IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ENDO PHARMACEUTICALS INC. and PENWEST PHARMACEUTICALS CO.,	)	
Plaintiffs,	)	
v.	)	C. A. No. _____
IMPAX LABORATORIES, INC.,	)	
Defendant.	)	

COMPLAINT

Plaintiffs Endo Pharmaceuticals Inc. ("Endo") and Penwest Pharmaceuticals Co. ("Penwest"), for their Complaint against defendant Impax Laboratories, Inc. ("Impax"), allege as follows.

PARTIES

1. Endo is a Delaware corporation, having its principal place of business at 100 Endo Boulevard, Chadds Ford, Pennsylvania 19317. Endo is a specialty pharmaceutical company engaged in the research, development, sale and marketing of prescription pharmaceuticals used primarily to treat and manage pain, including OPANA® ER.

2. Penwest is a Washington corporation, having its principal place of business at 39 Old Ridgebury Road, Suite 11, Danbury, Connecticut 06810-5120. Penwest is a drug development company focused primarily on the identification, development and commercialization of products for diseases of the nervous system using its expertise in drug development and drug delivery technology, including the extended-release technology used in OPANA® ER.

3. Upon information and belief, Impax is a Delaware corporation, having its principal place of business at 30831 Huntwood Avenue, Hayward, California 94544.

4. Upon information and belief, Impax is manufacturing generic drug products for sale and use throughout the United States, including in this judicial district.

NATURE OF ACTION

5. This is an action for infringement of United States Patent Nos. 5,662,933 ("the '933 patent") and 5,958,456 ("the '456 patent"). This action is based upon the Patent Laws of the United States, 35 U.S.C. § 100, *et seq.*

JURISDICTION AND VENUE

6. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a). Venue is proper in this judicial district pursuant to 28 U.S.C. §§ 1391(c) and 1400(b).

FACTUAL BACKGROUND

7. On September 2, 1997, the U.S. Patent and Trademark Office ("PTO") duly and legally issued the '933 patent, entitled "Controlled Release Formulation (Albuterol)" to Edward Mendell Co, Inc., as assignee. Edward Mendell Co., Inc. was renamed Penwest Pharmaceuticals Co. on October 20, 1997. A true and correct copy of the '933 patent is attached as Exhibit A.

8. On September 28, 1999, the PTO duly and legally issued the '456 patent, entitled "Controlled Release Formulation (Albuterol)" to Edward Mendell Co, Inc., as assignee. A true and correct copy of the '456 patent is attached as Exhibit B.

9. Penwest is the assignee and owner of the '933 and '456 patents, and Endo is an exclusive licensee of these patents in the relevant field of use pursuant to a strategic alliance agreement with Penwest.

10. On June 22, 2006, the United States Food and Drug Administration (the "FDA") approved Endo's new drug application No. 21-610 for OPANA® ER tablets, which

contain oxymorphone hydrochloride, under § 505(b) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355(b), for the relief of moderate-to-severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time.

11. On October 19, 2007, Endo submitted information regarding the '933 and '456 patents to the FDA for listing in its publication, the *Approved Drug Products with Therapeutic Equivalence Evaluations* (referred to as the "Orange Book"), with respect to OPANA® ER tablets. The FDA thereafter listed the '933 and '456 patents in the Orange Book with respect to OPANA® ER tablets, pursuant to 21 C.F.R. § 314.53(e).

12. Upon information and belief, prior to October 2007, Impax submitted to the FDA paperwork purporting to constitute an Abbreviated New Drug Application ("ANDA") under § 505(j) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355(j), seeking approval to engage in the commercial manufacture, use, and sale of oxymorphone hydrochloride extended-release tablets, as generic versions of OPANA® ER tablets.

13. Upon information and belief, although the FDA initially accepted Impax's ANDA for substantive review, it thereafter rescinded that acceptance.

14. Upon information and belief, Impax subsequently amended its ANDA.

15. Upon information and belief, by letter dated December 12, 2007, the FDA advised Impax that its ANDA 79-087 "has been deemed acceptable for filing and substantive review by FDA as of November 23, 2007." The FDA's letter also requested that IMPAX provide the notice and information required by 21 U.S.C. §§ 355(j)(2)(B)(i).

16. On December 13, 2007, Impax sent Penwest and Endo a notice stating that it had submitted ANDA No. 79-087 seeking approval to manufacture, use, or sell generic

oxymorphone hydrochloride extended-release tablets prior to the expiration of the '933 and '456 patents (the "Impax Notice").

17. The Impax Notice advised Penwest and Endo that Impax's ANDA included a certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) (a "paragraph IV certification") that, in Impax's opinion, the proposed manufacture, importation, use or sale of the generic oxymorphone hydrochloride extended-release tablets described in its ANDA would not infringe any claim of the '933 or '456 patents.

18. In the Impax Notice, Impax did not assert that either patent is invalid.

COUNT I

INFRINGEMENT OF THE '456 PATENT

19. Plaintiffs incorporate each of the preceding paragraphs 1 to 18 as if fully set forth herein.

20. Impax's submission of an amended ANDA to the FDA, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '456 patent under 35 U.S.C. § 271(e)(2)(A).

21. Impax's commercial manufacture, offer for sale or sale of its proposed generic oxymorphone hydrochloride extended-release tablets would infringe the '456 patent.

22. Upon information and belief, Impax was aware of the existence of the '456 patent as demonstrated by its reference to that patent in its ANDA, and was aware that the filing of its Paragraph IV Certification with respect to the '456 patent constitutes infringement of that patent. This is an exceptional case.

COUNT II

INFRINGEMENT OF THE '933 PATENT

23. Plaintiffs incorporate each of the preceding paragraphs 1 to 22 as if fully set forth herein.

24. Impax's submission of an amended ANDA to the FDA, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '933 patent under 35 U.S.C. § 271(e)(2)(A).

25. Impax's commercial manufacture, offer for sale or sale of its proposed generic oxymorphone hydrochloride extended-release tablets would infringe the '933 patent.

26. Upon information and belief, Impax was aware of the existence of the '933 patent as demonstrated by its reference to that patent in its ANDA, and was aware that the filing of its Paragraph IV Certification with respect to the '933 patent constitutes infringement of that patent. This is an exceptional case.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs respectfully request the following relief:

A. A judgment that Impax has infringed the '456 patent;

B. A judgment that Impax has infringed the '933 patent;

C. An order, pursuant to 35 U.S.C. § 271(e)(4)(A), that the effective date of any approval of Impax's ANDA No.79-087 under § 505(j) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355(j), shall not be earlier than the expiration date of the '456 and '933 patents, including any extensions;

D. A permanent injunction, pursuant to 35 U.S.C. § 271(e)(4)(B), restraining and enjoining Impax, its officers, agents, servants and employees, and those persons in active

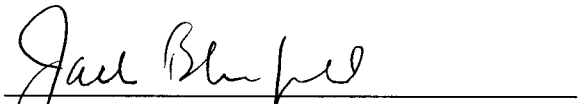
concert or participation with any of them, from infringement of the '456 and '933 patents for the full terms thereof, including any extensions; and

E. A declaration that this is an exceptional case and an award of reasonable attorneys' fees pursuant to 35 U.S.C. § 285;

F. Costs and expenses in this action; and

G. Such other and further relief as the Court may deem just and proper.

MORRIS, NICHOLS, ARSHT & TUNNELL LLP



Jack B. Blumenfeld (#1014)
Mary B. Graham (#2256)
Julia Heaney (#3052)
1201 N. Market Street
P.O. Box 1347
Wilmington, DE 19899-1347
(302) 658-9200
jblumenfeld@mnat.com
mgraham@mnat.com
jheaney@mnat.com

Attorneys for Plaintiffs Endo Pharmaceuticals Inc. and Penwest Pharmaceuticals Co.

Of Counsel:

Martin J. Black
George G. Gordon
Ann M. Caviani Pease
Robert D. Rhoad
DECHERT LLP
Cira Centre
2929 Arch Street
Philadelphia, PA 19104
(215) 994-4000
Attorneys for Plaintiff Endo Pharmaceuticals Inc.

Robert J. Gunther, Jr.
Lisa J. Pirozzolo
James P. Barabas
WILMER CUTLER PICKERING HALE AND DORR LLP
399 Park Avenue
New York, NY 10022
(212) 230-8800
Attorneys for Plaintiff Penwest Pharmaceuticals Co.

January 25, 2008

EXHIBIT A

US005662933A

United States Patent [19]

Baichwal et al.

[11] Patent Number: 5,662,933

[45] Date of Patent: *Sep. 2, 1997

[54] CONTROLLED RELEASE FORMULATION (ALBUTEROL)

[75] Inventors: Anand Baichwal, Wappingers Falls, N.Y.; Troy W. McCall, New Milford, Conn.

[73] Assignee: Edward Mendell Co., Inc., Patterson, N.Y.

[*] Notice: The term of this patent shall not extend beyond the expiration date of Pat. No. 5,455,046.

[21] Appl. No.: 553,008

[22] Filed: Nov. 3, 1995

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 118,924, Sep. 9, 1993, Pat. No. 5,455,046.

[51] Int. Cl.[6] A61K 9/14; A61K 9/22

[52] U.S. Cl. 424/457; 424/468; 424/488; 514/777; 514/778; 514/779; 514/780; 514/781; 514/964; 514/965

[58] Field of Search 424/457, 468, 424/488; 514/777, 778, 779, 780, 781, 964, 965

[56] References Cited

U.S. PATENT DOCUMENTS

4,412,986	11/1983	Kawata et al.	424/80
4,562,069	12/1985	Hegasy et al.	424/80
4,673,564	6/1987	Kawata et al.	424/494
4,764,382	8/1988	Kydonieus et al.	424/449
4,765,990	8/1988	Sugimoto et al.	424/494
4,792,450	12/1988	Kydonieus et al.	424/449
4,792,452	12/1988	Howard et al.	424/475
4,808,413	2/1989	Joshi et al.	424/458
4,851,229	7/1989	Magruder et al.	424/457
4,867,985	9/1989	Heafield et al.	424/461
4,892,741	1/1990	Ohm et al.	424/479
4,904,699	2/1990	Bauer	514/972
4,940,587	7/1990	Jenkins et al.	424/480
4,942,040	7/1990	Ragnarsson et al.	424/486
4,973,469	11/1990	Mulligan et al.	424/461
4,994,276	2/1991	Baichwal et al.	424/440
5,007,790	4/1991	Shell	424/451
5,019,397	5/1991	Wong et al.	424/473
5,051,263	9/1991	Barry et al.	424/490
5,071,642	12/1991	Lahr et al.	424/474
5,128,143	7/1992	Baichwal et al.	424/464
5,132,116	7/1992	Soumac et al.	424/469
5,133,974	7/1992	Paradissis et al.	424/480
5,135,757	8/1992	Baichwal et al.	424/465
5,145,683	9/1992	Rhodes	424/451
5,169,638	12/1992	Dennis et al.	424/457
5,215,758	6/1993	Krishnamurthy	424/488
5,264,459	11/1993	Chelmicka-Schorr et al.	514/646
5,273,760	12/1993	Oshlack et al.	424/480
5,286,493	2/1994	Oshlack et al.	424/468
5,356,467	10/1994	Oshlack et al.	106/153
5,455,046	10/1995	Baichwal	424/457

FOREIGN PATENT DOCUMENTS

1 288049	8/1991	Canada .
0232155A2	8/1987	European Pat. Off. .
0357793A1	3/1990	European Pat. Off. .
WO8902738	4/1989	WIPO .
WO9206680	4/1992	WIPO .

Primary Examiner—Nathan M. Nutter

Attorney, Agent, or Firm—Steinberg, Raskin & Davidson, P.C.

[57] ABSTRACT

A sustained release pharmaceutical formulation and methods of making and using the same are provided. The sustained release pharmaceutical formulation includes a sustained release excipient including a gelling agent, an inert pharmaceutical diluent, an optional hydrophobic material and/or hydrophobic coating, and a medicament for sustained oral administration.

48 Claims, 3 Drawing Sheets

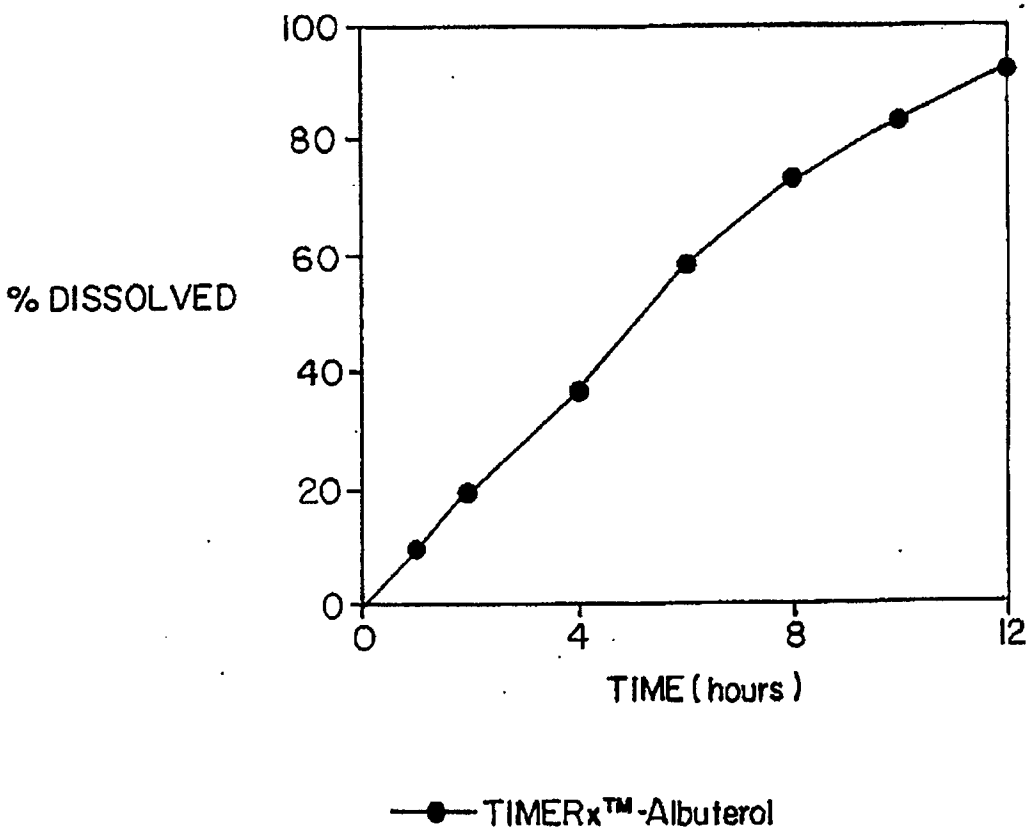

100
80
60
40
20
0
% DISSOLVED
0
4
8
12
TIME (hours)
TIMERx™-Albuterol

FIG. 1

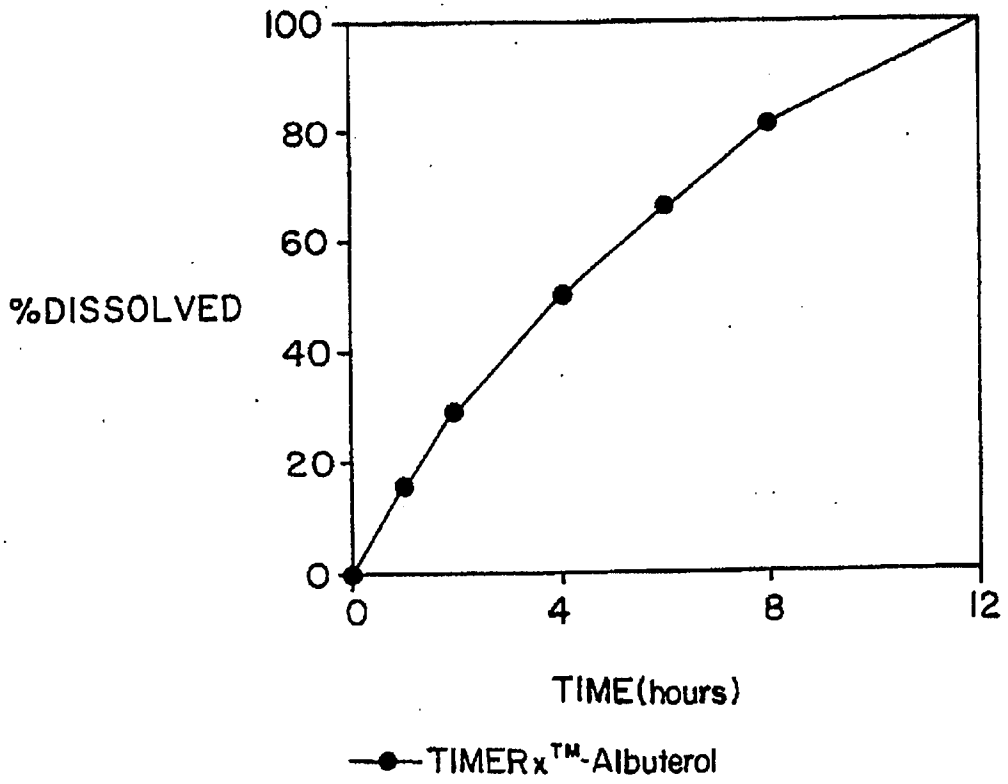

100
80
60
40
20
0
%DISSOLVED
0
4
8
12
TIME(hours)
TIMERx™-Albuterol

FIG. 2

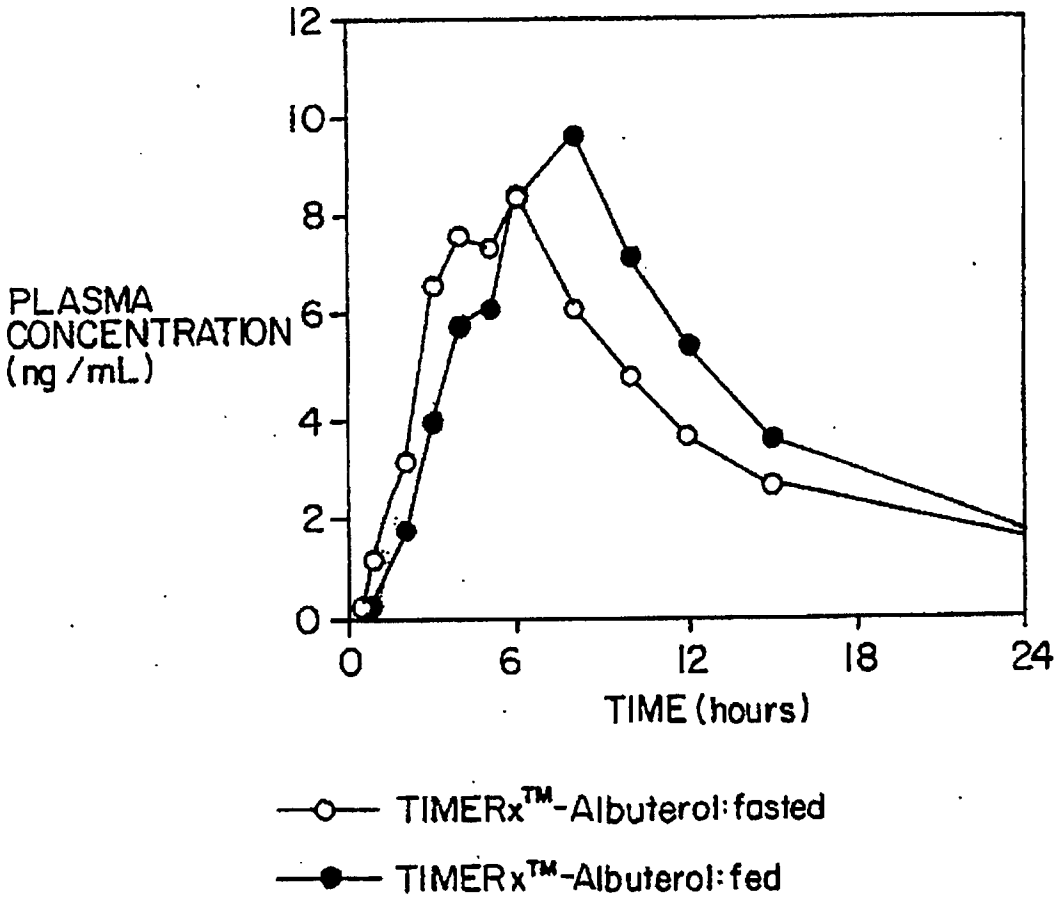

PLASMA CONCENTRATION (ng/mL)
12
10
8
6
4
2
0
0
6
12
18
24
TIME (hours)
TIMERx™-Albuterol: fasted
TIMERx™-Albuterol: fed

FIG. 3

CONTROLLED RELEASE FORMULATION (ALBUTEROL)

CROSS REFERENCE TO RELATED APPLICATIONS

The present application is a continuation-in-part of U.S. application Ser. No. 08/118,924, filed on Sep. 9, 1993, and now U.S. Pat. No. 5,455,046 the disclosure of which is incorporated by reference herein in its entirety.

FIELD OF THE INVENTION

The present invention relates to controlled release formulations which may be blended with a wide range of therapeutically active medicaments and made into controlled release solid dosage forms for oral administration.

BACKGROUND OF THE INVENTION

The advantages of controlled release products are well known in the pharmaceutical field and include the ability to maintain a desired blood level of a medicament over a comparatively longer period of time while increasing patient compliance by reducing the number administrations. These advantages have been attained by a wide variety of methods. For example, different hydrogels have been described for use in controlled release medicines, some of which are synthetic, but most of which are semi-synthetic or of natural origin. A few contain both synthetic and non-synthetic material. However, some of the systems require special process and production equipment, and in addition some of these systems are susceptible to variable drug release.

Oral controlled release delivery systems should ideally be adaptable so that release rates and profiles can be matched to physiological and chronotherapeutic requirements. In U.S. Pat. Nos. 4,994,276, 5,128,143, and 5,135,757, hereby incorporated by reference in their entireties, it is reported that a controlled release excipient which is comprised of a synergistic combination of heterodisperse polysaccharides (e.g., a heteropolysaccharide such as xanthan gum in combination with a polysaccharide gum capable of cross-linking with the heteropolysaccharide, such as locust bean gum, in an aqueous environment) is capable of being processed into oral solid dosage forms using either direct compression (i.e., dry granulation), following addition of drug and lubricant powder, conventional wet granulation, or a combination of the two. The release of the medicament from the formulations therein proceeded according to zero-order or first-order mechanisms.

The controlled release excipients disclosed in U.S. Pat. Nos. 4,994,276, 5,128,143, and 5,135,757 are commercially available under the trade name TIMERx® from Edward Mendell Co., Inc., Patterson, N.Y., which is the assignee of the present invention.

European Pat. No. 234670 B describes a controlled-release pharmaceutical formulation containing xanthan gum wherein the xanthan gum comprises from about 7.5 to about 28 percent, by weight, of the formulation except for a formulation wherein the controlled release carrier comprises a mixture of 15–50 parts by weight dimethylsiloxane, 30–100 parts by weight silicic acid, 30–100 parts by weight mannans or galactans or a mixture thereof, 50–150 parts by weight xanthans and 5–75 parts by weight micronized seaweed.

However, heretofore there has been no teaching of a controlled release formulation providing a novel and unexpected combination of suitable proportions of a homopolysaccharide such as, e.g., xanthan gum, a heteropolysaccharide, such as, e.g., locust bean gum, together with an inert diluent and a pharmacologically acceptable hydrophobic material, so as to provide an improvement in controlled release properties for such an active medicament.

OBJECTS AND SUMMARY OF THE INVENTION

It is therefore an object of the present invention to provide a controlled release formulation for a therapeutically active medicament.

It is a further object of the present invention to provide a method for preparing a controlled release formulation for a therapeutically active medicament.

It is yet another object of the present invention to provide a controlled release excipient which may be used in the preparation of a sustained release oral solid dosage form of a therapeutically active medicament that provides an even rate of release of an active medicament.

It is a further object of the present invention to provide a controlled release excipient which, when combined with an effective amount of a bronchodilator, such as albuterol, is suitable for providing a sustained release of that medicament so as to provide a therapeutically effective blood level of the medicament for e.g., 12 or 24 hours, without allowing an excessive early release of medication, and where the release kinetics are unaffected by the contents of the patient's gastrointestinal tract.

It is yet a further object of the present invention to provide a method for treating patients with an active medication in controlled release form.

The above-mentioned objects and others are achieved by virtue of the present invention, which relates in-part to a controlled release formulation comprising a therapeutically effective amount of a medicament, and a controlled release excipient comprising a gelling agent and a swelling agent, such as, for example, a homopolysaccharide, a heteropolysaccharide, an inert diluent.

In certain preferred embodiments of the invention, the ratio of the heteropolysaccharide gum to the homopolysaccharide gum is from about 1:3 to about 3:1. More preferably, the ratio is about 1:1. Preferably, the heteropolysaccharide gum includes xanthan gum and the homopolysaccharide gum includes locust bean gum.

The present invention is also related to a sustained release oral solid dosage form for albuterol or salts or derivatives thereof in an amount necessary to render a therapeutic effect in a human patient. The albuterol is present in an amount ranging from, e.g., about 2 through about 50% by weight of the total formulation, or preferably from about 1 through about 10% by weight or more preferably from about 1 through about 6% by weight of the total formulation.

The dosage form includes an inert pharmaceutical diluent so that the ratio of the inert diluent to the gelling agent is from about 1:8 to about 8:1. Preferably, the diluent is from the group consisting of a pharmaceutically acceptable saccharide, polyhydric alcohol, a pre-manufactured direct compression diluent, and mixtures of any of the foregoing. The diluent can also be a saccharide such as sucrose, dextrose, lactose, microcrystalline cellulose, fructose, xylitol, sorbitol, a starch, and mixtures thereof.

The dosage form optionally includes a pharmaceutically acceptable hydrophobic material. Any pharmaceutically acceptable hydrophobic material may be suitably employed.

Suitable hydrophobic materials include carboxymethylcellulose, cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl-methylcellulose phthalate, ethylcellulose, a copolymer of acrylic and methacrylic and esters, waxes, shellac, zein, hydrogenated vegetable oils, and mixtures of any of the foregoing. Preferably, the hydrophobic material selected from cellulose ether, a cellulose ester and an alkylcellulose, such as ethylcellulose and carboxymethylcellulose. The hydrophobic material may be included in the dosage form in an amount effective to slow the hydration of the gelling agent when exposed to an environmental fluid.

The hydrophobic material is preferably present in an amount ranging from about 1 through about 90%, by weight, of the solid dosage form, and can also be present in an amount ranging from about 25% through about 50%, by weight, of the solid dosage form.

The medicament can be any medicament for which an orally administered controlled release form is desired. Preferably, the formulation is prepared to include a pharmaceutically effective amount of albuterol or a salt or derivative thereof.

The controlled release solid dosage form can be prepared in any conventional orally administered dosage form, including a tablet, as a granular form and as a granular form administered in a gelatin capsule containing a sufficient amount of the granules to provide an effective dose of the included therapeutically active medicament. For a tablet dosage form, at least part of a surface of the tablet can optionally be coated with a hydrophobic material to a weight gain from about 1 to about 20 percent, by weight. Further, a granular dosage form can optionally be coated with a hydrophobic coating material to a weight gain that ranges from about 1% to about 20%. The hydrophobic material can be selected from, e.g., a cellulose ether, a cellulose ester and an alkylcellulose. The hydrophobic material can optionally be applied before, during or after the process of tableting. In addition, if there is a need for an early release of the active medicament, the coating can optionally be formulated to include from about 10 to about 40 percent of the total amount of the active medicament in a quick release external layer.

The invention also relates to methods for preparing a controlled release solid dosage form as described above for providing an active medicament in an amount effective for treating a patient for from 12 to about 24 hours. The method includes the steps of preparing a sustained release excipient comprising from about 10 to about 99 percent by weight of a gelling agent comprising a heteropolysaccharide gum and a homopolysaccharide gum capable of cross-linking said heteropolysaccharide gum when exposed to an environmental fluid, the ratio of said heteropolysaccharide gum to said homopolysaccharide gum being from about 1:3 to about 3:1, and from about 0 to about 89 percent by weight of an inert pharmaceutical diluent, and optionally from about 1 to 90% by weight of a pharmaceutically acceptable hydrophobic material; and adding an effective amount of a medicament to provide a final product having a ratio of medicament to gelling agent from about 1:3 to about 1:8, so that a gel matrix is created.

The medicament to be added is preferably albuterol or salts or derivatives thereof in an amount ranging from, e.g., about 2 to about 50% by weight of the total formulation, or preferably from about 1 to about 10% by weight or more preferably from about 1 to about 6% by weight of the total formulation.

The resulting mixture of the sustained release excipient preferably includes from about 10 to about 75 percent gelling agent, from about 0 to about 90% hydrophobic material and from about 30 to about 75 percent inert diluent. Thereafter, the dosage form can be tableted, granulated with a pharmaceutically acceptable hydrophobic material or placed in gelatine capsules. Optionally the tablet can be coated with a hydrophobic coating to a weight gain from about 1% to about 20%.

Preferably, the medicament is albuterol or a salt or derivative thereof in an amount effective to provide therapeutically effective blood levels of said medicament for at least 24 hours.

The present invention is further related to a method of treating a patient comprising orally administering the sustained release albuterol tablets to a patient, thereby providing therapeutically effective blood levels of the medicament for at least about 24 hours.

By "sustained release" it is meant for purposes of the present invention that the therapeutically active medicament is released from the formulation at a controlled rate such that therapeutically beneficial blood levels (but below toxic levels) of the medicament are maintained over an extended period of time, e.g., providing a 24 hour dosage form.

The term "environmental fluid" is meant for purposes of the present invention to encompass, e.g., an aqueous solution, such as that used for in-vitro dissolution testing, or gastrointestinal fluid.

In one aspect the invention provides formulations having particular pharmacokinetic properties. Thus, simply by way of example, the invention provides formulations suitable for oral administration that, when orally administered to a patient, provide a medicament plasma concentration-time curve with an area under the curve-calculated to infinity ("AUC_{∞}"), ranging from about 89 to about 150 (ng-hours/ml) or even from about 112 to about 129 (ng-hours/ml). Further, the formulations according to the invention can provide, e.g., an AUC_{∞} ranging from about 57 to about 157 (ng-hours/ml) (fasting patient) or from about 75 to about 162 (ng-hours/ml) (fed patient).

In addition, for example, mean peak plasma concentrations (Cmax) ranging from about 7 to about 12 ng/ml or even from about, 9.5 to about 12 ng/ml. are provided. Further, the formulations according to the invention can provide, e.g., a Cmax ranging from about 4.5 to about 19 ng/ml (fasting patient) or from about 6 to about 16 ng/ml (fed patient).

In another example, time to mean peak plasma concentration (Tmax) ranging from about 3 to about 10 hours or even from about 3.5 to about 8 hours are provided. Further, the formulations according to the invention can provide, e.g., a Tmax ranging from about 3 to about 6 hours (fasting patient) or from about 3 to about 8 hours (fed patient).

In a further example, the formulation according to the invention provides, for example, ratios of AUC_{∞} (fasting patient) to AUC_{∞} (fed patient) that range from about 0.50 to about 0.70.

Further still, the formulation provides, for example ranges of Cmax (fasting patient) divided by Cmax (fed patient) from about 0.90 to about 1.10.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 shows a dissolution profile of an albuterol containing tablet formulated according to Table 14 and Table 15 (Example 10) and conducted as a Type II dissolution with a pH change to simulate gastric passage and stirring at 50 rpm.

FIG. 2 shows a dissolution profile of an albuterol containing tablet formulated according to Table 14 and Table 15 (Example 10) and conducted as a Type III dissolution with a pH change to simulate gastric passage and stirring at 15 rpm.

FIG. 3 shows an albuterol plasma profile of provided by ingestion of an albuterol containing tablet formulated according to Table 14 and Table 15 (Example 10): solid circles mark curve of plasma profile in fed subject; open circles mark curve of plasma profile in fasted subject.

DETAILED DESCRIPTION

As reported in U.S. Pat. Nos. 4,994,276, 5,128,143, and 5,135,757, the disclosures of which are hereby incorporated by reference herein in their entireties, the heterodisperse excipient comprises a gelling agent of both hetero- and homo-polysaccharides which exhibit synergism, e.g., the combination of two or more polysaccharide gums produce a higher viscosity and faster hydration than that which would be expected by either of the gums alone, the resultant gel being faster-forming and more rigid.

In the present invention, it has been found that a sustained release excipient comprising only the gelling agent (heterodisperse polysaccharides, e.g., xanthan gum and locust bean gum, may not be sufficient to provide a suitable sustained release of an active medicament to provide a 12 or 24 hour formulation, when the formulation is exposed to a fluid in an environment of use, e.g. an aqueous solution or gastrointestinal fluid.

In certain embodiments, the present invention is related to the surprising discovery that by granulating the sustained release excipient with a solution or dispersion of a pharmacologically acceptable hydrophobic material prior to admixture of the sustained release excipient with the medicament and tableting, the medicament may provide therapeutically effective blood levels for extended periods of time, e.g., from about 12 to about 24 hours. The hydrophobic material is present in a range from about 0 to about 90%, by weight, of the sustained release excipient and in a preferred embodiment, is present in a range from about 1 to 20 percent of the sustained release excipient or from about 25 to about 75 percent of the sustained release excipient.

The sustained release excipient can be granulated with a pharmacologically acceptable hydrophobic material such as, for, example, an alkylcellulose, a cellulose ether, a cellulose ester. In particular, the hydrophobic material can be alkylcellulose such as carboxymethylcellulose ("CMC"), cellulose acetate phthalate ("CAP"), hydroxypropylmethylcellulose phthalate ("HPMCP") or a polyvinyl acetate polymer such as polyvinyl acetate phthalate "PVAP").

In certain preferred embodiments of the present invention, the sustained release excipient is prepared by mixing the gelling agent and an inert diluent. The gelling agent preferably ranges, e.g., from about 10 to about 75 percent of the sustained release excipient. Thereafter, the mixture is granulated with a solution or dispersion of a hydrophobic material in an amount effective to slow the hydration of the gelling agent without disrupting the hydrophilic matrix. Next, the medicament is added, and the resultant mixture is tableted.

In other preferred embodiments of the present invention, the tablets prepared as set forth above are then coated with a hydrophobic material to a weight gain from about 1 to about 20 percent by weight. The hydrophobic material can be an alkylcellulose such as, for example, an aqueous dispersion of ethylcellulose (commercially available, for example, as Aquacoat®, available from FMC or Surelease®, available from Colorcon).

The term "heteropolysaccharide" as used in the present invention is defined as a water-soluble polysaccharide containing two or more kinds of sugar units, the heteropolysaccharide having a branched or helical configuration, and having excellent water-wicking properties and immense thickening properties.

An especially preferred heteropolysaccharide is xanthan gum, which is a high molecular weight ($>10^6$) heteropolysaccharide. Other preferred heteropolysaccharides include derivatives of xanthan gum, such as deacylated xanthan gum, the carboxymethyl ether, and the propylene glycol ester.

The homopolysaccharide gums used in the present invention which are capable of cross-linking with the heteropolysaccharide include the galactomannans, i.e., polysaccharides which are composed solely of mannose and galactose. Galactomannans which have higher proportions of unsubstituted mannose regions have been found to achieve more interaction with the heteropolysaccharide. Locust bean gum, which has a higher ratio of mannose to galactose, is especially preferred as compared to other galactomannans such as guar and hydroxypropyl guar.

The controlled release properties of the formulations of the present invention may be optimized when the ratio of heteropolysaccharide gum to homopolysaccharide material is about 1:1, although heteropolysaccharide gum in an amount of from about 20 to about 80 percent or more by weight of the heterodisperse polysaccharide material provides an acceptable slow release product. The combination of any homopolysaccharide gums known to produce a synergistic effect when exposed to aqueous solutions may be used in accordance with the present invention. It is also possible that the type of synergism which is present with regard to the gum combination of the present invention could also occur between two homogeneous or two heteropolysaccharides. Other acceptable gelling agents which may be used in the present invention include those gelling agents well-known in the art. Examples include vegetable gums such as alginates, carrageenan, pectin, guar gum, xanthan gum, modified starch, hydroxypropylmethylcellulose, methylcellulose, and other cellulosic materials such as sodium carboxymethylcellulose and hydroxypropylcellulose. This list is not meant to be exclusive.

The combination of xanthan gum with locust bean gum with or without the other homopolysaccharide gums is an especially preferred gelling agent. The chemistry of certain of the ingredients comprising the excipients of the present invention such as xanthan gum is such that the excipients are considered to be self-buffering agents which are substantially insensitive to the solubility of the medicament and likewise insensitive to the pH changes along the length of the gastrointestinal tract.

The inert pharmaceutical diluent (i.e., filler) of the sustained release excipient preferably comprises a pharmaceutically acceptable saccharide, including a monosaccharide, a disaccharide, or a polyhydric alcohol, a pre-manufactured direct compression diluent, and/or mixtures of any of the foregoing. Examples of suitable inert pharmaceutical fillers include sucrose, dextrose, lactose, microcrystalline cellulose, fructose, xylitol, sorbitol, a starch, mixtures thereof and the like. However, it is preferred that a soluble pharmaceutical filler such as lactose, dextrose, sucrose, or mixtures thereof be used. If the mixture is to be manufactured without a wet granulation step, and the final product is to be tableted, it is preferred that all or part of the inert

diluent comprise a pre-manufactured direct compression diluent. Such direct compression diluents are widely used in the pharmaceutical arts, and may be obtained from a wide variety of commercial sources. Examples of such pre-manufactured direct compression excipients include Emcocel® (microcrystalline cellulose, N.F.), Emdex® (dextrates, N.F.), and Tab-Fine® (a number of direct-compression sugars including sucrose, fructose, and dextrose), all of which are commercially available from Edward Mendell Co., Inc., Patterson, N.Y.). Other direct compression diluents include Anhydrous lactose (Lactose N.F., anhydrous direct tableting) from Sheffield Chemical, Union, N.J. 07083; Elcems® G-250 (Powdered cellulose, N.F.) from Degussa, D-600 Frankfurt (Main) Germany; Maltrin® (Agglomerated maltodextrin) from Grain Processing Corp., Muscatine, IA 52761; Neosorb 60® (Sorbitol, N.F., direct-compression) from Roquette Corp., 645 5th Ave., New York, N.Y. 10022; Nu-Tab® (Compressible sugar, N.F.) from Ingredient Technology, Inc., Pennsauken, N.J. 08110; Polyplasdone XL® (Crospovidone, N.F., cross-linked polyvinylpyrrolidone) from GAF Corp., New York, N.Y. 10020; Primojel® (Sodium starch glycolate, N.F., carboxymethyl starch) from Generichem Corp., Little Falls, N.J. 07424; Solka Floc® (Cellulose floc) from Edward Mendell Co., Carmel, N.Y. 10512; Fast-Flo Lactose® (Lactose N.F., spray dried) from Foremost Whey Products, Baraboo, Wis. 53913 and DMV Corp., Vehgel, Holland; and Sta-Rx 1500® (Starch 1500) (Pregelatinized starch, N.F., compressible) from Colorcon, Inc., West Point, Pa. 19486. However, it is preferred that a soluble pharmaceutical filler such as lactose, dextrose, sucrose, or mixtures thereof be used.

In certain embodiments of the present invention, the sustained release excipient comprises from about 10 to about 99 percent by weight of a gelling agent comprising a heteropolysaccharide gum and a homopolysaccharide gum and from about 0 to about 89 percent by weight of an inert pharmaceutical diluent. In other embodiments, the sustained release excipient comprises from about 10 to about 75 percent gelling agent, and from about 30 to about 75 percent inert diluent. In yet other embodiments, the sustained release excipient comprises from about 30 to about 75 percent gelling agent and from about 15 to about 65 percent inert diluent.

The sustained release excipient of the present invention may be further modified by incorporation of a hydrophobic material which slows the hydration of the gums without disrupting the hydrophilic matrix. This is accomplished in preferred embodiments of the present invention by granulating the sustained release excipient with the solution or dispersion of a hydrophobic material prior to the incorporation of the medicament. The hydrophobic material may be selected from an alkylcellulose such as ethylcellulose such as carboxymethyl-cellulose ("CMC"), other hydrophobic cellulosic materials, acrylic and/or methacrylic ester polymers, copolymers of acrylic and methacrylic esters, zein, waxes, other hydrophobic cellulosic materials, cellulose acetate phthalate ("CAP"), hydroxypropylmethylcellulose phthalate ("HPMCP") or a polyvinyl acetate polymer such as polyvinyl acetate phthalate ("PVAP"), hydrogenated vegetable oils, and any other pharmaceutically acceptable hydrophobic material known to those skilled in the art. The amount of hydrophobic material incorporated into the sustained release excipient is that which is effective to slow the hydration of the gums without disrupting the hydrophilic matrix formed upon exposure to an environmental fluid.

In certain preferred embodiments of the present invention, the hydrophobic material is included in the sustained release excipient in an amount from about 1 to about 20 percent by weight. The solvent for the hydrophobic material may be an aqueous or organic solvent, or mixtures thereof.

Examples of commercially available alkylcelluloses are Aquacoat® (aqueous dispersion of ethylcellulose available from FMC), Surelease® (aqueous dispersion of ethylcellulose available from Colorcon). Examples of commercially available acrylic polymers suitable for use as the hydrophobic material include Eudragit® RS and RL (copolymers of acrylic and methacrylic acid esters having a low content (e.g. 1:20 or 1:40) of quaternary ammonium compounds).

Once the sustained release excipient of the present invention has been prepared, it is then possible to blend the same with the medicament, e.g., in a high shear mixer. In one embodiment, the formulation is prepared by dry blending the components, e.g., a heteropolysaccharide, a homopolysaccharide, an inert filler, and a hydrophobic material, optionally followed by the addition of a suitable amount of water, with continued blending, followed by dry granulation in a fluid bed dryer and then milling of the resulting granulation product.

A wide variety of therapeutically active agents can be used in conjunction with the present invention. The therapeutically active agents (e.g., pharmaceutical agents) which may be used in the compositions of the present invention include drugs ranging in solubility from water soluble to water insoluble. Examples of such therapeutically active agents include antihistamines (e.g., dimenhydrinate, diphenhydramine, chlorpheniramine and dexchlorpheniramine maleate), analgesics (e.g., aspirin, codeine, morphine, dihydromorphone, oxycodone, etc.), non-steroidal anti-inflammatory agents (e.g., naproxyn, diclofenac, indomethacin, ibuprofen, sulindac), anti-emetics (e.g., metoclopramide), anti-epileptics (e.g., phenytoin, meprobamate and nitrazepam), vasodilators (e.g., nifedipine, papaverine, diltiazem and nicardirine), anti-tussive agents and expectorants (e.g., codeine phosphate), anti-asthmatics (e.g. theophylline), antacids, anti-spasmodics (e.g. atropine, scopolamine), antidiabetics (e.g., insulin), diuretics (e.g., ethacrynic acid, bendrofluazide), anti-hypotensives (e.g., propranolol, clonidine), antihypertensives (e.g., clonidine, methyldopa), bronchodilators (e.g., albuterol), steroids (e.g., hydrocortisone, triamcinolone, prednisone), antibiotics (e.g., tetracycline), antihemorrhoidals, hypnotics, psychotropics, antidiarrheals, mucolytics, sedatives, decongestants, laxatives, vitamins, stimulants (including appetite suppressants such as phenylpropanolamine). The above list is not meant to be exclusive.

In a preferred embodiment, the therapeutically active agents are sympathomimetics such as, dobutamine hydrochloride, dopamine hydrochloride, ephedrine sulfate, epinephrine, fenfluramine hydrochloride, isoetharine, isoproterenol, mephentermine sulfate, metaproterenol sulfate, metaraminol bitartrate, methoxamine hydrochloride, norepinephrine bitartrate, phenylephrine hydrochloride, phenylpropanolamine hydrochloride, pseudoephedrine, ritodrine hydrochloride, terbutaline sulfate, tetrahydrozoline hydrochloride, triprolidine and pseudoephedrine, xylometazoline hydrochloride, isoproterenol and dobutamine as well as beta2 selective adrenergic agonists, including, for example, terbutaline, albuterol, isoetharine, pirbuterol and bitolterol (GOODMAN AND GILMAN'S, THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, Eighth Edition, the disclosure of which is incorporated herein by reference in its entirety).

Generally any flavoring or food additive such as those described in *Chemicals Used in Food Processing*, pub 1274

by the National Academy of Sciences, pages 63–258, incorporated herein in its entirety, may be used. Generally, the final product may include from about 0.1% to about 5% by weight flavorant.

The tablets of the present invention may also contain effective amounts of coloring agents, (e.g., titanium dioxide, F.D. & C. and D. & C. dyes; see the Kirk-Othmer Encyclopedia of Chemical Technology, Vol. 5, pp. 857–884, hereby incorporated by reference in its entirety), stabilizers, binders, odor controlling agents, and preservatives.

Alternatively, the inventive formulation can be utilized in other applications wherein it is not compressed. For example, the granulate can be admixed with an active ingredient and the mixture then filled into capsules. The granulate can further be molded into shapes other than those typically associated with tablets. For example, the granulate together with active ingredient can be molded to "fit" into a particular area in an environment of use (e.g., an implant). All such uses would be contemplated by those skilled in the art and are deemed to be encompassed within the scope of the appended claims.

A hydrophobic material (e.g., a hydrophobic polymer) may be dissolved in an organic solvent or dispersed in an aqueous solution. Thereafter, the hydrophobic material may be used to coat the granulate of medicament/sustained release excipient. The granulate may be coated with the hydrophobic coating to a weight gain of, e.g., from about 1 to about 20 percent, and preferably from about 5 to about 10 percent. The granulation is then preferably dried. Thereafter, the granulate may be further formulated into an appropriate oral dosage form, for example, by compression of the resulting granulate into appropriately sized tablets, by filling gelatin capsules with an appropriate amount of the granulate (with or without compression of the granulate), as well as use in the manufacture of other oral dosage forms known to those skilled in the art. This embodiment may be particularly beneficial to reduce the amount of drug released during the initial phases of dissolution when the formulation is exposed to fluid in an environment of use, e.g., in vitro dissolution or in the gastrointestinal tract.

An effective amount of any generally accepted pharmaceutical lubricant, including the calcium or magnesium soaps may be added to the above-mentioned ingredients of the excipient be added at the time the medicament is added, or in any event prior to compression into a said dosage form. An example of a suitable lubricant is magnesium stearate in an amount of about 0.5 to about 3% by weight of the solid dosage form. An especially preferred lubricant is sodium stearyl fumarate, NF, commercially available under the trade name Pruv® from the Edward Mendell Co., Inc.

The sustained release excipients of the present invention have uniform packing characteristics over a range of different particle size distributions and are capable of processing into the final dosage form (e.g., tablets) using either direct compression, following addition of drug and lubricant powder, or conventional wet granulation.

The properties and characteristics of a specific excipient system prepared according to the present invention is dependent in part on the individual characteristics of the homo and hetero polysaccharide constituents, in terms of polymer solubility, glass transition temperatures etc., as well as on the synergism both between different homo- and heteropolysaccharides and between the homo and heteropolysaccharides and the inert saccharide constituent(s) in modifying dissolution fluid-excipient interactions.

The combination of the gelling agent (i.e., a mixture of xanthan gum and locust beam gum) with the inert diluent provides a ready-to-use product in which a formulator need only blend the desired active medicament and an optional lubricant with the excipient and then compress the mixture to form slow release tablets. The excipient may comprise a physical admix of the gums along with a soluble excipient such as compressible sucrose, lactose or dextrose, although it is preferred to granulate or agglomerate the gums with plain (i.e., crystalline) sucrose, lactose, dextrose, etc., to form an excipient. The granulate form has certain advantages including the fact that it can be optimized for flow and compressibility; it can be tableted, formulated in a capsule, extruded and spheronized with an active medicament to form pellets, etc.

The pharmaceutical excipients prepared in accordance with the present invention may be prepared according to any agglomeration technique to yield an acceptable excipient product. In dry granulation techniques, the excipients, i.e., the desired amounts of the heteropolysaccharide gum, the homopolysaccharide gum, and the inert diluent are mixed with an active medicament and the mixture is then formed into tablets and the like by compression, without the addition of water or other solvent.

In wet granulation techniques, the desired amounts of the heteropolysaccharide gum, the homopolysaccharide gum, and the inert diluent are mixed together and thereafter a moistening agent such as water, propylene glycol, glycerol, alcohol or the like is added to prepare a moistened mass. Next, the moistened mass is dried. The dried mass is then milled with conventional equipment into granules. Therefore, the excipient product is ready to use.

The sustained release excipient is free-flowing and directly compressible. Accordingly, the excipient may be mixed in the desired proportion with a therapeutically active medicament and optional lubricant (dry granulation). Alternatively, all or part of the excipient may be subjected to a wet granulation with the active ingredient and thereafter tableted. When the final product to be manufactured is tablets, the complete mixture, in an amount sufficient to make a uniform batch of tablets, is then subjected to tableting in a conventional production scale tableting machine at normal compression pressure, i.e. about 2000–1600 lbs/sq in. However, the mixture should not be compressed to such a degree that there is subsequent difficulty in its hydration when exposed to gastric fluid.

One of the limitations of direct compression as a method of tablet manufacture is the size of the tablet. If the amount of active (drug) is high, a pharmaceutical formulator may choose to wet granulate the active medicament with other excipients to attain a more compact tablet. Usually the amount of filler/binder or excipients needed in wet granulation is less than that in direct compression since the process of wet granulation contributes to some extent toward the desired physical properties of a tablet.

The average tablet size for round tablets is preferably about 300 mg to 750 mg and for capsule-shaped tablets about 750 mg to 1000 mg.

The average particle size of the granulated excipient of the present invention ranges from about 50 microns to about 400 microns and preferably from about 185 microns to about 265 microns. The particle size of the granulation is not narrowly critical, the important parameter being that the average particle size of the granules, must permit the formation of a directly compressible excipient which forms pharmaceutically acceptable tablets. The desired tap and bulk densities of the granulation of the present invention are normally between from about 0.3 to about 0.8 g/ml, with an

average density of from about 0.5 to about 0.7 g/ml. For best results, the tablets formed from the granulations of the present invention are from about 6 to about 8 kg hardness. The average flow of the granulations prepared in accordance with the present invention are from about 25 to about 40 g/sec. Tablets compacted using an instrumented rotary tablet machine have been found to possess strength profiles which are largely independent of the inert saccharide component. Scanning electron photomicrographs of largely tablet surfaces have provided qualitative evidence of extensive plastic deformation on compaction, both at the tablet surface and across the fracture surface, and also show evidence of surface pores through which initial solvent ingress and solution egress may occur.

In certain embodiments of the invention, the tablet is coated with a sufficient amount of a hydrophobic material, such as, e.g., a hydrophobic polymer, to render the formulation capable of providing a release of the medicament such that a 12 or 24 hour formulation is obtained. The hydrophobic material included in the tablet coating may be the same or different material as compared to the hydrophobic material which is optionally granulated with the sustained release excipient.

In other embodiments of the present invention, the tablet coating may comprise an enteric coating material in addition to or instead of the hydrophobic coating. Examples of suitable enteric polymers include cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, polyvinylacetate phthalate, methacrylic acid copolymer, shellac, hydroxypropylmethylcellulose succinate, cellulose acetate trimellitate, and mixtures of any of the foregoing. An example of a suitable commercially available enteric material is available under the trade name Eudragit™ L 100–555.

In further embodiments, the dosage form may be a coating with a hydrophilic coating in addition to or instead of the above-mentioned coatings. An example of a suitable material which may be used for such a hydrophilic coating is hydroxypropylmethylcellulose (e.g., Opadry®, commercially available from Colorcon, West Point, Pa.).

The coatings may be applied in any pharmaceutically acceptable manner known to those skilled in the art. For example, in one embodiment, the coating is applied via a fluidized bed or in a coating pan. For example, the coated tablets may be dried, e.g., at about 60°–70° C. for about 3–4 hours in a coating pan. The solvent for the hydrophobic material or enteric coating may be organic, aqueous, or a mixture of an organic and an aqueous solvent. The organic solvents may be, e.g., isopropyl alcohol, ethanol, and the like, with or without water.

In additional embodiments of the present invention, a support platform is applied to the tablets manufactured in accordance with the present invention. Suitable support platforms are well known to those skilled in the art. An example of suitable support platforms is set forth, e.g., in U.S. Pat. No. 4,839,177, hereby incorporated by reference herein in its entirety. In that patent, the support platform partially coats the tablet, and consists of a polymeric material insoluble in aqueous liquids. The support platform may, for example, be designed to maintain its impermeability characteristics during the transfer of the therapeutically active medicament. The support platform may be applied to the tablets, e.g., via compression coating onto part of the tablet surface, by spray coating the polymeric materials comprising the support platform onto all or part of the tablet surface, or by immersing the tablets in a solution of the hydrophobic materials.

The support platform may have a thickness of, e.g., about 2 mm if applied by compression, and about 10μ if applied via spray-coating or immersion-coating. Generally, in embodiments of the invention wherein a hydrophobic material or enteric coating is applied to the tablets, the tablets are coated to a weight gain from about 1 to about 20%, and in certain embodiments preferably from about 5% to about 10%.

Materials useful in the hydrophobic coatings and support platforms of the present invention include derivatives of acrylic acid (such as esters of acrylic acid, methacrylic acid, and copolymers thereof) celluloses and derivatives thereof (such as ethylcellulose), polyvinylalcohols, and the like.

In certain embodiments of the present invention, the tablet core includes an additional dose of the medicament included in either the hydrophobic or enteric coating, or in an additional overcoating coated on the outer surface of the tablet core (without the hydrophobic or enteric coating) or as a second coating layer coated on the surface of the base coating comprising the hydrophobic or enteric coating material. This may be desired when, for example, a loading dose of a therapeutically active agent is needed to provide therapeutically effective blood levels of the active agent when the formulation is first exposed to gastric fluid. The loading dose of medicament included in the coating layer may be, e.g., from about 10% to about 40% of the total amount of medicament included in the formulation.

Albuterol Controlled Release Formulation

In a more preferred embodiment, the therapeutically active agent is albuterol, or salts or derivatives thereof (e.g., albuterol sulfate). Albuterol sulfate is a beta2—selective adrenergic agonist and is indicated for the relief of bronchospasm in patients with reversible obstructive airway disease. Patient compliance and evenly maintained blood levels of the active drug are important for achieving good control of the symptoms of bronchospasm in such patients. The half-life of albuterol sulfate in the human body is only about 5 hours. Thus, a controlled release form for the sustained delivery of albuterol provides improved patient compliance by reducing the number of doses per day and also provides more consistent blood levels of albuterol for patients in need of such treatment.

The albuterol controlled release formulation is composed of synergistic heterodisperse polysaccharides together with a saccharide component. The synergism between the homo- and hetero-polysaccharide components enables the manipulation of different rate controlling mechanisms. In order to achieve appropriate drug release, the saccharides were optimized based upon the magnitude of interactions and the ratio of one saccharide to another.

Preparation

The albuterol containing formulation according to the invention is prepared, for example, by dry blending the components, e.g., a heteropolysaccharide, a homopolysaccharide, an inert filler, and a hydrophobic material, followed by the addition of a suitable amount of water, with continued blending, followed by dry granulation in a fluid bed dryer and then milling of the resulting granulation product. Albuterol sulfate, in an amount ranging from, e.g., about 2 through about 50% by weight of the total formulation, or preferably from about 1 through about 10% by weight or more preferably from about 1 through about 6% by weight of the total formulation, is then compounded with the granulation product and formed into pills, caplets or

capsules. Whatever the formulation, it is preferred that such pills, caplets or capsules each contain an effective therapeutic amount of albuterol or a derivative or salt thereof. Simply by way of example, the pills, caplets or capsules can contain an amount of albuterol sulfate equivalent to about 4 to about 16 mg of albuterol free base per dosage unit of the free base. More preferably, the pills, caplets or capsules can contain an amount of albuterol sulfate equivalent to about 8 to about 12 mg of the free base. Simply by way of comparison, 9.6 mg of albuterol sulfate is equivalent to 8 mg of free base. Effective amounts of other pharmaceutically acceptable albuterol derivatives or salts thereof may be used, with the amounts adjusted in proportion to the weight ranges provided for albuterol free base.

Dissolution Testing

The test formulations were evaluated under a variety of dissolution conditions to determine the effects of pH, media, agitation and apparatus. Dissolution tests were performed using a USP Type III (VanKel Bio-Dis II) apparatus. Effects of pH, agitation, polarity, enzymes and bile salts were evaluated.

Bioavailability Study

A study was conducted to evaluate the bioavailability of a test formulation of albuterol sulfate using a randomized, balanced, open label, single dose, crossover design. The study was performed using 12 healthy male and female volunteers between the ages of 18 and 35. Blood samples were removed at 0, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 15 and 25 hours. Except for the "fed" treatment in which the subjects received a standard high fat breakfast, no food was allowed until a standard lunch was served four hours after the dose was administered. The data from each time point were used to derive pharmacokinetic parameters: area under plasma concentration-time curve ("AUC") such as AUC0-t, AUC0-∞, mean peak plasma concentration ("Cmax") and time to mean peak plasma concentration ("Tmax") which data confirmed that the formulation according to the invention provided controlled release of albuterol sulfate.

The invention is further described in the following examples, based upon the above described methods, which are in no way intended to limit the scope of the invention.

EXAMPLES 1–2

Preparation of Controlled Release Formulations with Carboxymethylcellulose and Dissolution Tests Thereon

The sustained release excipient was prepared by dry blending the requisite amounts of xanthan gum, locust bean gum, a pharmaceutically acceptable hydrophobic polymer and an inert diluent in a high-speed mixer/granulator for 2 minutes. While running choppers/impellers, the water was added and the mixture was granulated for another 2 minutes. The granulation was then dried in a fluid bed dryer to a loss on drying weight ("LOD") of between 4 and 7%. The granulation was then milled using 20 mesh screens. The ingredients of the sustained release excipients used for Examples 1–2 are set forth in Table 1 below:

TABLE 1

The hydrophobic polymer is carboxymethylcellulose ("CMC").

Component	Example 1	Example 2
1. Xanthan gum	10%	10%
2. Locust bean gum	10	10
3. CMC	10	30
4. Dextrose	70	50
5. Water	23*	23*

*Removed during processing.

Next, the sustained release excipient prepared as detailed above is dry blended with a desired amount of medicament (in the following examples the medicament is albuterol sulfate), in a V-blender for 10 minutes. A suitable amount of tableting lubricant Pruv® (sodium stearyl fumarate, NF, commercially available from the Edward Mendell Co., Inc.) for the following examples is added and the mixture is blended for another 5 minutes. This final mixture is compressed into tablets, each tablet containing 2.9% (Ex. 1) or 4.7% (Ex. 2) by weight, respectively, of albuterol sulfate. The tablets produced by Examples 1 and 2 weighed 334.6 mg and 204.7 mg, respectively. The proportions of the tablets of Examples 1 and 2 are set forth in Table 2 below.

TABLE 2

Component	Example 1	Example 2
1. SRE*	95.6%	93.8%
2. Albuterol sulfate	2.9	4.7
3. Sodium stearyl fumarate	1.5	1.5

*Sustained release excipient.

Dissolution tests were then carried out on the tablets of Examples 1 and 2. The dissolution tests were conducted in an automated USP dissolution apparatus (Paddle Type II, pH 7.5 buffer, 50 rpm in 500 mL.) The results are set forth as percent release as a function of time, in hours.

TABLE 3

Time (hrs)	Example 1	Example 2
0 (% release)	0.0	0.0
2	28.2	30.7
4	41.5	49.5
6	54.5	67.2
8	64.3	79.8
10	71.0	91.2
12	78.7	96.5
Tablet wt(mg)	334.6	204.7
Diameter (in)	3/8	3/8
Hardness (Kp)	6.5	2.6

The tablet of Example 1, with a higher percentage of sustained release excipient, provided the most prolonged release in the dissolution test.

EXAMPLES 3–4

Preparation of Controlled Release Formulations with Cellulose Acetate Phthalate and Dissolution Tests Thereon

The sustained release excipient was prepared by dry blending the requisite amounts of xanthan gum, locust bean gum, a pharmaceutically acceptable hydrophobic polymer and an inert diluent as described for Examples 1–2, supra.

but with cellulose acetate phthalate ("CAP") as the hydrophobic polymer, as detailed by Table 4, below, for Examples 3 and 4.

TABLE 4

Component	Example 3	Example 4
1. Xanthan gum	15%	15%
2. Locust bean gum	15	15%
3. CAP	10	30
4. Dextrose	60	40
5. Water	10*	17*

*Removed during processing.

Next, the sustained release excipient prepared as detailed above was dry blended with a desired amount of albuterol sulfate, as described for Examples 1–2, supra. This final mixture was then compressed into tablets, each tablet containing 2.9% by weight of albuterol sulfate. The tablets produced by Examples 3 and 4 weighed 334.6 mg. The proportions of the tablets of Examples 3 and 4 are set forth in Table 5 below:

TABLE 5

Component	Example 3	Examples 4
1. SRE*	95.6%	95.6%
2. Albuterol sulfate	2.9	2.9
3. Sodium stearyl fumarate	1.5	1.5

*Sustained release excipient.

Dissolution tests were then carried out on the tablets of Examples 3 and 4. The dissolution tests were conducted in an automated USP dissolution apparatus in such a way as to model passage through the gastrointestinal tract, in the stomach (acid buffer with a pH of 1.5 for time: 0 though 1 hour) and in the intestines (alkaline buffer with a pH of 7.5 for time: 1 through 12 hours) (Paddle Type II, 50 rpm in 500 mL.) The results are set forth as percent release as a function of time, in hours, in Table 6 below.

TABLE 6

Time (hrs)	Example 3	Example 4
0 (% release)	0.0	0.0
1	36.0	36.2
2	50.2	49.4
4	65.1	61.4
6	73.5	70.7
8	83.1	77.0
10	86.3	81.6
12	91.0	86.1
Tablet wt(mg)	334.6	334.6
Diameter (in)	3/8	3/8
Hardness (Kp)	5.8	5.8

The tablet tested in Example 4 provided the most prolonged release in the dissolution test.

EXAMPLES 5–6

Preparation of Controlled Release Formulations with Polyvinyl Acetate Phthalate and Dissolution Tests Thereon

The sustained release excipient was prepared by dry blending the requisite amounts of xanthan gum, locust bean gum, a pharmaceutically acceptable hydrophobic polymer and an inert diluent as described for Examples 1–2, supra, but with polyvinyl acetate phthalate ("PVAP") as the hydrophobic polymer, as detailed by Table 7, below, for Examples 5 and 6.

TABLE 7

Component	Example 5	Example 6
1. Xanthan gum	15%	15%
2. Locust bean gum	15	15
3. PVAP	10	30
4. Dextrose	60	40
5. Water	18*	23*

*Removed during processing.

Next, the sustained release excipient prepared as detailed above was dry blended with a desired amount of albuterol sulfate, as described for Examples 1–2, supra. This final mixture was then compressed into tablets, each tablet containing 2.9% by weight of albuterol sulfate. The tablets produced by Examples 5 and 6 weighed 334.6 mg, respectively. The proportions of the tablets of Examples 5 and 6 are set forth in Table 8 below:

TABLE 8

Component	Example 5	Example 6
1. SRE*	95.6%	95.6%
2. Albuterol sulfate	2.9	2.9
3. Sodium stearyl fumarate	1.5	1.5

*Sustained release excipient.

Dissolution tests were then carried out on the tablets of Examples 5 and 6. The dissolution tests were conducted in an automated USP dissolution apparatus in such a way as to model passage through the gastrointestinal tract, in the stomach (acid buffer with a pH of 1.5 for time: 0 though 1 hour) and in the intestines (alkaline buffer with a pH of 7.5 for time: 1 through 12 hours) (Paddle Type II, 50 rpm in 500 mL.) The results are set forth as percent release as a function of time, in hours, in Table 9 below.

TABLE 9

Time (hrs)	Example 5	Example 6
0 (% release)	0.0	0.0
1	36.4	36.5
2	51.3	47.4
4	66.2	57.6
6	71.8	66.0
8	79.9	70.4
10	84.2	77.2
12	86.4	77.7
Tablet wt(mg)	334.6	334.6
Diameter (in)	3/8	3/8
Hardness (Kp)	5.9	8.6

The tablet tested in Example 6 provided the most prolonged release in the dissolution test.

EXAMPLES 7–8

Preparation of Controlled Release Formulations with Hydroxypropylmethylcellulose Phthalate and Dissolution Tests Thereon

The sustained release excipient was prepared by dry blending the requisite amounts of xanthan gum, locust bean gum, a pharmaceutically acceptable hydrophobic polymer and an inert diluent as described for Examples 1–2, supra,

but with hydroxypropylmethylcellulose phthalate ("HPMCP") as the hydrophobic polymer, as detailed by Table 10, below, for Examples 7 and 8.

TABLE 10

Component	Example 7	Example 8
1. Xanthan gum	15%	15%
2. Locust bean gum	15	15
3. HPMCP	10	30
4. Dextrose	60	40
5. Water	13*	18*

*Removed during processing.

As for the previous examples, the sustained release excipient was prepared as detailed above and then dry blended with a desired amount of albuterol sulfate, as described for Examples 1–2, supra. This final mixture was then compressed into tablets, each tablet containing 2.9% by weight of albuterol sulfate. The tablets produced by Examples 7 and 8 weighed 334.6 mg. respectively. The proportions of the tablets of Examples 7 and 8 are set forth in Table 11 below:

TABLE 11

Component	Example 7	Example 8
1. SRE*	95.6%	95.6%
2. Albuterol sulfate	2.9	2.9
3. Sodium stearyl fumarate	1.5	1.5

*Sustained release excipient.

The dissolution tests were conducted in an automated USP dissolution apparatus in such a way as to model passage through the gastrointestinal tract, as described supra for, e.g., Examples 5–6. The results are set forth as percent release as a function of time, in hours, in Table 12 below.

TABLE 12

Time (hrs)	Example 7	Example 8
0 (% release)	0.0	0.0
1	33.7	32.7
2	48.2	42.8
4	69.9	60.3
6	74.8	71.2
8	79.6	74.6
10	85.6	82.3
12	87.0	87.2
Tablet wt(mg)	334.6	334.6
Diameter (in)	3/8	3/8
Hardness (Kp)	6.5	8.3

The data of Table 12 indicates that both Examples 7 and 8 provided effective prolongation of albuterol release in the dissolution test.

EXAMPLES 9–12

Preparation of Controlled Release Formulations with Ethylcellulose Coating and Dissolution Tests Thereon

The sustained release excipient was prepared by dry blending the requisite amounts of xanthan gum, locust bean gum and an inert diluent as described for Examples 1–2, supra, but with no hydrophobic polymer, and with an extra 2 minutes of granulation after the addition of the components (for 4 total minutes of post-addition granulation). Ethylcellulose aqueous dispersion was substituted for water in the above methods. The components of the excipient for Examples 9–12 are detailed by Table 13, below.

TABLE 13

Component	Excipient for Examples 9–12
1. Xanthan gum	12%
2. Locust bean gum	18
3. Dextrose	65
4. EAD*	5*

*EAD is an ethylcellulose aqueous dispersion containing approximately 25% by weight of solids. The amount added to the formulation (i.e., 5%) is solids only. Available commercially as, e.g., Surelease ®, from Colorcon.

The xanthan gum and locust bean gum was dry blended in a V-blender for 10 minutes, the dextrose was added and the mixture blended for another 5 minutes. The EAD was then added, followed by an additional 5 minutes of blending. The resulting granulation was then compressed into tablets with sodium stearyl fumarate, as a tableting lubricant. The tablets were then coated with additional ethylcellulose aqueous dispersion. To accomplish this, ethylcellulose (Surelease®, 400 g) was mixed with water (100 g) to form an aqueous suspension. Thereafter, the tablets were coated in a Keith Machinery coating pan (diameter 350 mm; pan speed 20 rpm; spray-gun nozzle 0.8 mm; tablets bed temperature 40°–50° C.; charge per batch 1 kg; dry air—Conair Prostyle 1250, 60°–70° C.). The tablets were coated to a weight gain of about 5%.

The tablets weighed 181.4 mg, respectively. The proportions of the tablets are set forth in Table 14 below:

TABLE 14

Component	Percent
1. SRE*	8.2%
2. Albuterol sulfate	5.3
3. Polyvinyl acetate phthalate	5.0
4. Sodium stearyl fumarate	1.5

*Sustained release excipient.

The dissolution tests were conducted in an automated USP dissolution apparatus in such a way as to model passage through the gastrointestinal tract, as described supra for, e.g., Examples 5–6. The results are set forth as percent release as a function of time, in hours, in Table 15, below. The columns are identified as "Uncoated" (Ex. 9) 2% (Ex. 10), 3% (Ex. 11) and 4% (Ex. 12) coating by weight.

TABLE 15

Time (hrs)	Ex. 9 Uncoated	Ex. 10 2%	Ex. 11 3%	Ex. 12 4% (coat % w/w)
0 (% release)	0.0	0.0	0.0	0.0
1	41.7	11.2	0.0	0.0
2	56.7	21.9	2.3	0.0
4	73.0	41.2	16.2	4.6
6	82.5	60.3	37.1	21.3
8	87.9	74.9	54.5	40.3
10	91.0	82.5	65.2	54.0
12	93.9	88.5	84.1	67.5
Tablet wt (mg)	181.4			
Diameter (in)	3/8			
Hardness (Kp)	7.9			

The above table clearly indicates that a prolongation of release is obtained that is proportional to the percent of hydrophobic coating, by weight.

In order to determine the differences, if any, in dissolution kinetics between a fed state and a fasting state for the series of coated tablets as tested above in Examples 9–12, the same tablets were tested, in vitro, for dissolution rates in a solution containing 30% peanut oil ("fed") to model a gastrointestinal tract with a typical dietary fat load. The control determined the dissolution rates in a solution lacking the fat load ("fasted"). The pH—time protocol (ranging from acid to alkaline to model digestive processes) is set forth below in Table 16, below.

TABLE 16

Fed/Fast Dissolution Protocol

	"Fasted"		"Fed"
Apparatus:	Type III		Type III
Media:	0–1 hr	pH 1.5	30% peanut oil
	1–2 hr	pH 3.5	
	2–4 hr	pH 5.5	
	4–12 hr	pH 7.5	
Agitation:	15 cpm		15 cpm
Volume:	250 mL		250 mL

TABLE 17

Fed/Fast Dissolution Results

Time (hrs)	"Fasted" Uncoated	"Fasted" 2%	"Fed" Uncoated	"Fed" 2%
0 (% release)	0.0	0.0	0.0	0.0
1	48.8	15.5	28.8	18.4
2	68.5	28.8	49.8	39.9
4	87.2	49.5	91.9	78.9
6	96.1	65.9	100.0	97.3
8	100.0	80.7	100.0	100.0
12	100.0	100.0	100.0	100.0

As can be appreciated from table 17, the dissolution rates (in vitro) in the presence of 30% peanut oil ("Fed") are not significantly different from the dissolution rates in the absence of the 30% peanut oil ("Fast"), thus demonstrating both the improved control of release rate provided by the 2% ethylcellulose coating and the freedom from significant "Fed/Fast" effects provided by the formulations of the present invention.

RESULTS AND DISCUSSION

FIGS. 1 and 2 show in vitro dissolution profiles for the product formulated according to Table 14 and Table 15 (Example 10) i.e., the formulation of Table 14 with a 2% ethylcellulose coating. The mean in vivo plasma profile for the test product is provided in FIG. 3. FIG. 1 shows a dissolution profile of an albuterol containing tablet formulated according to Table 14 and Table 15 (Example 10) as described above. The dissolution profile of FIG. 1 was conducted as a Type II dissolution with a pH change to simulate gastric and enteric passage and stirring at 50 rpm (acid buffer with a pH of 1.5 for time: 0 through 1 hour followed by alkaline buffer with a pH of 7.5 for time: 1 through 12 hours). FIG. 2 shows a dissolution profile of an albuterol containing tablet formulated formulated according to Table 14 and Table 15 as described above and conducted as a Type III dissolution with a pH change to simulate gastric and enteric passage (pH profile as described by Table 16 above) and stirring at 15 rpm. FIG. 3 shows an albuterol plasma profile of provided by ingestion of an albuterol containing tablet formulated formulated according to Table 14 and Table 15 (Example 10): solid circles mark curve of plasma profile in fed subject; open circles mark curve of plasma profile in fasted subjects.

Analysis of the pharmacokinetic parameters C_{max}, T_{max}, and AUC_{∞} (Table 18) confirms that the tested formulation is an ideal candidate for a 12 hour albuterol formulation. Furthermore, a comparison of the test product in the fed and fasted states show that the test product is not significantly affected by food. A delay of gastric emptying, which is expected in the fed state, accounts for the extended time required to reach the maximum plasma concentration.

TABLE 18

Albuterol Pharmacokinetics

Parameter		TIMERx fasted	TIMERx fed
Cmax	mean	10.5	10.6
	%CV	39.0	31.0
Tmax	mean	4.5	7.0
	%CV	29.0	23.0
AUCInf	mean	113.4	128.1
	%CV	30.0	20.0

Ratios	Cmax	Tmax	AUC Inf
TIMERx fasted: TIMERx fed	0.98	0.64	0.89
TIMERx fed: TIMERx fasted	1.02	1.57	1.13

Confidence Limits	Cmax LL	Cmax UL	AUCInf LL	AUCInf UL
TIMERx fed vs TIMERx fasted	89	124	102	133

TABLE 19

Parameter	TIMERx-fasted	TIMERx-fed
AUC_{∞}	57.3–156.2	75.6–161.1
Cmax	4.6–18.4	6.0–15.9
Tmax	3.0–6.0	3.0–8.0

Parameter	TIMERx-fed
AUC_{∞}	89.9–149.2
Cmax	7.0–11.9
Tmax	3.0–10.0

CONCLUSION

From the results provided in above examples, it can be seen that the formulations according to the invention provide a controlled release of an active medicament such as albuterol sulfate without any significant differences induced by a "fed/fast" effect due to the presence of food in the gastrointestinal tract. Accordingly, the results provide that the tablets produced according to the invention are suitable for delivering medicaments as an oral solid dosage form over a 24-hour oral period of time.

The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description. Such modifications are intended to fall within the scope of the claims. Various publications are cited herein, the disclosures of which are incorporated by reference in their entireties.

What is claimed is:

1. A controlled release solid dosage form for oral administration of a therapeutically active medicament to a patient in need thereof, comprising:

a pharmaceutically effective amount of a medicament to be administered to a patient in need of said medicament;

a sustained release excipient comprising a gelling agent comprising a heteropolysaccharide gum and a homopolysaccharide gum capable of reciprocally cross-linking when exposed to an environmental fluid, the ratio of said heteropolysaccharide gum to said homopolysaccharide gum being from about 1:3 to about 3:1; an inert pharmaceutical diluent selected from the group consisting of a pharmaceutically acceptable saccharide, polyhydric alcohol, a pre-manufactured direct compression diluent, and mixtures of any of the foregoing, the ratio of said inert diluent to said gelling agent being from about 1:8 to about 8:1, said dosage form providing a sustained release of said medicament when exposed to an environmental fluid and

a pharmaceutically acceptable hydrophobic material.

2. The controlled release solid dosage form according to claim 1 wherein said diluent is a saccharide selected from the group consisting of sucrose, dextrose, lactose, microcrystalline cellulose, fructose, xylitol, sorbitol, a starch, and mixtures thereof.

3. The controlled release solid dosage form according claim 1, wherein said heteropolysaccharide gum comprises xanthan gum and said homopolysaccharide gum comprises locust bean gum.

4. The controlled release solid dosage form according claim 2, wherein said xanthan gum and said locust bean gum are present in about a 1:1 ratio, respectively, by weight.

5. The controlled release solid dosage form according to claim 1, wherein said hydrophobic material is selected from the group consisting of a cellulose ether, a cellulose ester and an alkylcellulose.

6. The controlled release solid dosage form according claim 1, wherein said hydrophobic material is selected from the group consisting of ethylcellulose, carboxymethylcellulose, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate and a polyvinyl acetate polymer.

7. The controlled release solid dosage form according claim 1, wherein said hydrophobic material is present in an amount ranging from about 1 through about 90%, by weight, of the solid dosage form.

8. The controlled release solid dosage form according claim 1, wherein said hydrophobic material is present in an amount ranging from about 25% through about 50%, by weight, of the solid dosage form.

9. The controlled release solid dosage form according to claim 1 wherein said medicament is a pharmaceutically effective amount of albuterol or a salt or derivative thereof.

10. The controlled release solid dosage form according to claim 1 which is a tablet.

11. The controlled release solid dosage form according to claim 1 which is in granular form.

12. The controlled release solid dosage form according to claim 11, which comprises a gelatin capsule containing a sufficient amount of said granules to provide an effective dose of said therapeutically active medicament.

13. The controlled release solid dosage form according to claim 9, wherein said hydrophobic material is selected from the group consisting of carboxymethylcellulose, cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropylmethylcellulose phthalate, ethylcellulose, a copolymer of acrylic and methacrylic and esters, waxes, shellac, zein, and mixtures of any of the foregoing, prior to incorporation of said medicament, said hydrophobic material being included in said dosage form in an amount effective to slow the hydration of said gelling agent when exposed to an environmental fluid.

14. The controlled release solid dosage form according to claim 12 which is a tablet, at least part of a surface of said tablet being coated with a hydrophobic material to a weight gain from about 1 to about 20 percent, by weight.

15. The controlled release solid dosage form according to claim 1 which comprises a granulation which is coated with a hydrophobic material to a weight gain from about 1% to about 20%.

16. The controlled release solid dosage form according to claim 14, wherein said hydrophobic material is selected from the group consisting of a cellulose ether, a cellulose ester and an alkylcellulose.

17. The controlled release solid dosage form according to claim 16 which is a tablet, at least part of a surface of said tablet being coated with a hydrophobic material to a weight gain from about 1 to about 20 percent, by weight.

18. The controlled release solid dosage form according to claim 17, wherein said mixture of sustained release excipient and medicament are coated with a hydrophobic material prior to tableting.

19. The controlled release solid dosage form according to claim 1 which is a tablet, said tablet further comprising a coating containing from about 10 to about 40 percent of the total amount of said medicament included in said dosage form.

20. The controlled release solid dosage form according to claim 1 wherein the amount of albuterol is an amount equivalent to about 4 mg to about 16 mg of albuterol free base.

21. A method of preparing a controlled release solid dosage form comprising a medicament for oral administration, the method comprising

preparing a sustained release excipient comprising from about 10 to about 99 percent by weight of a gelling agent comprising a heteropolysaccharide gum and a homopolysaccharide gum capable of cross-linking said heteropolysaccharide gum when exposed to an environmental fluid, the ratio of said heteropolysaccharide gum to said homopolysaccharide gum being from about 1:3 to about 3:1, and from about 0 to about 89 percent by weight of an inert pharmaceutical diluent, and from about 1 to 90% by weight of a pharmaceutically acceptable hydrophobic material; and

adding an effective amount of a medicament thereto, such that a final product is obtained having a ratio of said medicament to said gelling agent from about 1:3 to about 1:8, such that a gel matrix is created when said formulation is exposed to environmental fluid and said formulation provides therapeutically effective blood levels of said medicament for at least 12 hours.

22. The method of claim 21, further comprising tableting said mixture of said sustained release excipient and said medicament.

23. The method of claim 21, further comprising coating said tablets with a hydrophobic coating to a weight gain from about 1% to about 20%.

24. The method of claim 21, further comprising granulating said sustained release excipient with a hydrophobic material.

25. The method of claim 21, wherein said medicament is albuterol or a salt or derivative thereof.

26. The method of claim 21, wherein said hydrophobic coating comprises ethylcellulose.

27. The method of claim 25, wherein the amount of albuterol is an amount equivalent to about 4 mg to about 16 mg of albuterol free base.

28. The method of claim 21, wherein said sustained release excipient comprises from about 10 to about 75 percent gelling agent, from about 0 to about 90% hydrophobic material and from about 30 to about 75 percent inert diluent.

29. The method of claim 21, wherein said formulation provides therapeutically effective blood levels of said medicament for at least 24 hours.

30. The method of claim 21, further comprising compressing the mixture of said sustained release excipient and said tablet into tablets.

31. The method of claim 21, wherein said medicament comprises a therapeutically effective dose of albuterol or salts and derivatives of the same.

32. A method of treating a patient with albuterol comprising,

preparing a sustained release excipient comprising from about 10 to about 99 percent by weight of a gelling agent comprising a heteropolysaccharide gum and a homopolysaccharide gum capable of cross-linking said heteropolysaccharide gum when exposed to an environmental fluid, the ratio of said heteropolysaccharide gum to said homopolysaccharide gum being from about 1:3 to about 3:1, and from about 0 to about 89 percent by weight of an inert pharmaceutical diluent, and from about 1 to 90% by weight of a pharmaceutically acceptable hydrophobic material; and

adding an effective amount of a albuterol, or a salt or derivative thereof, to said sustained release excipient, such that a final product is obtained having a ratio of albuterol to said gelling agent from about 1:3 to about 1:8, such that a gel matrix is created when said formulation is exposed to environmental fluid and said formulation provides therapeutically effective blood levels of albuterol for at least 12 hours.

adding an amount of albuterol effective to render a desired therapeutic effect;

tableting the resultant mixture such that a final product is obtained having a ratio of albuterol to said gelling agent from about 1:3 to about 1:8, such that a gel matrix is created when said tablet is exposed to gastrointestinal fluid and said tablet provides therapeutically effective blood levels of albuterol; and

administering said tablet to a patient at a predetermined dosage interval from about 12 to about 24 hours.

33. The method of claim 32, further comprising coating said tablets with a hydrophobic material to a weight gain from about 1% to about 20%.

34. The method of claim 32, further comprising preparing said formulation such that it provides therapeutically effective blood levels of said medicament for at least 24 hours.

35. The controlled release solid dosage form of claim 1 which, when orally administered to a patient, provides a medicament plasma concentration-time curve with an area under the curve, to infinity, ranging from about 89 to about 150 (ng-hours/ml).

36. The controlled release solid dosage form of claim 1 which, when orally administered to a fasting patient, provides a medicament plasma concentration-time curve with an area under the curve, to infinity, ranging from about 57 to about 157 (ng-hours/ml).

37. The controlled release solid dossage form of claim 1 which, when orally administered to a fed patient, provides a medicament plasma concentration-time curve with an area under the curve, to infinity, ranging from about 75 to about 162 (ng-hour s/ml).

38. The controlled release solid dosage form of claim 1 which, when orally administered to a patient, provides a mean peak plasma concentration ranging from about 7 to about 12 ng/ml.

39. The controlled release solid dossage form of claim 1 which, when orally administered to a fasting patient, provides a mean peak plasma concentration ranging from about 4.5 to about 19 ng/ml.

40. The controlled release solid dosage form of claim 1 which, when orally administered to a fed patient, provides a mean peak plasma concentration ranging from about 6 to about 16 ng/ml.

41. The controlled release solid dosage form of claim 1 which, when orally administered to a patient, provides a time to mean peak plasma concentration ranging from about 3 to about 10 hours.

42. The controlled release solid dosage form of claim 1 which, when orally administered to a fasting patient, provides a time to mean peak plasma concentration ranging from about 3 to about 6 hours.

43. The controlled release solid dosage form of claim 1 which, when orally administered to a fed patient, provides a time to mean peak plasma concentration ranging from about 3 to about 8 hours.

44. The controlled release solid dosage form of claim 35 wherein the area under the plasma concentration curve, to infinity, ranges from about 112 to about 129 (ng-hours/ml).

45. The controlled release solid dosage form of claim 38 wherein the mean peak plasma concentration ranges from about, 9.5 to about 12 ng.

46. The controlled release solid dosage form of claim 42 wherein the time to mean peak plasma concentration ranges from about 3.5 to about 8 hours.

47. The controlled release solid dosage form of claim 1 which, when orally administered to a patient, provides a medicament plasma concentration-time curve wherein time to peak plasma concentration in a fasted patient divided by a time to peak plasma concentration in a fed patient ranges from about 0.50 to about 0.70.

48. The controlled release solid dosage form of claim 1 which, when orally administered to a patient, provides a medicament plasma concentration-time curve wherein peak plasma concentration in a fasted patient divided by peak plasma concentration in a fed patient ranges from about 0.90 to about 1.10.

* * * * *

EXHIBIT B

US005958456A

United States Patent [19]

Baichwal et al.

[11] Patent Number: 5,958,456

[45] Date of Patent: *Sep. 28, 1999

[54] **CONTROLLED RELEASE FORMULATION (ALBUTEROL)**

[75] Inventors: **Anand Baichwal**, Wappingers Falls, N.Y.; **Troy W. McCall**, New Milford, Conn.

[73] Assignee: **Edward Mendell Co., Inc.**, Patterson, N.Y.

[*] Notice: This patent is subject to a terminal disclaimer.

[21] Appl. No.: **08/886,496**

[22] Filed: **Jul. 1, 1997**

Related U.S. Application Data

[63] Continuation of application No. 08/553,008, Nov. 3, 1995, Pat. No. 5,662,933, which is a continuation-in-part of application No. 08/118,924, Sep. 9, 1993, Pat. No. 5,455,046.

[51] **Int. Cl.**[6] **A61K 9/14**

[52] **U.S. Cl.** **424/489**; 424/488; 424/457; 424/468

[58] **Field of Search** 424/489, 488, 424/457, 468

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,412,986	11/1983	Kawata et al.	424/80
4,562,069	12/1985	Hegasy et al.	424/80
4,673,564	6/1987	Kawata et al.	424/494
4,764,382	8/1988	Kydonieus et al.	424/449
4,765,990	8/1988	Sugimoto et al.	424/494
4,792,450	12/1988	Kydonieus et al.	424/449
4,792,452	12/1988	Howard et al.	424/475
4,808,413	2/1989	Joshi et al.	424/458
4,851,229	7/1989	Magruder et al.	424/457
4,867,985	9/1989	Heafield et al.	424/461
4,892,741	1/1990	Ohm et al.	424/479
4,904,699	2/1990	Bauer	514/972
4,940,587	7/1990	Jenkins et al.	424/480
4,942,040	7/1990	Ragnarsson et al.	424/486
4,973,469	11/1990	Mulligan et al.	424/461
4,994,276	2/1991	Baichwal et al.	424/440
5,007,790	4/1991	Shell	424/451
5,019,397	5/1991	Wong et al.	424/473
5,051,263	9/1991	Barry et al.	424/490
5,071,642	12/1991	Lahr et al.	424/474
5,128,143	7/1992	Baichwal et al.	424/464
5,132,116	7/1992	Sournac et al.	424/469
5,133,974	7/1992	Paradissis et al.	424/480
5,135,757	8/1992	Baichwal et al.	424/465
5,145,683	9/1992	Rhodes	424/451
5,169,638	12/1992	Dennis et al.	424/457
5,215,758	6/1993	Krishnamurthy	424/488
5,264,459	11/1993	Chelmicka-Schorr et al.	514/646
5,273,760	12/1993	Oshlack et al.	424/480
5,286,493	2/1994	Oshlack et al.	424/468
5,356,467	10/1994	Oshlack et al.	106/153
5,455,046	10/1995	Baichwal	424/457
5,662,933	9/1997	Baichwal et al.	424/457

FOREIGN PATENT DOCUMENTS

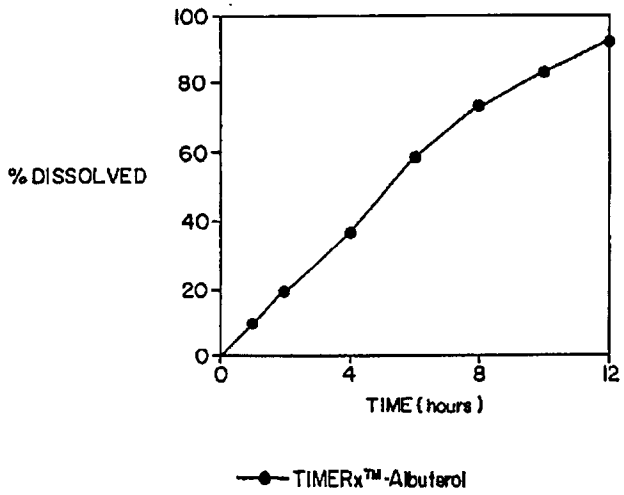
1288049	8/1991	Canada .
0357793	3/1990	European Pat. Off. .
0232155	8/1997	European Pat. Off. .
WO8902738	4/1989	WIPO .
WO9206680	4/1992	WIPO .

Primary Examiner—Thurman K. Page
Assistant Examiner—William E. Benston, Jr.
Attorney, Agent, or Firm—Davidson,Davidson & Kappel,LLC

[57] **ABSTRACT**

A sustained release pharmaceutical formulation and methods of making and using the same are provided. The sustained release pharmaceutical formulation includes a sustained release excipient including a gelling agent, an inert pharmaceutical diluent, an optional hydrophobic material and/or hydrophobic coating, and a medicament for sustained oral administration.

16 Claims, 3 Drawing Sheets



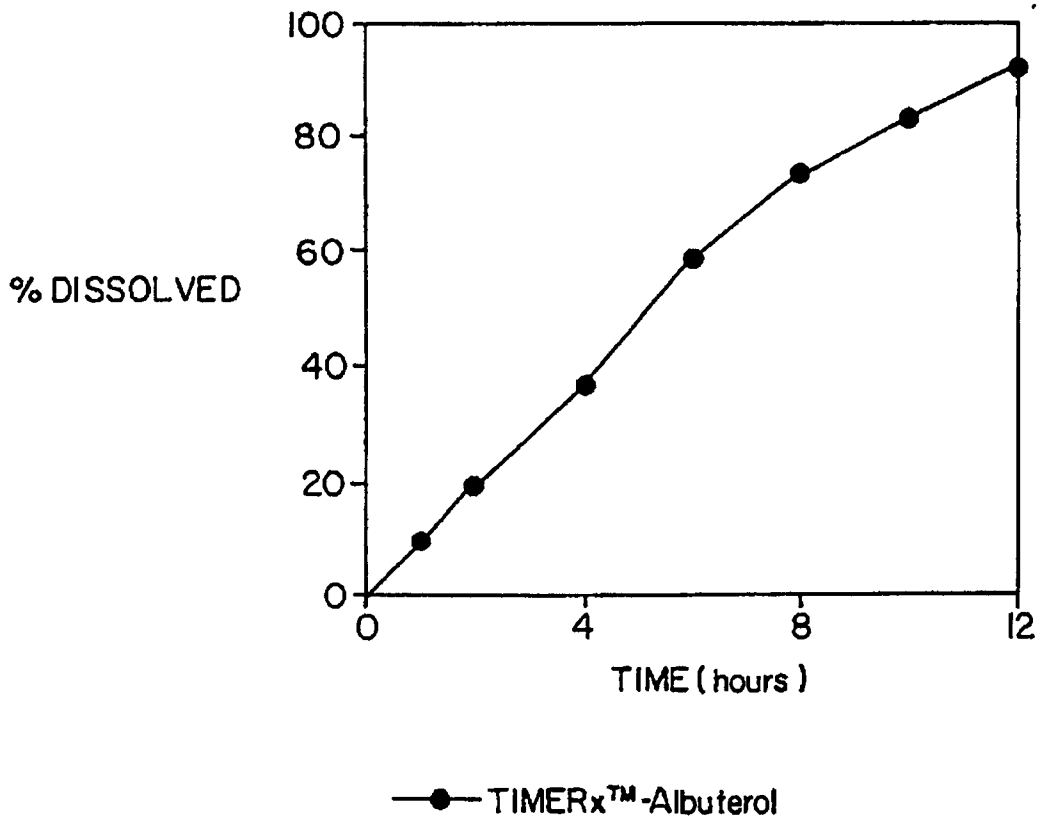

100
80
60
40
20
0
% DISSOLVED
0
4
8
12
TIME (hours)
TIMERx™-Albuterol

FIG. 1

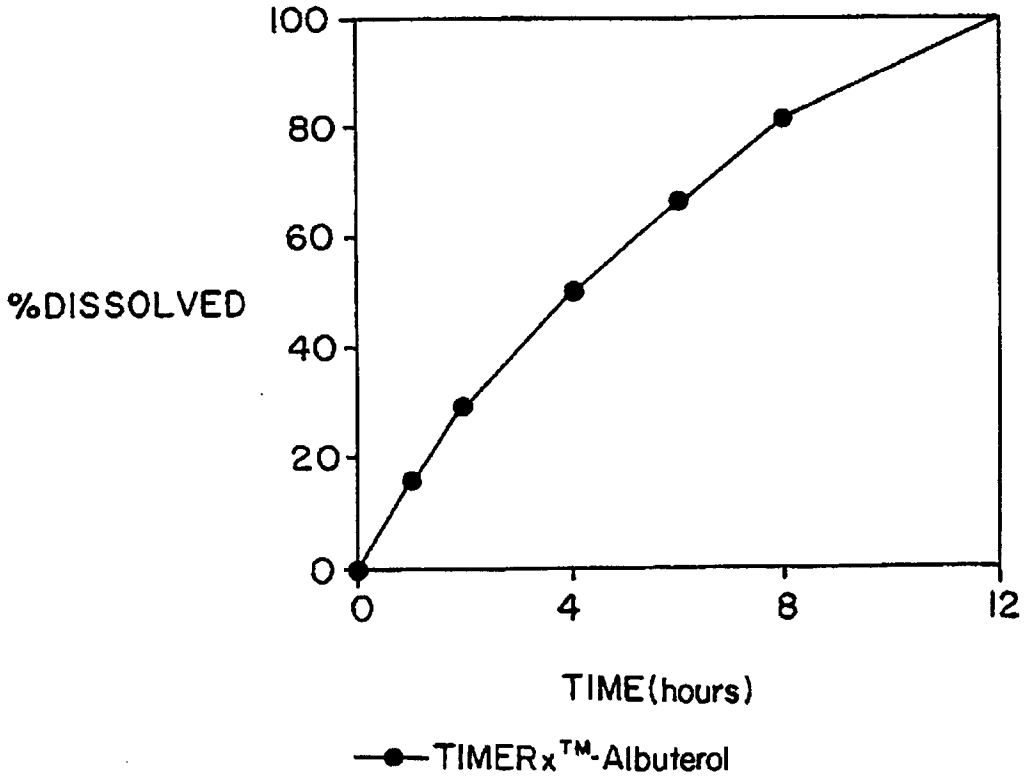

100
80
60
40
20
0
%DISSOLVED
0
4
8
12
TIME(hours)
TIMERx™-Albuterol

FIG. 2

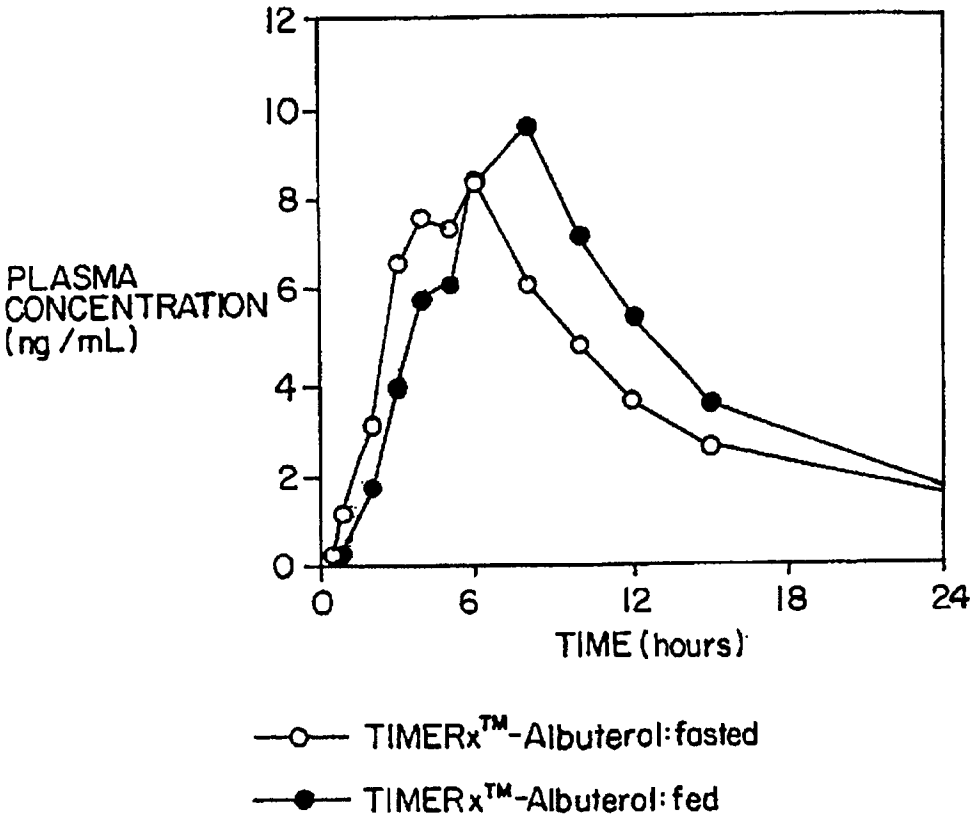

PLASMA CONCENTRATION (ng/mL)
12
10
8
6
4
2
0
0
6
12
18
24
TIME (hours)
TIMERx™-Albuterol: fasted
TIMERx™-Albuterol: fed

FIG. 3

CONTROLLED RELEASE FORMULATION (ALBUTEROL)

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. Ser. No. 08/553,008, filed Nov. 3, 1995, now U.S. Pat. No. 5,662,933, which is a continuation-in-part of Ser. No. 08/118,924, filed Sep. 9, 1993, now U.S. Pat. No. 5,455,046.

FIELD OF THE INVENTION

The present invention relates to controlled release formulations which may be blended with a wide range of therapeutically active medicaments and made into controlled release solid dosage forms for oral administration.

BACKGROUND OF THE INVENTION

The advantages of controlled release products are well known in the pharmaceutical field and include the ability to maintain a desired blood level of a medicament over a comparatively longer period of time while increasing patient compliance by reducing the number administrations. These advantages have been attained by a wide variety of methods. For example, different hydrogels have been described for use in controlled release medicines, some of which are synthetic, but most of which are semi-synthetic or of natural origin. A few contain both synthetic and non-synthetic material. However, some of the systems require special process and production equipment, and in addition some of these systems are susceptible to variable drug release.

Oral controlled release delivery systems should ideally be adaptable so that release rates and profiles can be matched to physiological and chronotherapeutic requirements. In U.S. Pat. Nos. 4,994,276, 5,128,143, and 5,135,757, hereby incorporated by reference in their entireties, it is reported that a controlled release excipient which is comprised of a synergistic combination of heterodisperse polysaccharides (e.g., a heteropolysaccharide such as xanthan gum in combination with a polysaccharide gum capable of cross-linking with the heteropolysaccharide, such as locust bean gum, in an aqueous environment) is capable of being processed into oral solid dosage forms using either direct compression (i.e., dry granulation), following addition of drug and lubricant powder, conventional wet granulation, or a combination of the two. The release of the medicament from the formulations therein proceeded according to zero-order or first-order mechanisms.

The controlled release excipients disclosed in U.S. Pat. Nos. 4,994,276, 5,128,143, and 5,135,757 are commercially available under the trade name TIMERx® from Edward Mendell Co., Inc., Patterson, N.Y., which is the assignee of the present invention.

European Pat. No. 234670 B describes a controlled-release pharmaceutical formulation containing xanthan gum wherein the xanthan gum comprises from about 7.5 to about 28 percent, by weight, of the formulation except for a formulation wherein the controlled release carrier comprises a mixture of 15–50 parts by weight dimethylsiloxane, 30–100 parts by weight silicic acid, 30–100 parts by weight mannans or galactans or a mixture thereof, 50–150 parts by weight xanthans and 5–75 parts by weight micronized seaweed.

However, heretofore there has been no teaching of a controlled release formulation providing a novel and unexpected combination of suitable proportions of a homopolysaccharide such as, e.g., xanthan gum, a heteropolysaccharide, such as, e.g., locust bean gum, together with an inert diluent and a pharmacologically acceptable hydrophobic material, so as to provide an improvement in controlled release properties for such an active medicament.

OBJECTS AND SUMMARY OF THE INVENTION

It is therefore an object of the present invention to provide a controlled release formulation for a therapeutically active medicament.

It is a further object of the present invention to provide a method for preparing a controlled release formulation for a therapeutically active medicament.

It is yet another object of the present invention to provide a controlled release excipient which may be used in the preparation of a sustained release oral solid dosage form of a therapeutically active medicament that provides an even rate of release of an active medicament.

It is a further object of the present invention to provide a controlled release excipient which, when combined with an effective amount of a bronchodilator, such as albuterol, is suitable for providing a sustained release of that medicament so as to provide a therapeutically effective blood level of the medicament for e.g., 12 or 24 hours, without allowing an excessive early release of medication, and where the release kinetics are unaffected by the contents of the patient's gastrointestinal tract.

It is yet a further object of the present invention to provide a method for treating patients with an active medication in controlled release form.

The above-mentioned objects and others are achieved by virtue of the present invention, which relates in-part to a controlled release formulation comprising a therapeutically effective amount of a medicament, and a controlled release excipient comprising a gelling agent and a swelling agent, such as, for example, a homopolysaccharide, a heteropolysaccharide, an inert diluent.

In certain preferred embodiments of the invention, the ratio of the heteropolysaccharide gum to the homopolysaccharide gum is from about 1:3 to about 3:1. More preferably, the ratio is about 1:1. Preferably, the heteropolysaccharide gum includes xanthan gum and the homopolysaccharide gum includes locust bean gum.

The present invention is also related to a sustained release oral solid dosage form for albuterol or salts or derivatives thereof in an amount necessary to render a therapeutic effect in a human patient. The albuterol is present in an amount ranging from, e.g., about 2 through about 50% by weight of the total formulation, or preferably from about 1 through about 10% by weight or more preferably from about 1 through about 6% by weight of the total formulation.

The dosage form includes an inert pharmaceutical diluent so that the ratio of the inert diluent to the gelling agent is from about 1:8 to about 8:1. Preferably, the diluent is from the group consisting of a pharmaceutically acceptable saccharide, polyhydric alcohol, a pre-manufactured direct compression diluent, and mixtures of any of the foregoing. The diluent can also be a saccharide such as sucrose, dextrose, lactose, microcrystalline cellulose, fructose, xylitol, sorbitol, a starch, and mixtures thereof.

The dosage form optionally includes a pharmaceutically acceptable hydrophobic material. Any pharmaceutically acceptable hydrophobic material may be suitably employed.

Suitable hydrophobic materials include carboxymethylcellulose, cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl-methylcellulose phthalate, ethylcellulose, a copolymer of acrylic and methacrylic and esters, waxes, shellac, zein, hydrogenated vegetable oils, and mixtures of any of the foregoing. Preferably, the hydrophobic material selected from cellulose ether, a cellulose ester and an alkylcellulose, such as ethylcellulose and carboxymethylcellulose. The hydrophobic material may be included in the dosage form in an amount effective to slow the hydration of the gelling agent when exposed to an environmental fluid.

The hydrophobic material is preferably present in an amount ranging from about 1 through about 90%, by weight, of the solid dosage form, and can also be present in an amount ranging from about 25% through about 50%, by weight, of the solid dosage form.

The medicament can be any medicament for which an orally administered controlled release form is desired. Preferably, the formulation is prepared to include a pharmaceutically effective amount of albuterol or a salt or derivative thereof.

The controlled release solid dosage form can be prepared in any conventional orally administered dosage form, including a tablet, as a granular form and as a granular form administered in a gelatin capsule containing a sufficient amount of the granules to provide an effective dose of the included therapeutically active medicament. For a tablet dosage form, at least part of a surface of the tablet can optionally be coated with a hydrophobic material to a weight gain from about 1 to about 20 percent, by weight. Further, a granular dosage form can optionally be coated with a hydrophobic coating material to a weight gain that ranges from about 1% to about 20%. The hydrophobic material can be selected from, e.g., a cellulose ether, a cellulose ester and an alkylcellulose. The hydrophobic material can optionally be applied before, during or after the process of tableting. In addition, if there is a need for an early release of the active medicament, the coating can optionally be formulated to include from about 10 to about 40 percent of the total amount of the active medicament in a quick release external layer.

The invention also relates to methods for preparing a controlled release solid dosage form as described above for providing an active medicament in an amount effective for treating a patient for from 12 to about 24 hours. The method includes the steps of preparing a sustained release excipient comprising from about 10 to about 99 percent by weight of a gelling agent comprising a heteropolysaccharide gum and a homopolysaccharide gum capable of cross-linking said heteropolysaccharide gum when exposed to an environmental fluid, the ratio of said heteropolysaccharide gum to said homopolysaccharide gum being from about 1:3 to about 3:1, and from about 0 to about 89 percent by weight of an inert pharmaceutical diluent, and optionally from about 1 to 90% by weight of a pharmaceutically acceptable hydrophobic material; and adding an effective amount of a medicament to provide a final product having a ratio of medicament to gelling agent from about 1:3 to about 1:8, so that a gel matrix is created.

The medicament to be added is preferably albuterol or salts or derivatives thereof in an amount ranging from, e.g., about 2 to about 50% by weight of the total formulation, or preferably from about 1 to about 10% by weight or more preferably from about 1 to about 6% by weight of the total formulation.

The resulting mixture of the sustained release excipient preferably includes from about 10 to about 75 percent gelling agent, from about 0 to about 90% hydrophobic material and from about 30 to about 75 percent inert diluent. Thereafter, the dosage form can be tableted, granulated with a pharmaceutically acceptable hydrophobic material or placed in gelatine capsules. Optionally the tablet can be coated with a hydrophobic coating to a weight gain from about 1% to about 20%.

Preferably, the medicament is albuterol or a salt or derivative thereof in an amount effective to provide therapeutically effective blood levels of said medicament for at least 24 hours.

The present invention is further related to a method of treating a patient comprising orally administering the sustained release albuterol tablets to a patient, thereby providing therapeutically effective blood levels of the medicament for at least about 24 hours.

By "sustained release" it is meant for purposes of the present invention that the therapeutically active medicament is released from the formulation at a controlled rate such that therapeutically beneficial blood levels (but below toxic levels) of the medicament are maintained over an extended period of time, e.g., providing a 24 hour dosage form.

The term "environmental fluid" is meant for purposes of the present invention to encompass, e.g., an aqueous solution, such as that used for in-vitro dissolution testing, or gastrointestinal fluid.

In one aspect the invention provides formulations having particular pharmacokinetic properties. Thus, simply by way of example, the invention provides formulations suitable for oral administration that, when orally administered to a patient, provide a medicament plasma concentration-time curve with an area under the curve-calculated to infinity ("AUC_∞"), ranging from about 89 to about 150 (ng-hours/ml) or even from about 112 to about 129 (ng-hours/ml). Further, the formulations according to the invention can provide, e.g., an AUC_∞ ranging from about 57 to about 157 (ng-hours/ml) (fasting patient) or from about 75 to about 162 (ng-hours/ml) (fed patient).

In addition, for example, mean peak plasma concentrations (Cmax) ranging from about 7 to about 12 ng/ml or even from about, 9.5 to about 12 ng/ml. are provided. Further, the formulations according to the invention can provide, e.g., a Cmax ranging from about 4.5 to about 19 ng/ml (fasting patient) or from about 6 to about 16 ng/ml (fed patient).

In another example, time to mean peak plasma concentration (Tmax) ranging from about 3 to about 10 hours or even from about 3.5 to about 8 hours are provided. Further, the formulations according to the invention can provide, e.g., a Tmax ranging from about 3 to about 6 hours (fasting patient) or from about 3 to about 8 hours (fed patient).

In a further example, the formulation according to the invention provides, for example, ratios of AUC_∞ (fasting patient) to AUC_∞ (fed patient) that range from about 0.50 to about 0.70.

Further still, the formulation provides, for example ranges of Cmax (fasting patient) divided by Cmax (fed patient) from about 0.90 to about 1.10.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 shows a dissolution profile of an albuterol containing tablet formulated according to Table 14 and Table 15 (Example 10) and conducted as a Type II dissolution with a pH change to simulate gastric passage and stirring at 50 rpm.

FIG. 2 shows a dissolution profile of an albuterol containing tablet formulated according to Table 14 and Table 15 (Example 10) and conducted as a Type III dissolution with a pH change to simulate gastric passage and stirring at 15 rpm.

FIG. 3 shows an albuterol plasma profile of provided by ingestion of an albuterol containing tablet formulated according to Table 14 and Table 15 (Example 10): solid circles mark curve of plasma profile in fed subject; open circles mark curve of plasma profile in fasted subject.

DETAILED DESCRIPTION

As reported in U.S. Pat. Nos. 4,994,276, 5,128,143, and 5,135,757, the disclosures of which are hereby incorporated by reference herein in their entireties, the heterodisperse excipient comprises a gelling agent of both hetero- and homo-polysaccharides which exhibit synergism, e.g., the combination of two or more polysaccharide gums produce a higher viscosity and faster hydration than that which would be expected by either of the gums alone, the resultant gel being faster-forming and more rigid.

In the present invention, it has been found that a sustained release excipient comprising only the gelling agent (heterodisperse polysaccharides, e.g., xanthan gum and locust bean gum, may not be sufficient to provide a suitable sustained release of an active medicament to provide a 12 or 24 hour formulation, when the formulation is exposed to a fluid in an environment of use, e.g. an aqueous solution or gastrointestinal fluid.

In certain embodiments, the present invention is related to the surprising discovery that by granulating the sustained release excipient with a solution or dispersion of a pharmacologically acceptable hydrophobic material prior to admixture of the sustained release excipient with the medicament and tableting, the medicament may provide therapeutically effective blood levels for extended periods of time, e.g., from about 12 to about 24 hours. The hydrophobic material is present in a range from about 0 to about 90%, by weight, of the sustained release excipient and in a preferred embodiment, is present in a range from about 1 to 20 percent of the sustained release excipient or from about 25 to about 75 percent of the sustained release excipient.

The sustained release excipient can be granulated with a pharmacologically acceptable hydrophobic material such as, for, example, an alkylcellulose, a cellulose ether, a cellulose ester. In particular, the hydrophobic material can be alkylcellulose such as carboxymethylcellulose ("CMC"), cellulose acetate phthalate ("CAP"), hydroxypropylmethylcellulose phthalate ("HPMCP") or a polyvinyl acetate polymer such as polyvinyl acetate phthalate ("PVAP").

In certain preferred embodiments of the present invention, the sustained release excipient is prepared by mixing the gelling agent and an inert diluent. The gelling agent preferably ranges, e.g., from about 10 to about 75 percent of the sustained release excipient. Thereafter, the mixture is granulated with a solution or dispersion of a hydrophobic material in an amount effective to slow the hydration of the gelling agent without disrupting the hydrophilic matrix. Next, the medicament is added, and the resultant mixture is tableted.

In other preferred embodiments of the present invention, the tablets prepared as set forth above are then coated with a hydrophobic material to a weight gain from about 1 to about 20 percent by weight. The hydrophobic material can be an alkylcellulose such as, for example, an aqueous dispersion of ethylcellulose (commercially available, for example, as Aquacoat®, available from FMC or Surelease®, available from Colorcon).

The term "heteropolysaccharide" as used in the present invention is defined as a water-soluble polysaccharide containing two or more kinds of sugar units, the heteropolysacharide having a branched or helical configuration, and having excellent water-wicking properties and immense thickening properties.

An especially preferred heteropolysaccharide is xanthan gum, which is a high molecular weight ($>10^6$) heteropolysaccharide. Other preferred heteropolysaccharides include derivatives of xanthan gum, such as deacylated xanthan gum, the carboxymethyl ether, and the propylene glycol ester.

The homopolysaccharide gums used in the present invention which are capable of cross-linking with the heteropolysaccharide include the galactomannans, i.e., polysaccharides which are composed solely of mannose and galactose. Galactomannans which have higher proportions of unsubstituted mannose regions have been found to achieve more interaction with the heteropolysaccharide. Locust bean gum, which has a higher ratio of mannose to galactose, is especially preferred as compared to other galactomannans such as guar and hydroxypropyl guar.

The controlled release properties of the formulations of the present invention may be optimized when the ratio of heteropolysaccharide gum to homopolysaccharide material is about 1:1, although heteropolysaccharide gum in an amount of from about 20 to about 80 percent or more by weight of the heterodisperse polysaccharide material provides an acceptable slow release product. The combination of any homopolysaccharide gums known to produce a synergistic effect when exposed to aqueous solutions may be used in accordance with the present invention. It is also possible that the type of synergism which is present with regard to the gum combination of the present invention could also occur between two homogeneous or two heteropolysaccharides. Other acceptable gelling agents which may be used in the present invention include those gelling agents well-known in the art. Examples include vegetable gums such as alginates, carrageenan, pectin, guar gum, xanthan gum, modified starch, hydroxypropylmethylcellulose, methylcellulose, and other cellulosic materials such as sodium carboxymethylcellulose and hydroxypropylcellulose. This list is not meant to be exclusive.

The combination of xanthan gum with locust bean gum with or without the other homopolysaccharide gums is an especially preferred gelling agent. The chemistry of certain of the ingredients comprising the excipients of the present invention such as xanthan gum is such that the excipients are considered to be self-buffering agents which are substantially insensitive to the solubility of the medicament and likewise insensitive to the pH changes along the length of the gastrointestinal tract.

The inert pharmaceutical diluent (i.e., filler) of the sustained release excipient preferably comprises a pharmaceutically acceptable saccharide, including a monosaccharide, a disaccharide, or a polyhydric alcohol, a pre-manufactured direct compression diluent, and/or mixtures of any of the foregoing. Examples of suitable inert pharmaceutical fillers include sucrose, dextrose, lactose, microcrystalline cellulose, fructose, xylitol, sorbitol, a starch, mixtures thereof and the like. However, it is preferred that a soluble pharmaceutical filler such as lactose, dextrose, sucrose, or mixtures thereof be used. If the mixture is to be manufactured without a wet granulation step, and the final product is to be tableted, it is preferred that all or part of the inert

diluent comprise a pre-manufactured direct compression diluent. Such direct compression diluents are widely used in the pharmaceutical arts, and may be obtained from a wide variety of commercial sources. Examples of such pre-manufactured direct compression excipients include Emcocel® (microcrystalline cellulose, N.F.), Emdex® (dextrates, N.F.), and Tab-Fine® (a number of direct-compression sugars including sucrose, fructose, and dextrose), all of which are commercially available from Edward Mendell Co., Inc., Patterson, N.Y.). Other direct compression diluents include Anhydrous lactose (Lactose N.F., anhydrous direct tableting) from Sheffield Chemical, Union, N.J. 07083; Elcems® G-250 (Powdered cellulose, N.F.) from Degussa, D-600 Frankfurt (Main) Germany; Maltrin® (Agglomerated maltodextrin) from Grain Processing Corp., Muscatine, Iowa 52761; Neosorb 60® (Sorbitol, N.F., direct-compression) from Roquette Corp., 645 5th Ave., New York, N.Y. 10022; Nu-Tab® (Compressible sugar, N.F.) from Ingredient Technology, Inc., Pennsauken, N.J. 08110; Polyplasdone XL® (Crospovidone, N.F., cross-linked polyvinylpyrrolidone) from GAF Corp., New York, N.Y. 10020; Primojel® (Sodium starch glycolate, N.F., carboxymethyl starch) from Generichem Corp., Little Falls, N.J. 07424; Solka Floc® (Cellulose floc) from Edward Mendell Co., Carmel, N.Y. 10512; Fast-Flo Lactose® (Lactose N.F., spray dried) from Foremost Whey Products, Baraboo, Wis. 53913 and DMV Corp., Vehgel, Holland; and Sta-Rx 1500® (Starch 1500) (Pregelatinized starch, N.F., compressible) from Colorcon, Inc., West Point, Pa. 19486. However, it is preferred that a soluble pharmaceutical filler such as lactose, dextrose, sucrose, or mixtures thereof be used.

In certain embodiments of the present invention, the sustained release excipient comprises from about 10 to about 99 percent by weight of a gelling agent comprising a heteropolysaccharide gum and a homopolysaccharide gum and from about 0 to about 89 percent by weight of an inert pharmaceutical diluent. In other embodiments, the sustained release excipient comprises from about 10 to about 75 percent gelling agent, and from about 30 to about 75 percent inert diluent. In yet other embodiments, the sustained release excipient comprises from about 30 to about 75 percent gelling agent and from about 15 to about 65 percent inert diluent.

The sustained release excipient of the present invention may be further modified by incorporation of a hydrophobic material which slows the hydration of the gums without disrupting the hydrophilic matrix. This is accomplished in preferred embodiments of the present invention by granulating the sustained release excipient with the solution or dispersion of a hydrophobic material prior to the incorporation of the medicament. The hydrophobic material may be selected from an alkylcellulose such as ethylcellulose such as carboxymethyl-cellulose ("CMC"), other hydrophobic cellulosic materials, acrylic and/or methacrylic ester polymers, copolymers of acrylic and methacrylic esters, zein, waxes, other hydrophobic cellulosic materials, cellulose acetate phthalate ("CAP"), hydroxypropylmethylcellulose phthalate ("HPMCP") or a polyvinyl acetate polymer such as polyvinyl acetate phthalate ("PVAP"), hydrogenated vegetable oils, and any other pharmaceutically acceptable hydrophobic material known to those skilled in the art. The amount of hydrophobic material incorporated into the sustained release excipient is that which is effective to slow the hydration of the gums without disrupting the hydrophilic matrix formed upon exposure to an environmental fluid.

In certain preferred embodiments of the present invention, the hydrophobic material is included in the sustained release excipient in an amount from about 1 to about 20 percent by weight. The solvent for the hydrophobic material may be an aqueous or organic solvent, or mixtures thereof.

Examples of commercially available alkylcelluloses are Aquacoat® (aqueous dispersion of ethylcellulose available from FMC), Surelease® (aqueous dispersion of ethylcellulose available from Colorcon). Examples of commercially available acrylic polymers suitable for use as the hydrophobic material include Eudragit® RS and RL (copolymers of acrylic and methacrylic acid esters having a low content (e.g, 1:20 or 1:40) of quaternary ammonium compounds).

Once the sustained release excipient of the present invention has been prepared, it is then possible to blend the same with the medicament, e.g., in a high shear mixer. In one embodiment, the formulation is prepared by dry blending the components, e.g., a heteropolysaccharide, a homopolysaccharide, an inert filler, and a hydrophobic material, optionally followed by the addition of a suitable amount of water, with continued blending, followed by dry granulation in a fluid bed dryer and then milling of the resulting granulation product.

A wide variety of therapeutically active agents can be used in conjunction with the present invention. The therapeutically active agents (e.g., pharmaceutical agents) which may be used in the compositions of the present invention include drugs ranging in solubility from water soluble to water insoluble. Examples of such therapeutically active agents include antihistamines (e.g., dimenhydrinate, diphenhydramine, chlorpheniramine and dexchlorpheniramine maleate), analgesics (e.g., aspirin, codeine, morphine, dihydromorphone, oxycodone, etc.), non-steroidal anti-inflammatory agents (e.g., naproxyn, diclofenac, indomethacin, ibuprofen, sulindac), anti-emetics (e.g., metoclopramide), anti-epileptics (e.g., phenytoin, meprobamate and nitrazepam), vasodilators (e.g., nifedipine, papaverine, diltiazem and nicardirine), antitussive agents and expectorants (e.g., codeine phosphate), anti-asthmatics (e.g. theophylline), antacids, anti-spasmodics (e.g. atropine, scopolamine), antidiabetics (e.g., insulin), diuretics (e.g., ethacrynic acid, bendrofluazide), anti-hypotensives (e.g., propranolol, clonidine), antihypertensives (e.g., clonidine, methyldopa), bronchodilators (e.g., albuterol), steroids (e.g., hydrocortisone, triamcinolone, prednisone), antibiotics (e.g., tetracycline), antihemorrhoidals, hypnotics, psychotropics, antidiarrheals, mucolytics, sedatives, decongestants, laxatives, vitamins, stimulants (including appetite suppressants such as phenylpropanolamine). The above list is not meant to be exclusive.

In a preferred embodiment, the therapeutically active agents are sympathomimetics such as, dobutamine hydrochloride, dopamine hydrochloride, ephedrine sulfate, epinephrine, fenfluramine hydrochloride, isoetharine, isoproterenol, mephentermine sulfate, metaproterenol sulfate, metaraminol bitartrate, methoxamine hydrochloride, norepinephrine bitartrate, phenylephrine hydrochloride, phenylpropanolamine hydrochloride, pseudoephedrine, ritodrine hydrochloride, terbutaline sulfate, tetrahydrozoline hydrochloride, triprolidine and pseudoephedrine, xylometazoline hydrochloride, isoproterenol and dobutamine as well as beta2 selective adrenergic agonists, including, for example, terbutaline, albuterol, isoetharine, pirbuterol and bitolterol (GOODMAN AND GILMAN's, THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, Eighth Edition, the disclosure of which is incorporated herein by reference in its entirety).

Generally any flavoring or food additive such as those described in *Chemicals Used in Food Processing*, pub 1274

by the National Academy of Sciences, pages 63–258, incorporated herein in its entirety, may be used. Generally, the final product may include from about 0.1% to about 5% by weight flavorant.

The tablets of the present invention may also contain effective amounts of coloring agents, (e.g., titanium dioxide, F.D. & C. and D. & C. dyes; see the Kirk-Othmer Encyclopedia of Chemical Technology, Vol. 5, pp. 857–884, hereby incorporated by reference in its entirety), stabilizers, binders, odor controlling agents, and preservatives.

Alternatively, the inventive formulation can be utilized in other applications wherein it is not compressed. For example, the granulate can be admixed with an active ingredient and the mixture then filled into capsules. The granulate can further be molded into shapes other than those typically associated with tablets. For example, the granulate together with active ingredient can be molded to "fit" into a particular area in an environment of use (e.g., an implant). All such uses would be contemplated by those skilled in the art and are deemed to be encompassed within the scope of the appended claims.

A hydrophobic material (e.g., a hydrophobic polymer) may be dissolved in an organic solvent or dispersed in an aqueous solution. Thereafter, the hydrophobic material may be used to coat the granulate of medicament/sustained release excipient. The granulate may be coated with the hydrophobic coating to a weight gain of, e.g., from about 1 to about 20 percent, and preferably from about 5 to about 10 percent. The granulation is then preferably dried. Thereafter, the granulate may be further formulated into an appropriate oral dosage form, for example, by compression of the resulting granulate into appropriately sized tablets, by filling gelatin capsules with an appropriate amount of the granulate (with or without compression of the granulate), as well as use in the manufacture of other oral dosage forms known to those skilled in the art. This embodiment may be particularly beneficial to reduce the amount of drug released during the initial phases of dissolution when the formulation is exposed to fluid in an environment of use, e.g., in vitro dissolution or in the gastrointestinal tract.

An effective amount of any generally accepted pharmaceutical lubricant, including the calcium or magnesium soaps may be added to the above-mentioned ingredients of the excipient be added at the time the medicament is added, or in any event prior to compression into a said dosage form. An example of a suitable lubricant is magnesium stearate in an amount of about 0.5 to about 3% by weight of the solid dosage form. An especially preferred lubricant is sodium stearyl fumarate, NF, commercially available under the trade name Pruv® from the Edward Mendell Co., Inc.

The sustained release excipients of the present invention have uniform packing characteristics over a range of different particle size distributions and are capable of processing into the final dosage form (e.g., tablets) using either direct compression, following addition of drug and lubricant powder, or conventional wet granulation.

The properties and characteristics of a specific excipient system prepared according to the present invention is dependent in part on the individual characteristics of the homo and hetero polysaccharide constituents, in terms of polymer solubility, glass transition temperatures etc., as well as on the synergism both between different homo- and heteropolysaccharides and between the homo and heteropolysaccharides and the inert saccharide constituent(s) in modifying dissolution fluid-excipient interactions.

The combination of the gelling agent (i.e., a mixture of xanthan gum and locust beam gum) with the inert diluent provides a ready-to-use product in which a formulator need only blend the desired active medicament and an optional lubricant with the excipient and then compress the mixture to form slow release tablets. The excipient may comprise a physical admix of the gums along with a soluble excipient such as compressible sucrose, lactose or dextrose, although it is preferred to granulate or agglomerate the gums with plain (i.e., crystalline) sucrose, lactose, dextrose, etc., to form an excipient. The granulate form has certain advantages including the fact that it can be optimized for flow and compressibility; it can be tableted, formulated in a capsule, extruded and spheronized with an active medicament to form pellets, etc.

The pharmaceutical excipients prepared in accordance with the present invention may be prepared according to any agglomeration technique to yield an acceptable excipient product. In dry granulation techniques, the excipients, i.e., the desired amounts of the heteropolysaccharide gum, the homopolysaccharide gum, and the inert diluent are mixed with an active medicament and the mixture is then formed into tablets and the like by compression, without the addition of water or other solvent.

In wet granulation techniques, the desired amounts of the heteropolysaccharide gum, the homopolysaccharide gum, and the inert diluent are mixed together and thereafter a moistening agent such as water, propylene glycol, glycerol, alcohol or the like is added to prepare a moistened mass. Next, the moistened mass is dried. The dried mass is then milled with conventional equipment into granules. Therefore, the excipient product is ready to use.

The sustained release excipient is free-flowing and directly compressible. Accordingly, the excipient may be mixed in the desired proportion with a therapeutically active medicament and optional lubricant (dry granulation). Alternatively, all or part of the excipient may be subjected to a wet granulation with the active ingredient and thereafter tableted. When the final product to be manufactured is tablets, the complete mixture, in an amount sufficient to make a uniform batch of tablets, is then subjected to tableting in a conventional production scale tableting machine at normal compression pressure, i.e. about 2000–1600 lbs/sq in. However, the mixture should not be compressed to such a degree that there is subsequent difficulty in its hydration when exposed to gastric fluid.

One of the limitations of direct compression as a method of tablet manufacture is the size of the tablet. If the amount of active (drug) is high, a pharmaceutical formulator may choose to wet granulate the active medicament with other excipients to attain a more compact tablet. Usually the amount of filler/binder or excipients needed in wet granulation is less than that in direct compression since the process of wet granulation contributes to some extent toward the desired physical properties of a tablet.

The average tablet size for round tablets is preferably about 300 mg to 750 mg and for capsule-shaped tablets about 750 mg to 1000 mg.

The average particle size of the granulated excipient of the present invention ranges from about 50 microns to about 400 microns and preferably from about 185 microns to about 265 microns. The particle size of the granulation is not narrowly critical, the important parameter being that the average particle size of the granules, must permit the formation of a directly compressible excipient which forms pharmaceutically acceptable tablets. The desired tap and bulk densities of the granulation of the present invention are normally between from about 0.3 to about 0.8 g/ml, with an

average density of from about 0.5 to about 0.7 g/ml. For best results, the tablets formed from the granulations of the present invention are from about 6 to about 8 kg hardness. The average flow of the granulations prepared in accordance with the present invention are from about 25 to about 40 g/sec. Tablets compacted using an instrumented rotary tablet machine have been found to possess strength profiles which are largely independent of the inert saccharide component. Scanning electron photomicrographs of largely tablet surfaces have provided qualitative evidence of extensive plastic deformation on compaction, both at the tablet surface and across the fracture surface, and also show evidence of surface pores through which initial solvent ingress and solution egress may occur.

In certain embodiments of the invention, the tablet is coated with a sufficient amount of a hydrophobic material, such as, e.g., a hydrophobic polymer, to render the formulation capable of providing a release of the medicament such that a 12 or 24 hour formulation is obtained. The hydrophobic material included in the tablet coating may be the same or different material as compared to the hydrophobic material which is optionally granulated with the sustained release excipient.

In other embodiments of the present invention, the tablet coating may comprise an enteric coating material in addition to or instead or the hydrophobic coating. Examples of suitable enteric polymers include cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, polyvinylacetate phthalate, methacrylic acid copolymer, shellac, hydroxypropylmethylcellulose succinate, cellulose acetate trimellitate, and mixtures of any of the foregoing. An example of a suitable commercially available enteric material is available under the trade name Eudragit™ L 100–555.

In further embodiments, the dosage form may be a coating with a hydrophilic coating in addition to or instead of the above-mentioned coatings. An example of a suitable material which may be used for such a hydrophilic coating is hydroxypropylmethylcellulose (e.g., Opadry®, commercially available from Colorcon, West Point, Pa.).

The coatings may be applied in any pharmaceutically acceptable manner known to those skilled in the art. For example, in one embodiment, the coating is applied via a fluidized bed or in a coating pan. For example, the coated tablets may be dried, e.g., at about 60–70° C. for about 3–4 hours in a coating pan. The solvent for the hydrophobic material or enteric coating may be organic, aqueous, or a mixture of an organic and an aqueous solvent. The organic solvents may be, e.g., isopropyl alcohol, ethanol, and the like, with or without water.

In additional embodiments of the present invention, a support platform is applied to the tablets manufactured in accordance with the present invention. Suitable support platforms are well known to those skilled in the art. An example of suitable support platforms is set forth, e.g., in U.S. Pat. No. 4,839,177, hereby incorporated by reference herein in its entirety. In that patent, the support platform partially coats the tablet, and consists of a polymeric material insoluble in aqueous liquids. The support platform may, for example, be designed to maintain its impermeability characteristics during the transfer of the therapeutically active medicament. The support platform may be applied to the tablets, e.g., via compression coating onto part of the tablet surface, by spray coating the polymeric materials comprising the support platform onto all or part of the tablet surface, or by immersing the tablets in a solution of the hydrophobic materials.

The support platform may have a thickness of, e.g., about 2 mm if applied by compression, and about 10 μ if applied via spray-coating or immersion-coating. Generally, in embodiments of the invention wherein a hydrophobic material or enteric coating is applied to the tablets, the tablets are coated to a weight gain from about 1 to about 20%, and in certain embodiments preferably from about 5% to about 10%.

Materials useful in the hydrophobic coatings and support platforms of the present invention include derivatives of acrylic acid (such as esters of acrylic acid, methacrylic acid, and copolymers thereof) celluloses and derivatives thereof (such as ethylcellulose), polyvinylalcohols, and the like.

In certain embodiments of the present invention, the tablet core includes an additional dose of the medicament included in either the hydrophobic or enteric coating, or in an additional overcoating coated on the outer surface of the tablet core (without the hydrophobic or enteric coating) or as a second coating layer coated on the surface of the base coating comprising the hydrophobic or enteric coating material. This may be desired when, for example, a loading dose of a therapeutically active agent is needed to provide therapeutically effective blood levels of the active agent when the formulation is first exposed to gastric fluid. The loading dose of medicament included in the coating layer may be, e.g., from about 10% to about 40% of the total amount of medicament included in the formulation.

Albuterol Controlled Release Formulation

In a more preferred embodiment, the therapeutically active agent is albuterol, or salts or derivatives thereof (e.g., albuterol sulfate). Albuterol sulfate is a beta2-selective adrenergic agonist and is indicated for the relief of bronchospasm in patients with reversible obstructive airway disease. Patient compliance and evenly maintained blood levels of the active drug are important for achieving good control of the symptoms of bronchospasm in such patients. The half-life of albuterol sulfate in the human body is only about 5 hours. Thus, a controlled release form for the sustained delivery of albuterol provides improved patient compliance by reducing the number of doses per day and also provides more consistent blood levels of albuterol for patients in need of such treatment.

The albuterol controlled release formulation is composed of synergistic heterodisperse polysaccharides together with a saccharide component. The synergism between the homo- and hetero-polysaccharide components enables the manipulation of different rate controlling mechanisms. In order to achieve appropriate drug release, the saccharides were optimized based upon the magnitude of interactions and the ratio of one saccharide to another.

Preparation

The albuterol containing formulation according to the invention is prepared, for example, by dry blending the components, e.g., a heteropolysaccharide, a homopolysaccharide, an inert filler, and a hydrophobic material, followed by the addition of a suitable amount of water, with continued blending, followed by dry granulation in a fluid bed dryer and then milling of the resulting granulation product. Albuterol sulfate, in an amount ranging from, e.g., about 2 through about 50% by weight of the total formulation, or preferably from about 1 through about 10% by weight or more preferably from about 1 through about 6% by weight of the total formulation, is then compounded with the granulation product and formed into pills, caplets or capsules. Whatever the formulation, it is preferred that such

pills, caplets or capsules each contain an effective therapeutic amount of albuterol or a derivative or salt thereof. Simply by way of example, the pills, caplets or capsules can contain an amount of albuterol sulfate equivalent to about 4 to about 16 mg of albuterol free base per dosage unit of the free base. More preferably, the pills, caplets or capsules can contain an amount of albuterol sulfate equivalent to about 8 to about 12 mg of the free base. Simply by way of comparison, 9.6 mg of albuterol sulfate is equivalent to 8 mg of free base. Effective amounts of other pharmaceutically acceptable albuterol derivatives or salts thereof may be used, with the amounts adjusted in proportion to the weight ranges provided for albuterol free base.

Dissolution Testing

The test formulations were evaluated under a variety of dissolution conditions to determine the effects of pH, media, agitation and apparatus. Dissolution tests were performed using a USP Type III (VanKel Bio-Dis II) apparatus. Effects of pH, agitation, polarity, enzymes and bile salts were evaluated.

Bioavailability Study

A study was conducted to evaluate the bioavailability of a test formulation of albuterol sulfate using a randomized, balanced, open label, single dose, crossover design. The study was performed using 12 healthy male and female volunteers between the ages of 18 and 35. Blood samples were removed at 0, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 15 and 25 hours. Except for the "fed" treatment in which the subjects received a standard high fat breakfast, no food was allowed until a standard lunch was served four hours after the dose was administered. The data from each time point were used to derive pharmacokinetic parameters: area under plasma concentration-time curve ("AUC") such as AUC0-t, AUC0-∞, mean peak plasma concentration ("Cmax") and $time_{\Delta}$ to mean peak plasma concentration ("Tmax") which data confirmed that the formulation according to the invention provided controlled release of albuterol sulfate.

The invention is further described in the following examples, based upon the above described methods, which are in no way intended to limit the scope of the invention.

EXAMPLES 1–2

Preparation of Controlled Release Formulations with Carboxymethylcellulose and Dissolution Tests Thereon

The sustained release excipient was prepared by dry blending the requisite amounts of xanthan gum, locust bean gum, a pharmaceutically acceptable hydrophobic polymer and an inert diluent in a high-speed mixer/granulator for 2 minutes. While running choppers/impellers, the water was added and the mixture was granulated for another 2 minutes. The granulation was then dried in a fluid bed dryer to a loss on drying weight ("LOD") of between 4 and 7%. The granulation was then milled using 20 mesh screens. The ingredients of the sustained release excipients used for Examples 1–2 are set forth in Table 1 below:

TABLE 1

The hydrophobic polymer is carboxymethylcellulose ("CMC").

Component	Example 1	Example 2
1. Xanthan gum	10%	10%
2. Locust bean gum	10	10
3. CMC	10	30
4. Dextrose	70	50
5. Water	23*	23*

*Removed during processing.

Next, the sustained release excipient prepared as detailed above is dry blended with a desired amount of medicament (in the following examples the medicament is albuterol sulfate), in a V-blender for 10 minutes. A suitable amount of tableting lubricant Pruv® (sodium stearyl fumarate, NF, commercially available from the Edward Mendell Co., Inc.) for the following examples is added and the mixture is blended for another 5 minutes. This final mixture is compressed into tablets, each tablet containing 2.9% (Ex. 1) or 4.7% (Ex. 2) by weight, respectively, of albuterol sulfate. The tablets produced by Examples 1 and 2 weighed 334.6 mg and 204.7 mg, respectively. The proportions of the tablets of Examples 1 and 2 are set forth in Table 2 below.

TABLE 2

Component	Example 1	Example 2
1. SRE*	95.6%	93.8%
2. Albuterol sulfate	2.9	4.7
3. Sodium stearyl fumarate	1.5	1.5

*Sustained release excipient.

Dissolution tests were then carried out on the tablets of Examples 1 and 2. The dissolution tests were conducted in an automated USP dissolution apparatus (Paddle Type II, pH 7.5 buffer, 50 rpm in 500 mL.) The results are set forth as percent release as a function of time, in hours.

TABLE 3

Time (hrs)	Example 1	Example 2
0 (% release)	0.0	0.0
2	28.2	30.7
4	41.5	49.5
6	54.5	67.2
8	64.3	79.8
10	71.0	91.2
12	78.7	96.5
Tablet wt (mg)	334.6	204.7
Diameter (in)	⅜	⅜
Hardness (Kp)	6.5	2.6

The tablet of Example 1, with a higher percentage of sustained release excipient, provided the most prolonged release in the dissolution test.

EXAMPLES 3–4

Preparation of Controlled Release Formulations with Cellulose Acetate Phthalate and Dissolution Tests Thereon

The sustained release excipient was prepared by dry blending the requisite amounts of xanthan gum, locust bean gum, a pharmaceutically acceptable hydrophobic polymer and an inert diluent as described for Examples 1–2, supra,

but with cellulose acetate phthalate ("CAP") as the hydrophobic polymer, as detailed by Table 4, below, for Examples 3 and 4.

TABLE 4

	Component	Example 3	Example 4
1.	Xanthan gum	15%	15%
2.	Locust bean gum	15	15
3.	CAP	10	30
4.	Dextrose	60	40
5.	Water	10*	17*

*Removed during processing.

Next, the sustained release excipient prepared as detailed above was dry blended with a desired amount of albuterol sulfate, as described for Examples 1–2, supra. This final mixture was then compressed into tablets, each tablet containing 2.9% by weight of albuterol sulfate. The tablets produced by Examples 3 and 4 weighed 334.6 mg. The proportions of the tablets of Examples 3 and 4 are set forth in Table 5 below:

TABLE 5

	Component	Example 3	Examples 4
1.	SRE*	95.6%	95.6%
2.	Albuterol sulfate	2.9	2.9
3.	Sodium stearyl fumarate	1.5	1.5

*Sustained release excipient.

Dissolution tests were then carried out on the tablets of Examples 3 and 4. The dissolution tests were conducted in an automated USP dissolution apparatus in such a way as to model passage through the gastrointestinal tract, in the stomach (acid buffer with a pH of 1.5 for time: 0 though 1 hour) and in the intestines (alkaline buffer with a pH of 7.5 for time: 1 through 12 hours) (Paddle Type II, 50 rpm in 500 mL.) The results are set forth as percent release as a function of time, in hours, in Table 6 below.

TABLE 6

	Example 3	Example 4
Time (hrs)		
0 (% release)	0.0	0.0
1	36.0	36.2
2	50.2	49.4
4	65.1	61.4
6	73.5	70.7
8	83.1	77.0
10	86.3	81.6
12	91.0	86.1
Tablet wt (mg)	334.6	334.6
Diameter (in)	⅜	⅜
Hardness (Kp)	5.8	5.8

The tablet tested in Example 4 provided the most prolonged release in the dissolution test.

EXAMPLES 5–6

Preparation of Controlled Release Formulations with Polyvinyl Acetate Phthalate and Dissolution Tests Thereon

The sustained release excipient was prepared by dry blending the requisite amounts of xanthan gum, locust bean gum, a pharmaceutically acceptable hydrophobic polymer and an inert diluent as described for Examples 1–2, supra, but with polyvinyl acetate phthalate ("PVAP") as the hydrophobic polymer, as detailed by Table 7, below, for Examples 5 and 6.

TABLE 7

	Component	Example 5	Example 6
1.	Xanthan gum	15%	15%
2.	Locust bean gum	15	15
3.	PVAP	10	30
4.	Dextrose	60	40
5.	Water	18*	23*

*Removed during processing.

Next, the sustained release excipient prepared as detailed above was dry blended with a desired amount of albuterol sulfate, as described for Examples 1–2, supra. This final mixture was then compressed into tablets, each tablet containing 2.9% by weight of albuterol sulfate. The tablets produced by Examples 5 and 6 weighed 334.6 mg, respectively. The proportions of the tablets of Examples 5 and 6 are set forth in Table 8 below:

TABLE 8

	Component	Example 5	Example 6
1.	SRE*	95.6%	95.6%
2.	Albuterol sulfate	2.9	2.9
3.	Sodium stearyl fumarate	1.5	1.5

*Sustained release excipient.

Dissolution tests were then carried out on the tablets of Examples 5 and 6. The dissolution tests were conducted in an automated USP dissolution apparatus in such a way as to model passage through the gastrointestinal tract, in the stomach (acid buffer with a pH of 1.5 for time: 0 though 1 hour) and in the intestines (alkaline buffer with a pH of 7.5 for time: 1 through 12 hours) (Paddle Type II, 50 rpm in 500 mL.) The results are set forth as percent release as a function of time, in hours, in Table 9 below.

TABLE 9

	Example 5	Example 6
Time (hrs)		
0 (% release)	0.0	0.0
1	36.4	36.5
2	51.3	47.4
4	66.2	57.6
6	71.8	66.0
8	79.9	70.4
10	84.2	77.2
12	86.4	77.7
Tablet wt (mg)	334.6	334.6
Diameter (in)	⅜	⅜
Hardness (Kp)	5.9	8.6

The tablet tested in Example 6 provided the most prolonged release in the dissolution test.

EXAMPLES 7–8

Preparation of Controlled Release Formulations with Hydroxypropylmethylcellulose Phthalate and Dissolution Tests Thereon

The sustained release excipient was prepared by dry blending the requisite amounts of xanthan gum, locust bean

gum, a pharmaceutically acceptable hydrophobic polymer and an inert diluent as described for Examples 1–2, supra, but with hydroxypropylmethylcellulose phthalate ("HPMCP") as the hydrophobic polymer, as detailed by Table 10, below, for Examples 7 and 8.

TABLE 10

	Component	Example 7	Example 8
1.	Xanthan gum	15%	15%
2.	Locust bean gum	15	15
3.	HPMCP	10	30
4.	Dextrose	60	40
5.	Water	13*	18*

*Removed during processing.

As for the previous examples, the sustained release excipient was prepared as detailed above and then dry blended with a desired amount of albuterol sulfate, as described for Examples 1–2, supra. This final mixture was then compressed into tablets, each tablet containing 2.9% by weight of albuterol sulfate. The tablets produced by Examples 7 and 8 weighed 334.6 mg, respectively. The proportions of the tablets of Examples 7 and 8 are set forth in Table 11 below:

TABLE 11

	Component	Example 7	Example 8
1.	SRE*	95.6%	95.6%
2.	Albuterol sulfate	2.9	2.9
3.	Sodium stearyl fumarate	1.5	1.5

*Sustained release excipient.

The dissolution tests were conducted in an automated USP dissolution apparatus in such a way as to model passage through the gastrointestinal tract, as described supra for, e.g., Examples 5–6. The results are set forth as percent release as a function of time, in hours, in Table 12 below.

TABLE 12

	Example 7	Example 8
Time (hrs)		
0 (% release)	0.0	0.0
1	33.7	32.7
2	48.2	42.8
4	63.9	60.3
6	74.8	71.2
8	79.6	74.6
10	85.6	82.3
12	87.0	87.2
Tablet wt (mg)	334.6	334.6
Diameter (in)	⅜	⅜
Hardness (Kp)	6.5	8.3

The data of Table 12 indicates that both Examples 7 and 8 provided effective prolongation of albuterol release in the dissolution test.

EXAMPLES 9–12

Preparation of Controlled Release Formulations with Ethylcellulose Coating and Dissolution Tests Thereon

The sustained release excipient was prepared by dry blending the requisite amounts of xanthan gum, locust bean gum and an inert diluent as described for Examples 1–2, supra, but with no hydrophobic polymer, and with an extra 2 minutes of granulation after the addition of the components (for 4 total minutes of post-addition granulation). Ethylcellulose aqueous dispersion was substituted for water in the above methods. The components of the excipient for Examples 9–12 are detailed by Table 13, below.

TABLE 13

	Component	Excipient for Examples 9–12
1.	Xanthan gum	12%
2.	Locust bean gum	18
3.	Dextrose	65
4.	EAD*	5*

*EAD is an ethylcellulose aqueous dispersion containing approximately 25% by weight of solids. The amount added to the formulation (i.e., 5%) is solids only. Available commercially as, e.g., Surelease ®, from Colorcon.

The xanthan gum and locust bean gum was dry blended in a V-blender for 10 minutes, the dextrose was added and the mixture blended for another 5 minutes. The EAD was then added, followed by an additional 5 minutes of blending. The resulting granulation was then compressed into tablets with sodium stearyl fumarate, as a tableting lubricant. The tablets were then coated with additional ethylcellulose aqueous dispersion. To accomplish this, ethylcellulose (Surelease®, 400 g) was mixed with water (100 g) to form an aqueous suspension. Thereafter, the tablets were coated in a Keith Machinery coating pan (diameter 350 mm; pan speed 20 rpm; spray-gun nozzle 0.8 mm; tablets bed temperature 40°–50° C.; charge per batch 1 kg; dry air—Conair Prostyle 1250, 60°–70° C.). The tablets were coated to a weight gain of about 5%.

The tablets weighed 181.4 mg, respectively. The proportions of the tablets are set forth in Table 14 below:

TABLE 14

	Component	Percent
1.	SRE*	8.2%
2.	Albuterol sulfate	5.3
3.	Polyvinyl acetate phthalate	5.0
4.	Sodium stearyl fumarate	1.5

*Sustained release excipient.

The dissolution tests were conducted in an automated USP dissolution apparatus in such a way as to model passage through the gastrointestinal tract, as described supra for, e.g., Examples 5–6. The results are set forth as percent release as a function of time, in hours, in Table 15, below. The columns are identified as "Uncoated" (Ex. 9) 2% (Ex. 10), 3% (Ex. 11) and 4% (Ex. 12) coating by weight.

TABLE 15

Time (hrs)	Ex. 9 Uncoated	Ex. 10 2%	Ex. 11 3%	Ex. 12 4% (coat % w/w)
0 (% release)	0.0	0.0	0.0	0.0
1	41.7	11.2	0.0	0.0
2	56.7	21.9	2.3	0.0
4	73.0	41.2	16.2	4.6
6	82.5	60.3	37.1	21.3
8	87.9	74.9	54.5	40.3
10	91.0	82.5	65.2	54.0
12	93.9	88.5	84.1	67.5
Tablet wt (mg)	181.4			
Diameter (in)	⅜			
Hardness (Kp)	7.9			

The above table clearly indicates that a prolongation of release is obtained that is proportional to the percent of hydrophobic coating, by weight.

In order to determine the differences, if any, in dissolution kinetics between a fed state and a fasting state for the series of coated tablets as tested above in Examples 9–12, the same tablets were tested, in vitro, for dissolution rates in a solution containing 30% peanut oil ("fed") to model a gastrointestinal tract with a typical dietary fat load. The control determined the dissolution rates in a solution lacking the fat load ("fasted"). The pH—time protocol (ranging from acid to alkaline to model digestive processes) is set forth below in Table 16, below.

TABLE 16

Fed/Fast Dissolution Protocol

	"Fasted"	"Fed"
Apparatus:	Type III	Type III
Media:	0–1 hr pH 1.5 1–2 hr pH 3.5 2–4 hr pH 5.5 4–12 hr pH 7.5	30% peanut oil
Agitation:	15 cpm	15 cpm
Volume:	250 mL	250 mL

TABLE 17

Fed/Fast Dissolution Results

Time (hrs)	"Fasted" Uncoated	"Fasted" 2%	"Fed" Uncoated	"Fed" 2%
0 (% release)	0.0	0.0	0.0	0.0
1	48.8	15.5	28.8	18.4
2	68.5	28.8	49.8	39.9
4	87.2	49.5	91.9	78.9
6	96.1	65.9	100.0	97.3
8	100.0	80.7	100.0	100.0
12	100.0	100.0	100.0	100.0

As can be appreciated from table 17, the dissolution rates (in vitro) in the presence of 30% peanut oil ("Fed") are not significantly different from the dissolution rates in the absence of the 30% peanut oil ("Fast"), thus demonstrating both the improved control of release rate provided by the 2% ethylcellulose coating and the freedom from significant "Fed/Fast" effects provided by the formulations of the present invention.

Results and Discussion

FIGS. 1 and 2 show in vitro dissolution profiles for the product formulated according to Table 14 and Table 15 (Example 10) i.e., the formulation of Table 14 with a 2% ethylcellulose coating. The mean in vivo plasma profile for the test product is provided in FIG. 3. FIG. 1 shows a dissolution profile of an albuterol containing tablet formulated according to Table 14 and Table 15 (Example 10) as described above. The dissolution profile of FIG. 1 was conducted as a Type II dissolution with a pH change to simulate gastric and enteric passage and stirring at 50 rpm (acid buffer with a pH of 1.5 for time: 0 though 1 hour followed by alkaline buffer with a pH of 7.5 for time: 1 through 12 hours). FIG. 2 shows a dissolution profile of an albuterol containing tablet formulated formulated according to Table 14 and Table 15 as described above and conducted as a Type III dissolution with a pH change to simulate gastric and enteric passage (pH profile as described by Table 16 above) and stirring at 15 rpm. FIG. 3 shows an albuterol plasma profile of provided by ingestion of an albuterol containing tablet formulated formulated according to Table 14 and Table 15 (Example 10): solid circles mark curve of plasma profile in fed subject; open circles mark curve of plasma profile in fasted subjects.

Analysis of the pharmacokinetic parameters C_{max}, T_{max} and AUC_{28} (Table 18) confirms that the tested formulation is an ideal candidate for a 12 hour albuterol formulation. Furthermore, a comparison of the test product in the fed and fasted states show that the test product is not significantly affected by food. A delay of gastric emptying, which is expected in the fed state, accounts for the extended time required to reach the maximum plasma concentration.

TABLE 18

Albuterol Pharmacokinetics

Parameter	TIMERx fasted	TIMERx fed
Cmax		
mean	10.5	10.6
% CV	39.0	31.0
Tmax		
mean	4.5	7.0
% CV	29.0	23.0
AUCInf		
mean	113.4	128.1
% CV	30.0	20.0

Ratios	Cmax	Tmax	AUC Inf
TIMERx fasted:TIMERx fed	0.98	0.64	0.89
TIMERx fed:TIMERx fasted	1.02	1.57	1.13

Confidence Limits	Cmax LL	Cmax UL	AUCInf LL	AUCInf UL
TIMERx fed vs TIMERx fasted	89	124	102	133

TABLE 19

Parameter	TIMERx-fasted	TIMERx-fed
AUC_{∞}	57.3–156.2	75.6–161.1
Cmax	4.6–18.4	6.0–15.9
Tmax	3.0–6.0	3.0–8.0

Parameter	TIMERx-fed
AUC_{∞}	89.9–149.2
Cmax	7.0–11.9
Tmax	3.0–10.0

Conclusion

From the results provided in above examples, it can be seen that the formulations according to the invention provide a controlled release of an active medicament such as albuterol sulfate without any significant differences induced by a "fed/fast" effect due to the presence of food in the gastrointestinal tract. Accordingly, the results provide that the tablets produced according to the invention are suitable for delivering medicaments as an oral solid dosage form over a 24-hour oral period of time.

The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various

modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description. Such modifications are intended to fall within the scope of the claims. Various publications are cited herein, the disclosures of which are incorporated by reference in their entireties.

What is claimed is:

1. A controlled release solid dosage form for oral administration of a therapeutically active medicament to a patient in need thereof, comprising:

a pharmaceutically effective amount of a medicament to be administered to a patient in need of said medicament;

a sustained release excipient comprising a gelling agent; a pharmaceutically acceptable hydrophobic material; and an inert pharmaceutical diluent wherein the ratio of said inert diluent to said gelling agent is from about 1:8 to about 8:1, said dosage form providing a sustained release of said medicament when exposed to an environmental fluid.

2. The controlled release solid dosage form according to claim 1 wherein said inert diluent is selected from the group consisting of pharmaceutically acceptable saccharides, polyhydric alcohols, pre-manufactured direct compression diluents, and mixtures of any of the foregoing.

3. The controlled release solid dosage form according to claim 1, wherein said hydrophobic material is selected from the group consisting of a cellulose ether, a cellulose ester and an alkylcellulose.

4. The controlled release solid dosage form according to claim 1, wherein said hydrophobic material is selected from the group consisting of ethylcellulose, carboxymethylcellulose, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate and a polyvinyl acetate polymer.

5. The controlled release solid dosage form according claim 1, wherein said hydrophobic material is present in an amount ranging from about 25 percent to about 50 percent, by weight, of the solid dosage form.

6. The controlled release solid dosage form according to claim 1, wherein said medicament is a pharmaceutically effective amount of albuterol or a salt or derivative thereof.

7. The controlled release solid dosage form according to claim 1 which is a tablet.

8. The controlled release solid dosage form according to claim 1, which is in granulate form.

9. The controlled release solid dosage form according to claim 8, wherein said granulate is coated with a hydrophobic material to a weight gain from about 1 percent to about 20 percent.

10. The controlled release solid dosage form according to claim 1, wherein the medicament comprises an amount of albuterol equivalent to about 4 mg to about 16 mg of albuterol free base.

11. A method of preparing a controlled release solid dosage form comprising a medicament for oral administration, the method comprising

preparing of a sustained release excipient comprising from about 10 to about 99 percent by weight of a gelling agent, from about 0 to about 89 percent by weight of an inert pharmaceutical diluent, and from about 1 to about 90 percent by weight of a pharmaceutically acceptable hydrophobic material; and

adding a therapeutically effective amount of a medicament to said excipient, such that

a final product is obtained having a ratio of said medicament to said gelling agent from about 1:3 to about 1:8, wherein said formulation provides therapeutically effective blood levels of said medicament for at least 12 hours.

12. The method of claim 11, further comprising compressing said mixture of said sustained release excipient and said medicament into tablets.

13. The method of claim 11, wherein said medicament is albuterol or a salt or derivative thereof.

14. The method of claim 13, further comprising coating the resultant tablets with a hydrophobic coating to a weight gain from about 1 percent to about 20 percent.

15. A method of treating a patient with albuterol comprising:

preparing a sustained release excipient comprising from about 10 to about 99 percent by weight of a gelling agent from about 0 to about 89 percent by weight of an inert pharmaceutical diluent, and from about 1 to 90 percent by weight of a pharmaceutically acceptable hydrophobic material; and

adding an effective amount of albuterol or a salt or derivative thereof to said sustained release excipient, tableting the resultant mixture into tablets such that said tablets have a ratio of albuterol to said gelling agent from about 1:3 to about 1:8, such that a gel matrix is created when said tablet is exposed to gastrointestinal fluid and said tablet provides therapeutically effective blood levels of albuterol for at least 12 hours; and

administering said tablet to a patient on a once-a-day or twice-a-day basis.

16. The method of claim 15, further comprising preparing said formulation such that it provides therapeutically effective blood levels of said medicament for at least 24 hours.

* * * * *

JS 44 (Rev. 11/04)

CIVIL COVER SHEET

The JS 44 civil cover sheet and the information contained herein neither replace nor supplement the filing and service of pleadings or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. (SEE INSTRUCTIONS ON THE REVERSE OF THE FORM.)

I. (a) PLAINTIFFS
Endo Pharmaceuticals Inc. and
Penwest Pharmaceuticals Co.

(b) County of Residence of First Listed Plaintiff _____
(EXCEPT IN U.S. PLAINTIFF CASES)

(c) Attorney's (Firm Name, Address, and Telephone Number)
Jack B. Blumenfeld/Julia Heaney,
MORRIS, NICHOLS, ARSHT & TUNNELL LLP, 1201 North Market Street,
P.O. Box 1347, Wilmington, DE 19899-1347, (302) 658-9200

DEFENDANTS
Impax Laboratories, Inc.

County of Residence of First Listed Defendant _____
(IN U.S. PLAINTIFF CASES ONLY)
NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE LAND INVOLVED.

Attorneys (If Known)

II. BASIS OF JURISDICTION (Place an "X" in One Box Only)

- ☐ 1 U.S. Government Plaintiff
- ☒ 3 Federal Question (U.S. Government Not a Party)
- ☐ 2 U.S. Government Defendant
- ☐ 4 Diversity (Indicate Citizenship of Parties in Item III)

III. CITIZENSHIP OF PRINCIPAL PARTIES (Place an "X" in One Box for Plaintiff and One Box for Defendant)
(For Diversity Cases Only)

	PTF	DEF		PTF	DEF
Citizen of This State	☐ 1	☐ 1	Incorporated *or* Principal Place of Business In This State	☐ 4	☐ 4
Citizen of Another State	☐ 2	☐ 2	Incorporated *and* Principal Place of Business In Another State	☐ 5	☐ 5
Citizen or Subject of a Foreign Country	☐ 3	☐ 3	Foreign Nation	☐ 6	☐ 6

IV. NATURE OF SUIT (Place an "X" in One Box Only)

CONTRACT
- ☐ 110 Insurance
- ☐ 120 Marine
- ☐ 130 Miller Act
- ☐ 140 Negotiable Instrument
- ☐ 150 Recovery of Overpayment & Enforcement of Judgment
- ☐ 151 Medicare Act
- ☐ 152 Recovery of Defaulted Student Loans (Excl. Veterans)
- ☐ 153 Recovery of Overpayment of Veteran's Benefits
- ☐ 160 Stockholders' Suits
- ☐ 190 Other Contract
- ☐ 195 Contract Product Liability
- ☐ 196 Franchise

REAL PROPERTY
- ☐ 210 Land Condemnation
- ☐ 220 Foreclosure
- ☐ 230 Rent Lease & Ejectment
- ☐ 240 Torts to Land
- ☐ 245 Tort Product Liability
- ☐ 290 All Other Real Property

TORTS

PERSONAL INJURY
- ☐ 310 Airplane
- ☐ 315 Airplane Product Liability
- ☐ 320 Assault, Libel & Slander
- ☐ 330 Federal Employers' Liability
- ☐ 340 Marine
- ☐ 345 Marine Product Liability
- ☐ 350 Motor Vehicle
- ☐ 355 Motor Vehicle Product Liability
- ☐ 360 Other Personal Injury

PERSONAL INJURY
- ☐ 362 Personal Injury - Med. Malpractice
- ☐ 365 Personal Injury - Product Liability
- ☐ 368 Asbestos Personal Injury Product Liability

PERSONAL PROPERTY
- ☐ 370 Other Fraud
- ☐ 371 Truth in Lending
- ☐ 380 Other Personal Property Damage
- ☐ 385 Property Damage Product Liability

CIVIL RIGHTS
- ☐ 441 Voting
- ☐ 442 Employment
- ☐ 443 Housing/ Accommodations
- ☐ 444 Welfare
- ☐ 445 Amer. w/Disabilities - Employment
- ☐ 446 Amer. w/Disabilities - Other
- ☐ 440 Other Civil Rights

PRISONER PETITIONS
- ☐ 510 Motions to Vacate Sentence

Habeas Corpus:
- ☐ 530 General
- ☐ 535 Death Penalty
- ☐ 540 Mandamus & Other
- ☐ 550 Civil Rights
- ☐ 555 Prison Condition

FORFEITURE/PENALTY
- ☐ 610 Agriculture
- ☐ 620 Other Food & Drug
- ☐ 625 Drug Related Seizure of Property 21 USC 881
- ☐ 630 Liquor Laws
- ☐ 640 R.R. & Truck
- ☐ 650 Airline Regs.
- ☐ 660 Occupational Safety/Health
- ☐ 690 Other

LABOR
- ☐ 710 Fair Labor Standards Act
- ☐ 720 Labor/Mgmt. Relations
- ☐ 730 Labor/Mgmt.Reporting & Disclosure Act
- ☐ 740 Railway Labor Act
- ☐ 790 Other Labor Litigation
- ☐ 791 Empl. Ret. Inc. Security Act

BANKRUPTCY
- ☐ 422 Appeal 28 USC 158
- ☐ 423 Withdrawal 28 USC 157

PROPERTY RIGHTS
- ☐ 820 Copyrights
- ☒ 830 Patent
- ☐ 840 Trademark

SOCIAL SECURITY
- ☐ 861 HIA (1395ff)
- ☐ 862 Black Lung (923)
- ☐ 863 DIWC/DIWW (405(g))
- ☐ 864 SSID Title XVI
- ☐ 865 RSI (405(g))

FEDERAL TAX SUITS
- ☐ 870 Taxes (U.S. Plaintiff or Defendant)
- ☐ 871 IRS—Third Party 26 USC 7609

OTHER STATUTES
- ☐ 400 State Reapportionment
- ☐ 410 Antitrust
- ☐ 430 Banks and Banking
- ☐ 450 Commerce
- ☐ 460 Deportation
- ☐ 470 Racketeer Influenced and Corrupt Organizations
- ☐ 480 Consumer Credit
- ☐ 490 Cable/Sat TV
- ☐ 810 Selective Service
- ☐ 850 Securities/Commodities/ Exchange
- ☐ 875 Customer Challenge 12 USC 3410
- ☐ 890 Other Statutory Actions
- ☐ 891 Agricultural Acts
- ☐ 892 Economic Stabilization Act
- ☐ 893 Environmental Matters
- ☐ 894 Energy Allocation Act
- ☐ 895 Freedom of Information Act
- ☐ 900Appeal of Fee Determination Under Equal Access to Justice
- ☐ 950 Constitutionality of State Statutes

V. ORIGIN (Place an "X" in One Box Only)
☒ 1 Original Proceeding ☐ 2 Removed from State Court ☐ 3 Remanded from Appellate Court ☐ 4 Reinstated or Reopened ☐ 5 Transferred from another district (specify) ☐ 6 Multidistrict Litigation ☐ 7 Appeal to District Judge from Magistrate Judgment

VI. CAUSE OF ACTION
Cite the U.S. Civil Statute under which you are filing (**Do not cite jurisdictional statutes unless diversity**):
35 U.S.C. § 271
Brief description of cause:
patent infringement

VII. REQUESTED IN COMPLAINT: ☐ CHECK IF THIS IS A **CLASS ACTION** UNDER F.R.C.P. 23 **DEMAND $**
CHECK YES only if demanded in complaint:
JURY DEMAND: ☐ Yes ☒ No

VIII. RELATED CASE(S) IF ANY (See instructions): JUDGE Judicial Vacancy DOCKET NUMBER 07-731

DATE January 25, 2008
SIGNATURE OF ATTORNEY OF RECORD Jack Blumenfeld

FOR OFFICE USE ONLY

RECEIPT # _____ AMOUNT _____ APPLYING IFP _____ JUDGE _____ MAG. JUDGE _____

AO FORM 85 RECEIPT (REV. 9/04)

United States District Court for the District of Delaware

Civil Action No. 08-57

ACKNOWLEDGMENT OF RECEIPT FOR AO FORM 85

NOTICE OF AVAILABILITY OF A UNITED STATES MAGISTRATE JUDGE TO EXERCISE JURISDICTION

I HEREBY ACKNOWLEDGE RECEIPT OF _____ COPIES OF AO FORM 85.

1-25-08
(Date forms issued)

(Signature of Party or their Representative)

Aaron Johnston
(Printed name of Party or their Representative)

Note: Completed receipt will be filed in the Civil Action