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(54) TIMED, SUSTAINED RELEASE SYSTEMS FOR PROPRANOLOL

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(57) ABSTRACT

A unit dosage form, such as a capsule or the like for delivering drugs into the body in a circadian release fashion, is comprising of one or more populations of propranolol-containing particles (beads, pellets, granules, etc.). Each bead population exhibits a pre-designed rapid or sustained release profile with or without a predetermined lag time of 3 to 5 hours. Such a circadian rhythm release cardiovascular drug delivery system is designed to provide a plasma concentration—time profile, which varies according to physiological need during the day, i.e., mimicking the circadian rhythm and severity/manifestation of a cardiovascular disease, predicted based on pharmaco-kinetic and pharmaco-dynamic considerations and in vitro/in vivo correlations.

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Serum Levels of Propranolol after 8:00 PM daily dose of Propranolol Hydrochloride MTSR Capsules, 160 mg (Simulated) and Systolic Blood Pressure

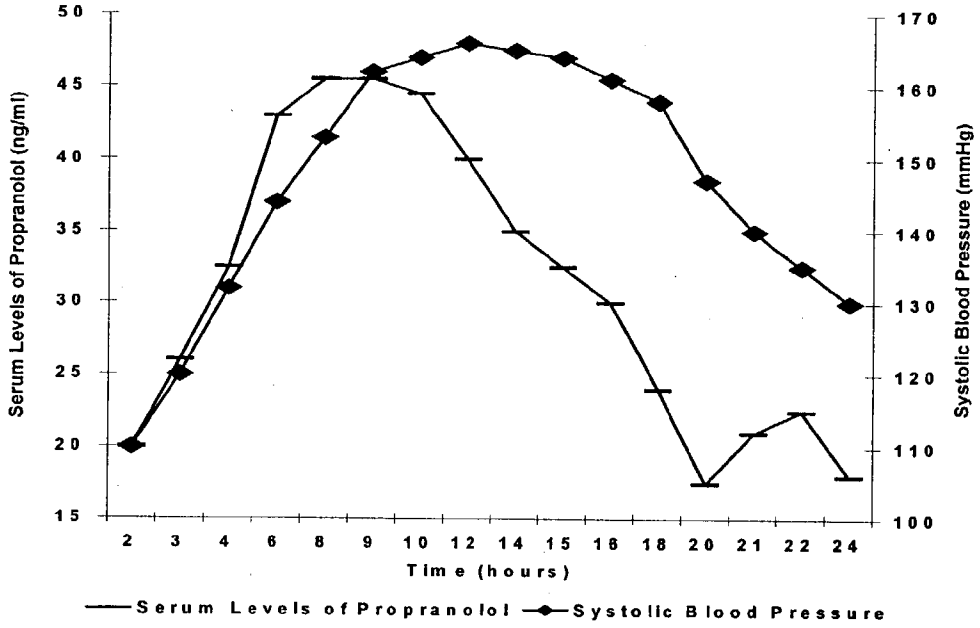

Fig. 1

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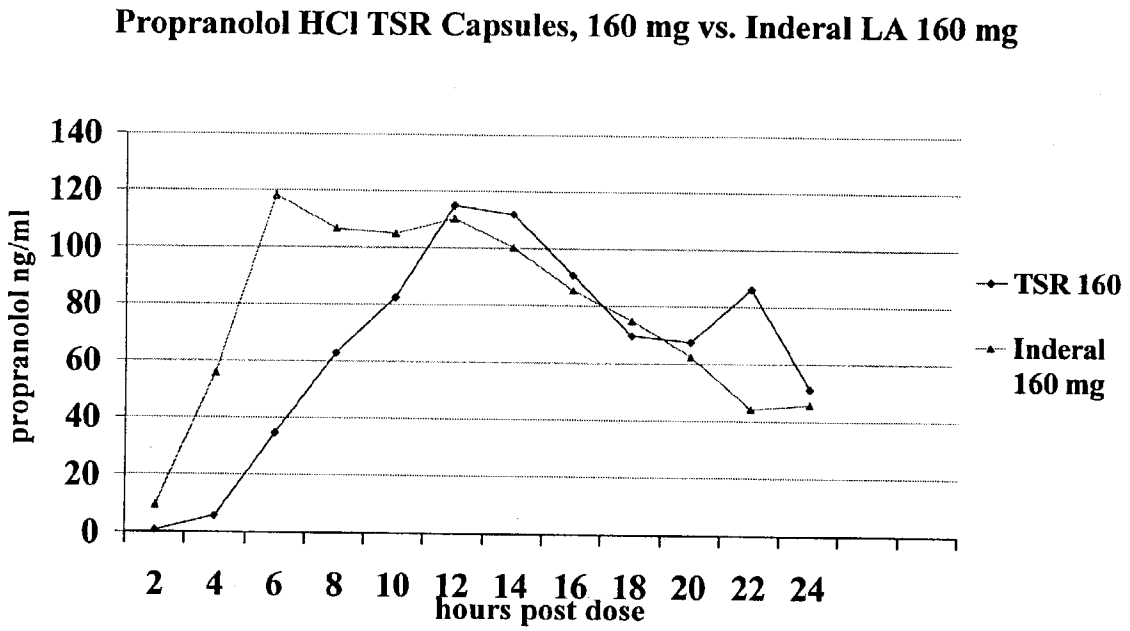

Fig. 2

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TIMED, SUSTAINED RELEASE SYSTEMS FOR PROPRANOLOL

TECHNICAL FIELD

[0001] A major objective of chronotherapy for cardiovascular diseases is to deliver the drug in higher concentrations during the time of greatest need, typically during the early morning hours, and in lesser concentrations when the need is less, such as during the late evening and early sleep hours. This can be accomplished by administration of the release dosage form of the present invention, which relates to a controlled absorption of propranolol from dosage forms. In particular, the present invention relates to a unit dosage form of an assembly of one or more bead populations, each of which is designed to release one or more therapeutic agents as a rapid or sustained release pulse after a predetermined delay ("time-controlled" drug delivery instead of "rate-controlled") with resulting plasma concentration(s) of propranolol varying in a circadian rhythm fashion following administration of a single dosage form at bedtime, thereby minimizing potential risks of a stroke and/or heart attack and enhancing patient compliance and therapeutic efficacy, while reducing cost of treatment.

BACKGROUND OF THE INVENTION

[0002] Many therapeutic agents are most effective when made available at a constant rate at or near the absorption site. The absorption of therapeutic agents thus made available generally results in desired plasma concentrations leading to maximum efficacy and minimum toxic side effects. Much effort has been devoted to developing sophisticated drug delivery systems, such as osmotic devices, for oral application. However, there are instances where maintaining a constant blood level of a drug is not desirable. For example, a "position-controlled" drug delivery system (e.g., treatment of colon disease or use of colon as an absorption site for peptide and protein based products) may prove to be more efficacious. A pulsatile delivery system is capable of providing one or more immediate release pulses at predetermined time points after a controlled lag time or at specific sites. However, there are only a few such orally applicable pulsatile release systems due to the potential limitation of the size or materials used for dosage forms. Ishino et al. disclose a dry-coated tablet form in Chemical Pharm. Bull. Vol. 40 (11), 3036-041 (1992). U.S. Pat. No. 4,851,229 to Magruder et al., U.S. Pat. No. 5,011,692 to Fujioka et al., U.S. Pat. No. 5,017,381 to Maruyama et al., U.S. Pat. No. 5,229,135 to Philippon et al., and U.S. Pat. No. 5,840,329 to Bai disclose preparation of pulsatile release systems. Some other devices are disclosed in U.S. Pat. No. 4,871,549 to Ueda et al. and U.S. Pat. Nos. 5,260,068; 5,260,069; and 5,508,040 to Chen. U.S. Pat. Nos. 5,229,135 and 5,567,441 both to Chen disclose a pulsatile release system consisting of pellets coated with delayed release or water insoluble polymeric membranes incorporating hydrophobic water insoluble agents or enteric polymers to alter membrane permeability. U.S. Pat. No. 5,837,284 to Mehta et al. discloses a dosage form which provides an immediate release dose of methylphenidate upon oral administration, followed by one or more additional doses spread over several hours.

[0003] The incidence of many cardiovascular diseases varies predictably in time over 24 hours, i.e., in a circadian rhythm fashion (See, e.g., Y. A. Anwar and W. B. White, *Chronotherapeutics for Cardiovascular Disease*, Drugs 1998, 55, pp 631-643, which is incorporated herein by reference). For example, a rapid increase in both acute myocardial infarction and systolic blood pressure has been reported in the well controlled studies on actual patients. In such cases, administration of a different kind of unit dosage form which delivers the drug in higher concentrations during the time of greatest need, typically during the early morning hours, and in lesser concentrations when the need is less, such as during late evening and early sleep hours. Commonly assigned and co-pending U.S. application Ser. No. 09/778,645, filed Feb. 7, 2001, which is incorporated in its entirety, discloses a pulsatile release system which includes a combination of two or three pellet populations, each with a well defined release profile. In accordance with the present invention, a plasma profile is obtained which varies in a circadian rhythm fashion following administration of the novel dosage form.

[0004] Propranolol [1-(isopropyl amino)-3-(1-naphthyloxy)-2-propanol] is a beta-adrenergic blocking agent and as such is a competitive inhibitor of the effects of catecholamines at beta-adrenergic receptor sites. The principal effect of propranolol is to reduce cardiac activity by diminishing or preventing beta-adrenergic stimulation. By reducing the rate and force of contraction of the heart, and decreasing the rate of conduction of impulses through the conducting system, the response of the heart to stress and exercise is reduced. These properties are used in the treatment of angina in an effort to reduce the oxygen consumption and increase the exercise tolerance of the heart. Propranolol is also used in the treatment of cardiac arrhythmias to block adrenergic stimulation of cardiac pacemaker potentials. Propranolol is also beneficial in the long term treatment of hypertension. Other uses of propranolol are in the treatment of migraine and anxiety.

[0005] Propranolol is normally administered as propranolol hydrochloride tablets.

SUMMARY OF THE INVENTION

[0006] The present invention provides a timed, sustained release multi-particulate dosage form comprising a propranolol core having a first membrane of a sustained release polymer and a second membrane of a mixture of water insoluble polymer and an enteric polymer (2^{nd} or outer coating), wherein the water insoluble polymer and the enteric polymer may be present at a weight ratio of from 10:1 to 1:2,and the total weight of the coatings is 10 to 60 weight % based on the total weight of the coated beads. In some cases depending on the type of drug release profile needed, an immediate release component may be included to provide a modified, timed, sustained release dosage form. When administered at bedtime, the dosage form comprising one or more bead populations delivers the drug in lesser concentrations during the time of least need, for example, during late evening and early sleep hours, and in higher concentrations during the time of greatest need, for example, during the early morning hours.

BRIEF DESCRIPTION OF THE FIGURES

[0007] The invention will be described in further detail with reference to the accompanying figures wherein:

[0008] **FIG. 1** shows simulated plasma level of propranolol hydrochloride following oral administration at about

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8:00 PM of one 160 mg modified, timed, sustained release (20 mg immediate release (IR) Beads/140 mg timed, sustained release (TSR) Beads) capsule versus systolic blood pressure.

[0009] **FIG. 2** shows plasma levels of propranolol following oral dosing at about 10:00 PM of one timed, sustained release (TSR) capsule, 160 mg versus one Inderal LA 160 mg.

DETAILED DESCRIPTION OF THE INVENTION

[0010] The active core of the novel dosage form of the present invention may comprise an inert particle or an acidic or alkaline buffer crystal, which is coated with a propranolol-containing film-forming formulation and preferably a water-soluble film forming composition to form a water-soluble/dispersible particle. Alternatively, the active core may be prepared by granulating and milling and/or by extrusion and spheronization of a polymer composition containing propranolol. Generally, the individual polymeric coating on the active core will be from 1 to 50% based on the weight of the coated particle. Those skilled in the art will be able to select an appropriate amount of propranolol for coating onto or incorporating into the core to achieve the desired dosage. In one embodiment, the inactive core may be a sugar sphere, a buffer crystal or an encapsulated buffer crystal, such as calcium carbonate, sodium bicarbonate, fumaric acid, tartaric acid, etc. Buffer crystals are useful to alter the microenvironment.

[0011] In accordance with one embodiment of the present invention, the water soluble/dispersible drug-containing particle is first coated with a water insoluble polymer (1^{st} or inner coating), and further coated with a mixture of a water insoluble polymer and an enteric polymer (2^{nd} or outer coating). The water insoluble polymer and enteric polymer may be present at a weight ratio of from 10:1 to 1:2, more preferably 2:1 to 1:1, and the total weight of the coatings is 10 to 60 weight % based on the total weight of the coated beads. The polymeric coatings typically contain plasticizers and may be applied from aqueous and/or solvent based systems.

[0012] The composition of the outer layer and the individual weights of the inner and outer layers of the polymeric membrane are optimized for achieving desired drug release profiles. The unit dosage form according to certain embodiments of the present invention may comprise an immediate release bead population which provides an immediate release component of propranolol to act as a bolus dose.

[0013] The invention also provides a method of making a timed, sustained release dosage form comprising the steps of:

[0014] 1. preparing an active-containing core by coating an inert particle such as a non-pareil seed, an acidic buffer crystal or an alkaline buffer crystal, with propranolol and polymeric binder or by granulation and milling or by extrusion/spheronization to form an immediate release (IR) bead;

[0015] 2. coating the core with a plasticized solution or suspension of a water insoluble polymer to form sustained release (SR) coated drug particle;

[0016] 3. coating the SR coated particle with a mixture of plasticized water insoluble and enteric polymers to form a Timed Sustained Release (TSR) coated drug particle; and filling capsules with TSR particles to produce Timed, Sustained Release (TSR) capsules.

[0017] The release profile for TSR beads can be determined according to the following procedure:

[0018] Dissolution testing is conducted with a USP Apparatus 2 (Paddles at 50 rpm) using a two-stage dissolution medium (first 2 hours in 700 mL 0.1N HCl at 37° C. followed by dissolution at pH=6.8 obtained by the addition of 200 mL of pH modifier). Drug release with time is determined by HPLC on samples pulled at selected intervals.

[0019] The TSR Beads prepared in accordance with present invention release not more than 20%, more preferably not more than 10%, and most preferably not more than 5% in 2 hours, about 5-35%, more preferably about 5-25%, and most preferably about 5-15% in 4 hours, about 10-60%, more preferably about 20-45%, and most preferably about 25-35% in 6 hours, about 40-90%, more preferable about 50-80%, and most preferably about 55-70% in 10 hours, and not less than 60%, more preferably not less than 70%, and most preferably not less than 75% in 16 hours.

[0020] In accordance with the present invention, the desired release properties are obtained as a result of the different characteristics of the two coating layers. The inner layer membrane provides sustained or extended drug release over several hours, while the second or outer membrane provides a lag time of three to four hours. Typical release profiles for SR beads (ethylcellulose coated drug particle) and TSR beads when tested by the two-stage dissolution medium are provided in the following table:

	(% Propanolol Released)	
Time	SR Beads	TSR Beads
1 hr	11.2	0.0
2 hr	32.1	0.1
3 hr	39.8	1.1
4 hr	52.3	8.6
5 hr	62.3	18.3
6 hr	69.2	27.4
8 hr	79.4	44.5
10 hr	84.6	58.4
12 hr	90.0	68.8
16 hr	95.6	90.0

[0021] It is also possible that the TSR Capsule may optionally also contain a population of Immediate Release (IR) beads or particles to provide an immediate release component of active to act as a bolus dose in addition to the timed, sustained release of active provided by the TSR beads. These dosage forms provide a Modified Timed Sustained Release (MTSR) profile.

[0022] An aqueous or a pharmaceutically acceptable solvent medium may be used for preparing drug containing core particles. The type of film forming binder that is used to bind propranolol to the inert sugar sphere is not critical but usually water-soluble, alcohol-soluble or acetone/water

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