US006488963B1

(12) **United States Patent**
McGinity et al.

(10) **Patent No.: US 6,488,963 B1**
(45) **Date of Patent: Dec. 3, 2002**

(54) **HOT-MELT EXTRUDABLE PHARMACEUTICAL FORMULATION**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/260,694**

(22) Filed: **Mar. 2, 1999**

Related U.S. Application Data

(60) Provisional application No. 60/020,623, filed on Jun. 26, 1996.

(51) **Int. Cl.**[7] **A61K 9/10**; A61K 47/34

(52) **U.S. Cl.** **424/486**; 514/953

(58) **Field of Search** 424/484, 486, 424/468, 457, 500, 422; 514/953, 964, 772.7

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(57) **ABSTRACT**

The present invention relates to pharmaceutical formulations comprising a hot-melt extrudable mixture of a therapeutic compound and a high molecular weight poly(ethylene oxide) in an essentially non-film like preparation. In some embodiments, the formulation further comprises poly (ethylene glycol). The present invention also includes efficient methods for hot-melt extruding pharmaceutical formulations in essentially non-film preparations.

6 Claims, 1 Drawing Sheet

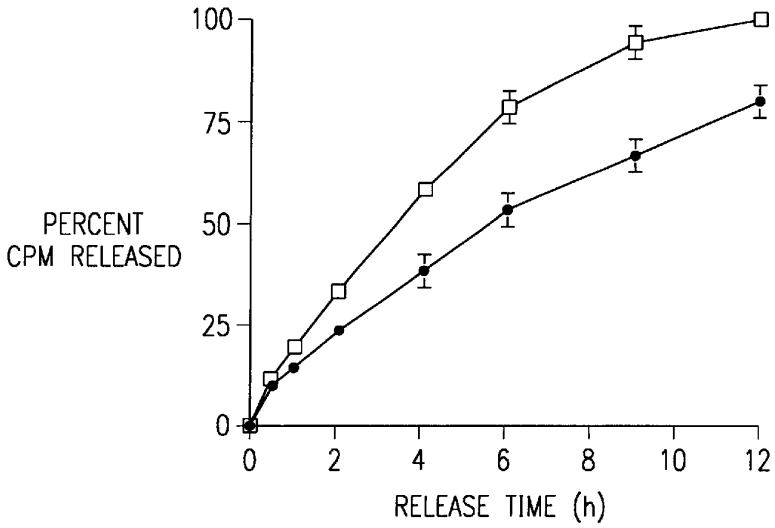


FIG. 1

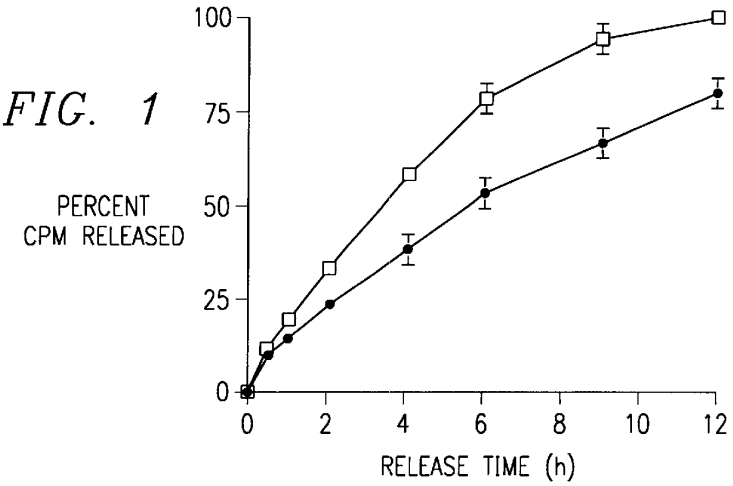


FIG. 2

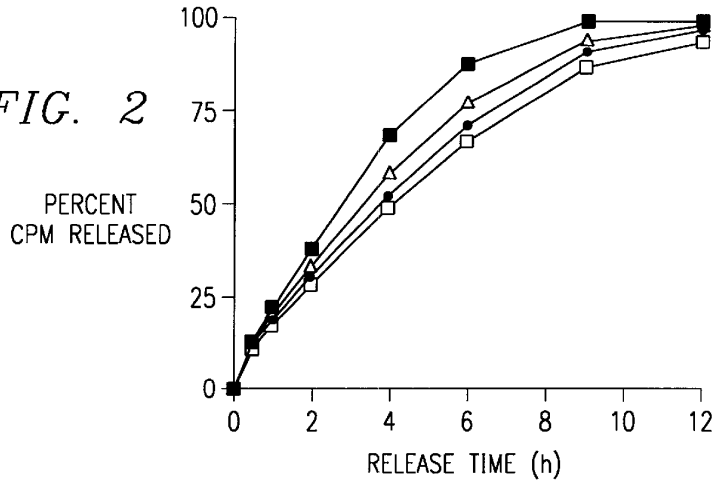
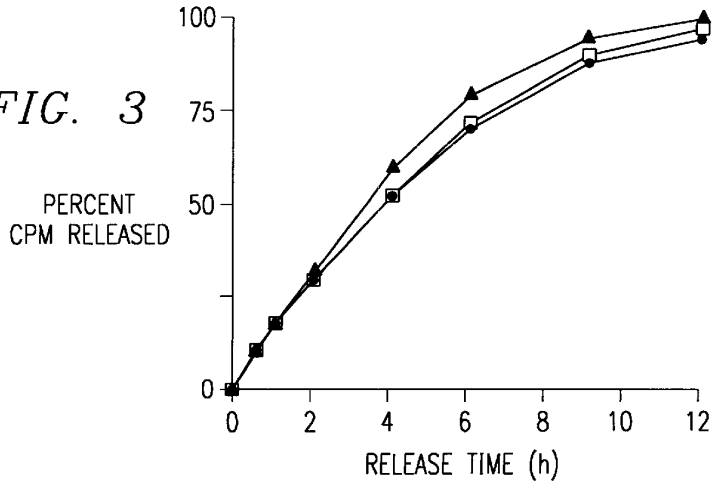


FIG. 3



HOT-MELT EXTRUDABLE PHARMACEUTICAL FORMULATION

The present application claims the benefit of PCT/US 97/11206, filed Jun. 24, 1997 which claims the benefit of of U.S. Pat. No. 60/202,623, filed Jun. 26, 1996.

FIELD OF THE INVENTION

The present invention relates to the field of poly(ethylene oxide) (PEO) based hot-melt extrudable pharmaceutical formulations that are not film-like preparations. The invention relates more specifically to non-film formulations which have been prepared by hot-melt extrusion of mixtures containing high molecular weight PEO and a therapeutic compound. The present formulations cited relate to the field of non-film controlled-release drug delivery preparations, as they provide preparations useful for providing controlled drug delivery.

BACKGROUND OF THE INVENTION

Hot-melt extrusion as a method for producing polymer-based sustained-release pharmaceutical formulations, such as with derivatized cellulose, poly(methacrylate) derivative, poly(ethylene-co-vinyl acetate), poly(ethylene), poly(vinyl acetate-co-methacrylic acid), epoxy resins and caprolactones is known. These methods do not teach the use of poly(ethylene oxide). Hot-melt extrusion as a method for producing poly(ethylene glycol) based pharmaceutical formulations comprising an "erosion rate modifier" has been disclosed. These particular compositions have, been described as further containing trace amounts of high molecular weight PEO, and the hot-melt extrusion process used to prepare them requires several steps. These particular compositions are also based upon a low melting matrix drug delivery system, and are predominantly for transdermal rather than oral administration.

Alderman et al. (EP 0177893 A2) relates to a thermoformable sustained release matrix for the prolonged release of an active organic material of a thermoplastic water-soluble gel having a water-soluble hydroxypropylmethylcellulose a plasticizer and an active organic material dispersed in said gel. The plasticizer may be a low molecular weight poly(ethylene glycol).

Mooney et al. (EP 0598606 A1) relates to compositions of a thermoplastic water-soluble polymer; a water-soluble polymer derived from a carboxylic acid or a pharmaceutically acceptable salt thereof; and a plasticizer. The thermoplastic water-soluble polymer may be poly(ethylene oxide), and the compositions can be prepared as hot-melts.

These various methods require several components to achieve a desired controlled release profile. Various technical disadvantages exist for each of them that creates a significant potential for loss in pharmacological activity of the included therapeutic agent.

Hot-melt extrusion processes in the art have generally required elevated temperatures. Elevated temperatures in processing have been recognized by those in the pharmaceutical formulation arts to cause decomposition of the therapeutic agent or polymer matrix. The process of hot-melt extrusion of a therapeutic agent and a high molecular weight polymer PEO has been primarily confined to the preparation of film-like preparations.

Although various hot-melt extrusion pharmaceutical formulations and methods for making them are known, development of simple formulations for drug delivery and methods for producing them remains a problem in the pharmaceutical industry.

There continues to exist a need in the art to develop controlled-release pharmaceutical formulations, as well as improved, more efficient methods for their preparation.

SUMMARY OF THE INVENTION

In one aspect of the present invention comprises a hot-melt extrudable controlled-release pharmaceutical formulation. This formulation in some embodiments is further described as comprising an effective amount of a therapeutic compound and a high molecular weight poly(ethylene oxide) homopolymer.

It is an object of the present invention to provide a hot-melt extrudable controlled-release pharmaceutical formulation comprising high molecular weight poly(ethylene oxide) and an effective amount of a therapeutic compound.

It is another object of the present invention to provide a hot-melt extrudable controlled-release pharmaceutical formulation comprising high molecular weight poly(ethylene oxide), an effective amount of a therapeutic compound and a plasticizer. By way of example, the plasticizer may comprise poly(ethylene glycol).

It is contemplated and within the scope of the present invention that the pharmaceutical formulation may be administered to a subject by any of a variety of methods known to the artisan. In some embodiments, the formulations are designed to be particularly well suited for oral delivery.

It is also contemplated and within the scope of the present invention that the pharmaceutical formulation may comprise other components.

The methods provided on some aspects of the present invention may comprise a single step or multiple steps for preparing the pharmaceutical formulation.

It is also contemplated that the particular combinations of therapeutic compound and PEO (of given molecular weight) will result in various formulations, each possessing a particular combination of properties. Some combinations may be better suited for particular types or classes of therapeutic compounds while another combination may be better suited for other types or classes of therapeutic compounds. Methods for the selection of a particular therapeutic compound/PEO (of a given molecular weight) combination are also provided as part of the present invention.

Some embodiments of the invention comprise a plasticizer. The particular combinations of therapeutic compound/plasticizer/PEO (of given molecular weight) may be selected to provide a desired combination of physical properties. Some particular combination of these ingredients may accordingly be better suited for a particular therapeutic compound while another combination may be better suited for a different therapeutic compound. Methods for the selection of a particular therapeutic compound/plasticizer/ PEO (of a given molecular weight) combination are also disclosed as part of the present invention.

Another aspect of the invention provides a process for preparing a controlled-release pharmaceutical formulation comprising a therapeutic compound and a high molecular weight poly(ethylene oxide) homopolymer. The process in some embodiments comprises hot-melt extruding a pharmaceutical formulation. The pharmaceutical formulation comprises a therapeutic compound and a high molecular weight poly(ethylene oxide) homopolymer.

Other embodiments of the present controlled-release pharmaceutical formulations comprise a therapeutic com-

pound and a high molecular weight poly(ethylene oxide) homopolymer, where the formulation is prepared by hot-melt extruding a mixture of its components.

In some embodiments, the pharmaceutical formulations of the invention may contain more than one therapeutic compound, as well as other non-therapeutic compound components. The pharmaceutical formulations may be formulated to provide sustained, extended, controlled, timed or other equivalent release dosage forms.

Other features, advantages and embodiments of the invention will be apparent to those skilled in the art from the following description, accompanying data and appended claims.

As used in the description of the present invention, the term "effective amount" is defined as an amount or dose sufficient to elicit a physiological response in vitro or in vivo

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** Influence of molecular weight of polyethylene oxide on the release of chlorpheniramine maleate from matrix tablets using USP method II at 37° C. and 100 rpm in 900 ml purified water.

1A=● 6% CPM, 20% PEG (3,350), PEO (7.0 m)

1B=□ 6% CPM, 20% PEG (3,350), PEO (1.0 m)

FIG. **2** Influence of polyethylene glycol (3,350) on the release of chlorpheniramine maleate from matrix tablets using USP method II at 37° C. and 100 rpm in 900 ml purified water.

2A=□ 6% CPM, 0% PEG, (3,350) and 94% PEO (1.0 m)

2B=● 6% CPM, 6% PEG, (3,350) and 88% PEO (1.0 m)

2C=▼ 6% CPM, 20% PEG, (3,350) and 74% PEO (1.0 m)

2D=■ 6% CPM, 40% PEG, (3,350) and 54% PEO (1.0 m)

FIG. **3** Influence of drug loading on the release of chlorpheniramine maleate from matrix tablets using USP method II at 37° C. and 100 rpm in 900 ml purified water

3A=● 6% CPM, 94% PEO (1.0 m)

3B=□ CPM, 88% PEO (1.0 m)

3C=▼ 6% CPM, 80% PEO (1.0 m)

DETAILED DESCRIPTION OF THE INVENTION

The use of hot-melt extrudable high molecular weight PEO for the preparation of pharmaceutical formulations has several advantages. The one-step process presented as part of the invention also provides therapeutic formulations with minimal thermal degradation of either the therapeutic compound or the PEO.

Poly(ethylene oxide)

As used herein, the term "poly(ethylene oxide)" includes all polymers which are comprised of repeating units of ethylene oxide. High molecular weight PEO is generally described as having an average molecular weight of from about 1,000,000 to about 10,000,000. The poly(ethylene oxides) comprising the present formulation are available commercially from sources such as Union Carbide Corporation. The amount of PEO used in the formulation will depend upon its average molecular weight, physical properties, interaction with other components of the formulation, ability to solubilize the therapeutic compound, ease of formulation extrudability, the pharmacological activity of the therapeutic compound, the indication being treated, the targeted dosing regimen, the projected method of administration, the integrity or stability of the final formulation, desired release profile or other such reasons. Generally, PEO content will not exceed about 99% wt. of the formulation.

The average molecular weight of the PEO employed will generally affect the processing conditions selected. A very high average molecular weight PEO, such as greater than about 5,000,000, will generally require higher processing temperature, torque and/or pressure than a PEO having an average molecular weight less than or equal to about 5,000,000. Antioxidants and/or plasticizers may be advantageously employed when preparing the formulation of the invention. Thus, although not required to obtain a hot-melt extrudable formulation, addition of one or more plasticizers and/or antioxidants to the formulation will generally facilitate the preparation process.

As shown in FIG. **1**, PEO average molecular weight also affects the release profile of the formulation. Generally, increasing average molecular weight decreases the release rate of the therapeutic compound.

Plasticizers

As used herein, the term "plasticizer" includes all compounds capable of plasticizing high molecular weight PEO. The plasticizer should be able to lower the glass transition temperature or softening point of the PEO in order to allow for lower processing temperature, extruder torque and pressure during the hot-melt extrusion process. Plasticizers, such as PEG and low molecular weight PEO, generally broaden the average molecular weight of the PEO thereby lowering its glass transition temperature or softening point. Plasticizers also generally reduce the viscosity of a polymer melt thereby allowing for lower processing temperature and extruder torque during hot-melt extrusion. It is possible the plasticizer will impart some particularly advantageous physical properties to the pharmaceutical formulation of PEO.

As used herein, the term "low molecular weight PEO" is intended to mean poly(ethylene oxide) homopolymer having an average molecular weight less than about 500,000.

Plasticizers are not required in order to practice the invention. Their addition to the formulation is contemplated as being within the scope of the invention. Plasticizers are advantageously included when very high molecular weight PEO, such as greater than about 5,000,000, is employed.

As shown in FIG. **2**, it is possible that including a plasticizer in the present formulation will alter its release profile. Generally, increasing the amount of plasticizer present will increase the release rate of the therapeutic compound.

It is contemplated and within the scope of the invention, that a combination of plasticizers may be used in the present formulation. One advantageous combination is that comprised of poly(ethylene glycol) and low molecular weight poly(ethylene oxide).

The plasticizer employed herein may be a solvent for the PEO at the temperature where the formulation is prepared. Such plasticizer, when mixed with the PEO above a characteristic temperature at which the PEO becomes soluble therein, may dissolve the PEO. Upon cooling, the mixture forms a matrix having especially useful properties for use in a sustained release dosage form.

Plasticizers useful in the invention include, by way of example and without limitation, low molecular weight polymners, oligomers, copolymers, oils, small organic molecules, low molecular weight polyols having aliphatic hydroxyls, ester-type plasticizers, glycol ethers, poly(propylene glycol), multi-block polymers, single block polymers, low molecular weight poly(ethylene oxide) (average molecular weight less than about 500,000) and poly(ethylene glycol).

Such plasticizers may be ethylene glycol, propylene glycol, 1.2-butylene glycol, 2,3-butylene glycol, styrene

glycol, diethylene glycol, triethylene glycol, tetraethylene glycol and other poly(ethylene glycol) compounds, monopropylene glycol monoisopropyl ether, propylene glycol monoethyl ether, ethylene glycol monoethyl ether, diethylene glycol monoethyl ether, sorbitol lactate, ethyl lactate, butyl lactate, ethyl glycolate, triethyl citrate, acetyl triethyl citrate, tributyl citrate and allyl glycolate. All such plasticizers are commercially available from sources such as Aldrich or Sigma Chemical Co.

The PEG based plasticizers are available commercially or may be made by a variety of methods, such as disclosed in *Poly (ethylene glycol) Chemistry: Biotechnical and Biomedical Applications* (J. M. Harris, Ed.; Plenum Press, NY) the teachings of which are hereby incorporated by reference.

The amount of plasticizer used in the formulation will depend upon its composition, physical properties, effect upon the PEO, interaction with other components of the formulation, ability to solubilize the therapeutic compound or other factors to be considered in the preparation of pharmaceutical formulations. The amount of plasticizer present in the formulation affects its properties. By way of example, when the plasticizer is PEG, its content will generally not exceed about 40% wt. of the formulation.

When present, the relative amount of plasticizer used may be expressed by the ratio high molecular weight PEO % wt.: plasticizer % wt., and will generally fall in the range of about 100:0 to about 60:40. The amount of plasticizer will generally not exceed the amount of PEO.

Therapeutic Preparations

As used herein, the term "therapeutic compound" is taken to mean an organic chemical substance having desired beneficial and therapeutic effects in mammals. Such compounds are generally classified as pharmaceuticals or biologicals. As long as the therapeutic compound can diffuse from the formulation when exposed to a biological fluid, its structure is not especially critical.

The therapeutic compounds contemplated within the scope of the invention include hydrophobic, hydrophilic and amphiphilic compounds. They may be in their free acid, free base, or pharmaceutically acceptable salt forms. They may be derivatives or prodrugs of a given pharmaceutical.

It will be appreciated that certain therapeutic compounds used in the present invention may contain an asymmetrically substituted carbon atom, and may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis, from optically active starting materials. Also, it is realized that cis and trans geometric isomers of the therapeutic compounds are described and may be isolated as a mixture of isomers or as separated isomeric forms. All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomer form is specifically indicated.

It is not necessary for the therapeutic compound to be soluble in any given formulation component. The therapeutic compound may be either dissolved, partially dissolved or suspended in the polymer matrix of the formulation. It is necessary for the therapeuticcompound to be stable during the hot-melt extrusion process conditions used. By stable, it is meant that a significant portion of the therapeutic compound will not be significantly degraded or decomposed throughout the hot-melt extrusion process.

The therapeutic compounds which may be hot-melt extruded in the formulation of the invention may be used for treating indications such as, by way of example and without limitation, inflammation, gout, hypercholesterolemia, microbial infection, AIDS, tuberculosis, fungal infection, amoebic infection, parasitic infection, cancer, tumor, organ rejection, diabetes, heart failure, arthritis, asthma, pain, congestion, urinary tract infections, vaginal infection, seizure related disorder, depression, psychosis, convulsion, diabetes, blood coagulation, hypertension and birth control.

The following therapeutic compounds can be administered by the pharmaceutical formulation of the present invention:

(1) analgesics such as aspirin, acetaminophen, deflunisal and the like;

(2) anesthetics such as lidocaine, procaine, benzocaine, xylocaine and the like;

(3) antiarthritics and anti-inflammatory agents such as phenylbutazone, indomethacin, sulindac, dexamethasone, ibuprofen, allopurinol, oxyphenbutazone probenecid, cortisone, hydrocortisone, betamethasone, dexamethasone, fluocortolone, prednisolone, triamncinolone, indomethacin, sulindac and its salts and corresponding sulfide and the like;

(4) antiasthma drugs such as theophylline, ephedrine, beclomethasone dipropionate, epinephrine and the like;

(5) urinary tract disinfectives such as sulfarmethoxazole, trimethoprim, nitrofurantoin, norfloxicin and the like;

(6) anticoagulants such as heparin, bishydroxy coumarin, warfarin and the like;

(7) anticonvulsants such as diphenylhydantoin, diazepam and the like;

(8) antidepressants such as amitriptyline, chlordiazepoxide, perphenazine, protriptyline, imipramine, doxepin and the like;

(9) agents useful in the treatment of diabetics and regulation of blood sugar, such as insulin, tolbutamide tolazamide, somatotropin, acetohexamide, chlorpropamide and the like;

(10) antineoplastics such as adriamycin, fluouracil, methotrexate, asparaginase and the like;

(11) antipsychotics such as prochlorperazine, lithium carbonate, lithium citrate, thioridazine, molindone, fluphenazine, trifluoperazine, perphenazine, amitriptyline, triflupromazine and the like;

(12) antihypertensives such as spironolactone, methyldopa, hydralazine, clonidine, chlorothiazide, deserpidine, timolol, propranolol, metaprotol, prazosin hydrochloride, reserpine and the like;

(13) muscle relaxants such as mephalan, danbrolene, cyclobenzaprine, methocarbarnol, diazepam, succinoyl chloride and the like;

(14) antiprotozoals such as chloramphenicol, chloroquine, trimethoprim and sulfamethoxazole;

(15) spermicidals such as nonoxynol;

(16) antibacterial substances such as beta-lactam antibiotics, tetracyclines, chloramphenicol, neomycin, cefoxitin, thienamycin, gramicidin, bacitracin, sulfonamides, aminoglycoside antibiotics, tobramycin, nitrofurazone, nalidixic acid and analogs and the antimicrobial combination of fludalanine/pentizidone;

(17) antihistamines and decongestants such as perilamine, chlorpheniramine, tetrahydrozoline and antazoline;

(18) antiparasitic compounds such as ivermectin; and

(19) antiviral compounds such as acyclovir and interferon.

For treatment of vaginal and urethral conditions requiring antiftungal, amoebicidal, trichomonacidal agents or

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