282,836, Jul. 29, 1994, abandoned.

[51] **Int. Cl.**[6] **A61K 9/26**; A61K 9/30; A61K 9/48; A61K 9/52

[52] **U.S. Cl.** **424/463**; 424/451; 424/456; 424/463; 424/464; 424/469; 424/474; 424/475; 424/479; 424/482

[58] **Field of Search** 424/451, 456, 424/458, 461, 463, 486, 489, 499, 464, 469, 474–482

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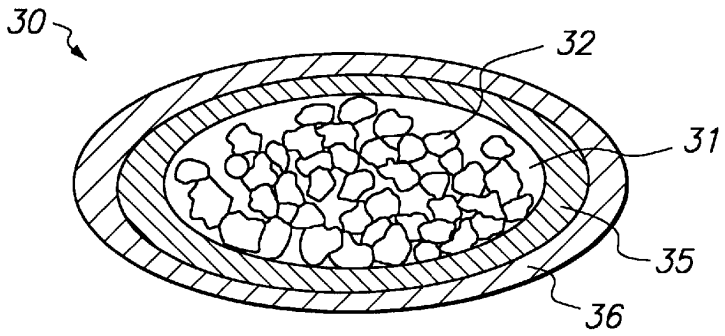
[57] **ABSTRACT**

Diseases of the colon are treated by oral ingestion of a unit dosage form containing a plurality of porous microscopic beads, the pores containing an active agent or drug and plugged with a polysaccharide that is chemically degradable by colon-specific bacteria. The dosage form further contains a coating of an enteric material that remains intact until the dosage form reaches the colon.

34 Claims, 1 Drawing Sheet



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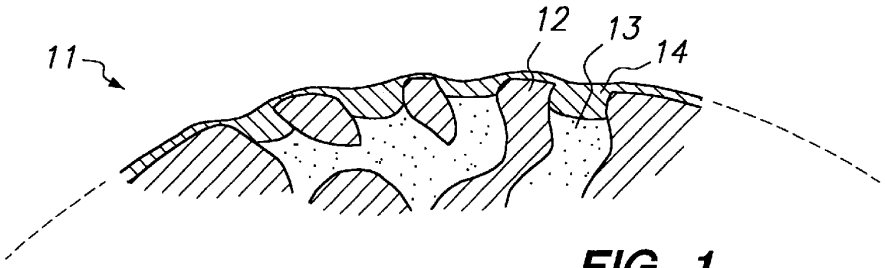

FIG. 1

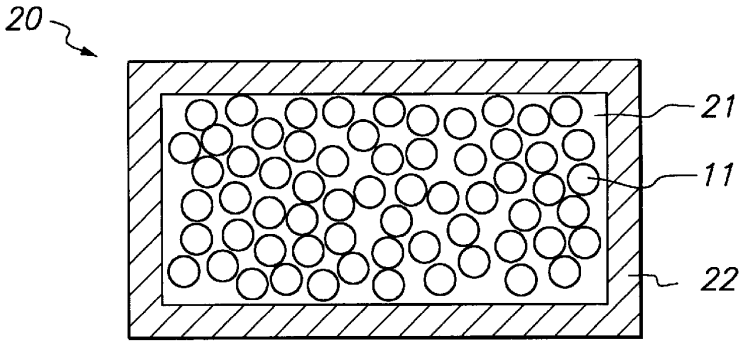

FIG. 2

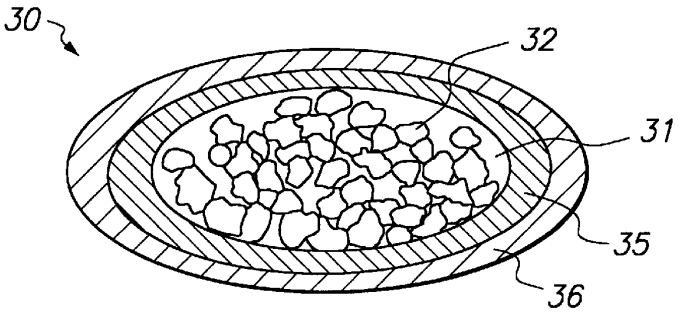

FIG. 3a

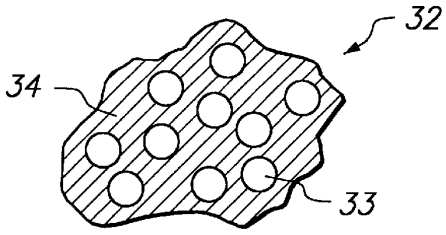

FIG. 3b

DELIVERY OF DRUGS TO THE LOWER GASTROINTESTINAL TRACT

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of U.S. Pat. application Ser. No. 08/432,619, filed May 2, 1995, now abandoned, which was a continuation-in-part of application Ser. No. 08/282,836, filed Jul. 29, 1994, now abandoned. The contents of both applications 08/432,619 and 08/282,836 are hereby incorporated herein by reference.

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to the treatment of diseases of the colon, such as inflammatory bowel disease. More particularly, it relates to a dosage form for an active agent and the method of its use in topically treating disease in the colon.

2. Description of the Prior Art

Many conditions either originate or are expressed in the lumen of the gastrointestinal (G.I.) tract or in the tissue intermediate to the lumen. Inflammatory bowel diseases, such as ulcerative colitis and Crohn's disease, are examples of such conditions. Current therapies for inflammatory bowel diseases involve systemic administration of a formulation containing an active drug. Unfortunately, the drug is absorbed systemically even though the site where the drug is needed is a localized area in the bowel. Thus, to achieve a therapeutically effective local concentration at the site of the disease, one must administer enough of the formulation that the systemic concentration is relatively high. The disadvantage is that high systemic concentrations can have damaging side effects. An example is the administration of prednisolone for inflammatory bowel disease. Although administered for purposes of localized action, this steroid is absorbed systemically, and prolonged exposure from continued systemic absorption can result in atrophy of adrenal glands. Steroids have also been administered by enema, but this does not prevent systemic absorption.

One method of preventing systemic absorption is the use of prodrug techniques. The prodrug is one that is not absorbed until it reaches a particular region of the G.I. tract where it is transformed to an absorbable form and thereby becomes active. An example is sulphasalazine which is used in the treatment of inflammatory bowel disease.

While the prodrug approach has worked for some drugs it is limited in scope due to its dependence upon the chemistry of the prodrug and the drug, and how the former is transformed to the latter in the G.I. environment. This approach requires the development of a new prodrug for each active species, and as new chemical entities, prodrugs require independent regulatory approval.

SUMMARY OF THE INVENTION

The disadvantages noted above are addressed by the present invention, which resides in a composition and method for the treatment of diseases of the colon by oral ingestion of a drug specially formulated to pass intact through the stomach and to be released at a controlled rate for therapeutic action upon reaching the colon. These effects are achieved in a manner independent of the chemistry of the drug or of any relationship between the drug itself and the environment of the G.I. tract. The formulation comprises microscopic beads with pores containing the drug, the pores

being plugged with a polysaccharide that is chemically degradable only by bacterial enzymes that are present in the colon, the beads being assembled into a unit dosage form suitable for oral administration yet coated with an enteric coating that protects that dosage form from the stomach environment and allows it to pass intact through the stomach and into the colon. The dosage form thus remains intact until it reaches the small intestine or regions close thereto, where the enteric coating degrades and exposes the polysaccharide that plugs the pores. While some dissolving of the polysaccharide occurs upon exposure in this manner, chemical degradation of the polysaccharide occurs only in the large intestine (i.e., the colon). Once the polysaccharide is degraded sufficiently to expose the active agent in the pores, the beads release the active agent at a rate which is slow and controlled due to the pore structure.

The microscopic beads are rigid polymeric beads that remain rigid and insoluble throughout their travel through the G.I. tract, each microscopic bead containing a substantially noncollapsible internal pore network accessible through openings on the surfaces of the beads. The polymer from which the beads are formed can be linear or crosslinked. The active agent retained in the pore network of the beads is any of a wide variety of therapeutic drugs, examples of which are corticosteroids and non-steroidal anti-inflammatory agents for treatment of inflammatory bowel disease, anti-tumor agents for treatment of colonic malignancies, anti-parasitic agents for treatment of parasites, antibiotics for treatment of infections, laxatives for treatment of constipation, and drugs such as bismuth subsalicylate, trimethoprim-sulfamethoxazole, and doxycycline and various other antibiotics for treatment of diarrhea.

The microscopic beads used in the present invention have previously been used as a delivery system for external topical skin administration of active agents. When topically administered, the beads were shown to be capable of releasing the active agents at a controlled rate. It has now been found that these microscopic beads when formulated with the polysaccharides and enteric coatings described above constitute a delivery system that can be administered orally for the safe and efficacious treatment of diseases of the colon without harm to, or substantial release of the active agent at, other locations along the G.I. tract. The inherently slow release rate of active agents from the pores of the microscopic beads is thus now further combined with localization of the release. In certain cases a small degree of systemic absorption of the active agents may occur, but side effects are substantially absent since the rate of systemic absorption is at most very slow due to the combination of drug, microbeads, pore structure, and polysaccharide in the formulation.

This method of administering the active agent is thus a topical administration since the active agent is not released from the dosage form until it reaches the site of interest. The agent thus contacts the site of interest directly through the wall of the colon, rather than being delivered to the colon through the blood stream which would carry the agent active to other (not diseased) parts of the body as well. The use of porous microbeads for a controlled and sustained release rate maximizes this topical effect and minimizes systemic effects.

In preferred embodiments, the dosage form is a pharmaceutical capsule (such as a gelatin capsule) or tablet containing a multitude of microscopic beads with the selected active agent in the porous network of the individual beads, the polysaccharide on the surfaces of the individual beads and plugging the pores, and an enteric coating surrounding

the capsule or tablet. The active agent can be present in the capsule or tablet in varying amounts not critical to this invention, although in most cases the amount per capsule or tablet will generally be in the range of about 0.1–100 mg, with additional acceptable ranges about 1–100 mg, about 3–20 mg, and about 5–20 mg.

Examples of microscopic beads are those formed from styrene-divinylbenzene copolmyer, methyl methacrylate-ethylene glycol dimethacrylate copolymer, poly(methyl acrylate), poly(methyl methacrylate), and polystyrene, and analogs thereof. Typical bead diameters are about 5–200 microns, preferably about 10–40 microns.

Two of the many conditions that can be successfully treated by the composition and method of this invention are ulcerative colitis, which affects only the large intestine (a portion or its entire length), and Crohn's disease, which affects both the terminal ileum and the ascending colon. A dosage form for ulcerative colitis according to the present invention is formulated so that it will initially remain intact in the G.I. tract and degrade only in or near the large intestine. For Crohn's disease the dosage form is formulated to initially remain intact in the G.I. tract until reaching the junction of the ileum with the colon where it will degrade and release the active agent.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a cross section of a porous microscopic bead impregnated with an pharmacological agent in the pores, and the pores plugged with a polysaccharide for use in the formulations of this invention. The view shown in the Figure is that of a region close to the surface of the bead.

FIG. **2** is a cross section of a tablet embodying a unit dosage form within the scope of this invention.

FIG. **3***a* is a cross section of a capsule embodying a unit dosage form within the scope of this invention. FIG. **3***b* is an enlarged cross section of one of the particles contained in the interior of the capsule of FIG. **3***a*.

DETAILED DESCRIPTION OF THE INVENTION AND PREFERRED EMBODIMENTS

Microscopic Beads

Microscopic beads that can be used in connection with the present invention are known in the art and are described in detail in Won, U.S. Pat. No. 5,145,675, entitled "Two Step Method for Preparation of Controlled Release Formulations," issued Sep. 8, 1992, assigned to Advanced Polymer Systems, Inc. The disclosure of U.S. Pat. No. 5,145,675 is incorporated herein by reference. One particular type of microscopic bead contemplated for use in this invention are co-polymers of styrene and divinylbenzene, whose preparation is disclosed in Example 1.1 of U.S. Pat. No. 5,145,675. The same example also illustrates a method for entrapping steroids within the porous network of the polymeric beads. Another type of microscopic bead contemplated for use herein are copolymers of methyl methacrylate and ethylene glycol dimethacrylate. The preparation of microscopic beads of this composition is described in Example 6.2 of U.S. Pat. No. 5,145,675. In general, the diameter of an individual bead is not critical and may vary. In most cases, however, the most convenient diameter is from about 5 microns to about 200 microns. Particles of the aforementioned types are commercially available from Advanced Polymer Systems, Inc., of Redwood City, Calif., in the form of empty particles or as particles which have been loaded with the active agents utilized in the present invention.

Pore-plugging Polysaccharide Degradable by Colonic Bacteria

As noted, one of the elements responsible for restricting release of the drug from the dosage form to locations in or near the colon is the polysaccharide that plugs the pore openings and seals the active agent inside the pores. The polysaccharide is one that is chemically degradable only by the action of bacteria that are specific to and generally confined in the colon. The degradation of the coating by these bacteria result in the removal of the polysaccharide from the pore openings and consequently the release of the drug. Examples of polysaccharides that meet this description are pectin, arabinogalactose, chitosan, chondroitin sulfate, cyclodextrin, dextran, galactomannan (guar gum), and xylan. A preferred polysaccharide is pectin.

The amount of colon-degradable polysaccharide present in the formulation can vary and is not critical, although amounts considered optimal will depend on the particular polysaccharide selected. The amount in any event will be sufficient to plug the pore openings. For pectin, it has been shown that dissolution and release will depend on the particular pectin composition, primarily its methoxy content. Thus, pectins with a high degree of methoxylation demonstrate a higher degree of protection for the dosage form than those pectins with a lower degree of methoxylation. Pectin USP with a degree of methoxylation of 70% is an example of a preferred material which can be obtained from Bulmer Pectin, UK.

Enteric Coating

Examples of enteric coating materials that are gastro resistant and yet degrade in the intestines are disclosed in Eury et al., U.S. Pat. No. 5,316,774, entitled "Blocked Polymeric Particles Having Internal Pore Networks for Delivering Active Substances to Selected Environments," issued May 31, 1994, the contents of which are hereby incorporated herein by reference. Other examples are known to those skilled in the art.

One class of enteric coating materials of the above description are those that remain intact in the environment of the stomach but solubilize at the higher pH of the intestines. Materials of this type are known in the art for use as coatings for solid core drug formulations. The most effective enteric materials are polyacids having a pK_a of from about 3 to 5. Preferred are those whose carboxylic acid groups are transformed to carboxylate groups at a pH of from about 5 to 7. These copolymers are resistant to gastric juices. Exemplary materials include fat-fatty acid mixtures, cellulose acetate phthalates, copolymers of methacrylic acid and methyl methacrylate, copolymers of methacrylic acid and ethylacrylate, and polymers or copolymers in general containing acrylic acid or alkyl-substituted acrylic acids as monomers. The polymers, and particularly those containing acrylic acid or an alkyl-substituted acrylic acid can be applied to the outer surface of the dosage form either by in situ polymerization or by deposition from an aqueous dispersion. Examples of copolymers useful as enteric coating materials are listed in Table I.

TABLE I

Copolymer	Molecular Weight	Preferred Monomer Ratio
poly(methacrylic acid, ethylacrylate)	250 kD	1:1
poly(methacrylic acid, methylmethacrylate)	135 kD	1:2

The coating thickness may vary and is not critical to this invention. In most applications and with most coating

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