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Role of a novel transdermal patch for both antihypertensive and antiparkinsonism activity

Shibanjan Paul Roy, Kamal Deka and Shyam Prakash Rai

Abstract
The present invention is generally directed to matrix type transdermal patches for treating hypertension and Parkinson's disease. The present invention comprises of rasagiline mesylate and prazosin hydrochloride prepared by using different ratios of Eudragit RL 400 and hydoxy propyl methyl cellulose. Effect of protease granuleson permeation of rasagiline and prazosin analyzed. The patch so formed is nonirritant to the skin and possess maximum permeability. The present invention also relates to the method of producing the same. The transdermal patch shows 50% and 80% drug release for rasagiline mesylate and prazosin hydrochloride respectively in 250 hours. In this research total works done under the guidance of Guide-Mr. Shibanjan Paul Roy. Mr. Kamal Deka and Mr. Shyam Prakash Rai performed for the practical works and others work and note the reading.

Keywords: Novel transdermal patch, both antihypertensive, antiparkinsonism activity

Introduction

Field of invention

The present invention relates to an antihypertensive formulation of transdermal patch. The invention also treats Parkinson's disease.

Background of the invention

It has been shown that transdermal route of administration is not subjected to the hepatic first pass effect which result in the required systemic bioavailability of the drug. However, the success of a transdermal drug delivery system (TDDS) depends on the ability of the drug to penetrate the skin in sufficient quantities to maintain therapeutic levels. Several methods have been reported in the literature to enhance the drug penetration across biological membranes. For many therapeutic agents, the desired effect may not be possible without the use of penetration enhancers. An ideal enhancer should be pharmacologically inactive, nonirritant, and should not damage the skin irreversibly. Many of the chemical enhancers such as dimethyl sulfoxide, surfactants, alcohols, and urea and its derivatives have been screened as penetration enhancers. The adverse effects of some of these enhancers restrict their use widely. Currently, there has been an upsurge in the use of naturally occurring chemicals such as terpenes which are isolated from natural essential oils and are safe and non-irritating penetration enhancers. d-limonene, a cyclic terpene is free from toxic effects and has been used as a penetration enhancer in the transdermal delivery of several drugs. The use of Eudragit RL100 (ERL) and hydroxypropyl methyl cellulose (HPMC) in preparation of matrix patches has been reported In reservoir type of system the drug is in polymer coating and release through rate controlling polymeric membrane. Drug is either in solution or in suspension and separated by adhesive layer. It has backing layer and follows zero order kinetics. It is generally of 3 types: injectable; implant; hydrogel. Drugs should fulfil requirements to be incorporated in a reservoir: high first pass metabolism; the size of the drug molecule – only small molecules can penetrate the skin – typically less than 500 Daltons; the lipophilicity of the drug will determine how readily the drug is absorbed. The drug's salt form also determines how quickly it can be absorbed into the skin.The dosage will depend on the duration of time the patch will be worn. Not only must the active ingredient in the drug be suitable to skin, but it can't be at a level where it prohibits the actual manufacture of the patch itself.

Objects of the invention

Some of the objects of the present disclosure, which at least one embodiment herein satisfies, are as follows:

It is an object of the present disclosure to provide a matrix type transdermal drug delivery system of rasagiline mesylate and prazosin hydrochloride. The drugs rasagiline mesylate and prazosin hydrochloride are in 0.3:0.7 ratio.
Another object of the present disclosure is to provide an antihypertensive and antiparkinsonian formulation of transdermal patch.
Another object of the present disclosure is to provide formulate and evaluate a transdermal patch of an antihypertensive drug by using different grades of polymers.
Another object of the present disclosure is to provide an anti-hypertensive transdermal patch having high skin permeation and reduce the amount of drug required due to synergistic action.
Still another object of the present disclosure is to provide transdermal patch causing no skin irritation.
Yet another object of the present disclosure is to provide matrix transdermal patches containing rasagiline and prazosin prepared using different ratios of Eudragit RL100 and hydroxy propyl methyl cellulose.
One more object of the present invention is to provide matrix type transdermal patch for parkinsonism patients to make it easy for them to be on treatment and in spite of physical constrains to take medicine due to shaky hand movement.

Summary of the invention

The following presents a simplified summary of the invention in order to provide a basic understanding of some aspects of the invention. This summary is not an extensive overview of the present invention. It is not intended to identify the key/critical elements of the invention or to delineate the scope of the invention. Its sole purpose is to present some concept of the invention in a simplified form as a prelude to a more detailed description of the invention presented
The present invention is generally directed to matrix type transdermal patches for treating hypertension and Parkinson's disease. The present invention comprises of rasagiline mesylate and prazosin hydrochloride prepared by using different ratios of Eudragit RL 100and hydoxy propyl methyl cellulose. Effect of protease granuleson permeation of rasagiline and prazosin was analyzed. The patch so formed is non-irritant to the skin and possess maximum bioavailability.

Detailed description of the invention

The following description is of exemplary embodiments only and is not intended to limit the scope, applicability or configuration of the invention in any way. Rather, the following description provides a convenient illustration for implementing exemplary embodiments of the invention. Various changes to the described embodiments may be made in the function and arrangement of the elements described without departing from the scope of the invention.
The present inventors have come up with the unique solution to overcome hypertension and Parkinson's disease with an easy approach of transdermal drug delivery system. The invention offers high bioavailability and rapid action with minimum side effects.
In an embodiment the invention provides a matrix type transdermal patches containing rasagiline mesylate and prazosin hydrochloride.
In an embodiment the invention provides a matrix type transdermal patch for treating hypertension and Parkinson' disease.
In an embodiment the invention provides a transdermal patch prepared by using different ratios of Eudragit RL 100 and hydroxyl propyl methyl cellulose.
In an embodiment the invention provides solvent casting method to prepare transdermal patches of rasagiline mesylate and prazosin hydrochloride. The drugs rasagiline mesylate and prazosin hydrochloride are in 0.3:0.7 ratio.
In an embodiment the invention provides ethylene vinyl acetate as backing layer.
In an embodiment theinvention provides a combination of polyethylene glycol 400 and DMSO as plasticizer and enhancer;2- ethyl-hexyl acrylate, a polyacrylate as pressure sensitive adhesive; protease granulesas permeation enhancers; ethylene vinyl acetate a backing laminate and chloroform and methanol as solvent.
In an embodiment the invention providesa transdermal patch of high permeation and minimum side effects.
In an embodiment the invention provides a transdermal patch which is non irritant to the skin.
The present disclosure is further described in light of the following experiments which are set forth for illustration purpose only and not to be construed for limiting the scope of the disclosure. The following experiments can be scaled up to industrial/commercial scale and the results obtained can be extrapolated to industrial scale.
Protease obtained from Bacillus *species* was procured commercially (1.5 AU-N/g).

Composition: drugs: rasagiline mesylate: [6-hydroxy-2-(4-hydroxyphenyl)-benzothiophen-3-yl]-[4-[2-(1-piperidyl)ethoxy]phenyl]-methanone and prazosin hydrochloride: [4-(4-Amino-6,7-dimethoxy-2-quinazolinyl)-1-piperazinyl](2-furyl)methanone; Eudragit RL 100 (*N*,*N*-dimethylmethanamine;2-methylprop-2-enoic acid) 50 mg; hydroxyl propyl methyl cellulose 150 mg; polyacrylate as pressure sensitive adhesive; 100 mg protease granulesas permeation enhancers; ethylene vinyl acetate a backing laminate; polyester foil a release liner of thickness 19-125 microns; a combination of polyethylene glycol 400 and dimethyl sulfoxide as plasticizer and enhancer; chloroform and methanol as solvent; 325 mg Eudragit RL 100; and 275 mg HPMC.

Methods

Example 1: Method of preparation: The matrix type transdermal patches containing rasagiline mesylate and prazosin hydrochloride prepared using different ratios of Eudragit RL 100 and hydroxyl propyl methyl cellulose. The drugs rasagiline mesylate and prazosin hydrochloride are in 0.3:0.7 ratio. The polymers were weighed in requisite ratios by keeping the total polymer weight at 1.0 gm and allowed to swell for 2 hours in solvent mixture (8:6) ratio of chloroform and methanol. The drug solution was added (drugs in ratio 1:1) to polymeric solution while stirring. Polyethylene glycol 400 and dimethyl sulfoxide incorporated as plasticizer and protease granules as a permeation enhancer. The solution was poured into the glass ring, placed on the surface of mercury and kept in petriplate. The solvent was allowed to evaporate for 24 hours. Aluminium foil used as a backing film. The patches were cut to give the required area and used for evaluation.

Formulations	Drugs (Rasagiline 0.3 and prazosin 0.7 ratio)	Polymer Eudragit: HPMC	Thickness (µ)	Folding Endurance	Drug content (mg)	Protease granules (mg)
A1	50mg both	2:8	306±8	9.3±7.51	8.9±1.09	10
A2	50 mg both	3:7	126±1.5	11.4±6.51	6.8±1.36	10
A3	50 mg both	6:8	375±2.2	6.3±6.0	7.4±2.09	10
A4	50 mg both	3.5:6:3	100±3.0	7.17±8.81	9.6±3.65	10
A5	50 mg both	7:3	386±1.2	17.8±9.01	6.6±4.11	10
A6	50 mg both	8:2	446±7.7	22.3±6.51	4.7±1.43	10

Example 2: Synthesis of protease granules

1. **Synthesis of protease:** 500 parts by volume of liquid medium, containing 5% defatted soybean meal, 5% glucose, 2% sodium dihydrogen phosphate, and adjusted to pH 7 is fed to fermenter (its capacity being 2000 parts by volume), sterilized, and inoculated with Fusarium sp. S-19-5 followed by inoculation at 28 °C for 5 days under aeration and agitation to prepare seed culture. The culture is inoculated to 30,000 parts by volume of a liquid medium having the same components as in above fermenter and is incubated at 25 °C for 144 hours with the aeration rate of 45000 parts by volume per minute under the agitation of 500 r.p.m. During the incubation foaming is suppressed by the addition of a suitable amount of soybean oil from time to time. The culture obtained after 144 hours is cooled to about 5 °C and then passed through a filter press with the filter aid hyflo super cel whereby mycelia are removed. To the resulting 20000 parts by volume of the filterateis added to 0.6 saturated ammonium sulfate and the salted-out precipitate collected by filtrationwith the filter aid. The resulting ammonium sulfate precipitate containing the filter aid is dissolved in about 6000 parts by volume of cold water and insoluble materials are removed by filtration, 0.6 saturated ammonium sulfate is then added to the filtrate so as to precipitate the enzyme again, which in turn is collected by centrifugation dissolved in 1000, parts by volume of cold water dialyzed against cold water by means of fish skin diaphragm for 4 days and lyophilizedto give a crude enzyme powder with brownish color. Thus the potent protease exhibits a potent activity in the pH range from 8 to 12 which means compatible to skin and is easily absorbed.
2. **Formation of protease granules:** 500 parts by volume of an aqueous solution containing 100 parts by weight of protease (48500 PU/ml) is blended with a solution of 500 parts by weight of sodium sulfate in 2000 parts by volume of water (37 °C) and while the temperature of the blend is held at 20°-25 °C., 5000 parts by volume of acetone is added, with agitation at 300 r.p.m. the mixture is stirred for further 3 minutes at the same temperature and then allowed to stand for a while whereby the granules are deposited. The mixture is subjected to centrifugation to collect the granules which are washed well with 5000 parts by volume of acetone and dried under reduced pressure at 35 °C.

Example 3: Evaluation of physicochemical properties

1. **Thickness and weight variation:** The thickness of patches was assessed at 6 different points using digital micrometer and for each formulation, three randomly selected patches were used. For weight variation test, 3 films (each 2.64 cm^2) from each batch were weighed individually and the average weight was calculated.
2. **Folding endurance:** The folding endurance was measured manually as the reported method. Briefly, a strip of the film (4×3 cm) was cut evenly and repeatedly folded at the same place till it broke.
3. **Flatness:** Longitudinal strips were cut from the prepared patch, the length of each strip was measured and then the variation in the length due to the non-uniformity in flatness was measured. Flatness was calculated by measuring constriction of strips, and 0% constriction was considered to be 100% flatness.
4. **Determination of drug content:** Patch (2.64 cm^2) from each formulation was taken, cut into small pieces and was allowed to dissolve in a 100 ml solution containing 15 ml of methanol and 85 ml of 25% v/v PEG 400 in PBS pH 7.4. The solution was filtered, diluted suitably and the drug content was measured against reference solution prepared with placebo films.
5. **Percentage of moisture content:** The films were weighed individually and kept in a desiccators containing activated silica at room temperature for 24 hrs. The individual films were weighed repeatedly until a constant weight was achieved. The percentage of moisture content was calculated as the difference between initial and final weight with respect to the final weight.
6. **Percentage of moisture uptake:** The films were weighed accurately and placed in a desiccator containing 200 ml of saturated solution of potassium chloride (84% relative humidity) at room temperature. After 3 days, the films were taken out and weighed. The percentage of moisture uptake was calculated as the difference between final and initial weight with respect to initial weight.
7. ***Ex-vivo* permeation studies:** Excised rat skin was mounted between the compartments of the diffusion cell with stratum corneum facing the donor compartment. The stratum corneum side of the skin was kept in intimate contact with the transdermal patch under the test. The receiver compartment contained 33 ml of 25% v/v PEG 400 in PBS of pH 7.4, stirred with a magnetic stirrer at a speed of 400 rpm. The whole assembly was kept on a magnetic stirrer and study was conducted at 37±0.5 °C. The amount of the permeated drug was determined by removing 3 ml at preset time points for 250 hrsand replenishing with an equal volume of fresh medium. The samples were filtered using syringe filter (Sartorius 0.45µ) and the drug content was analyzed.
8. **Primary skin irritancy studies:** The patch when tested animals shows no skin irritation in 10-day study.
9. **Drug release:** The transdermal patch shows 50% and 80%drug release for rasagiline mesylate and prazosin hydrochloride respectively in 250 hours.

While considerable emphasis has been placed herein on the specific features of the preferred embodiment, it will be appreciated that many additional features can be added and

that many changes can be made in the preferred embodiment without departing from the principles of the disclosure. These and other changes in the preferred embodiment of the disclosure will be apparent to those skilled in the art 25 from the disclosure herein, whereby it is to be distinctly understood that the foregoing descriptive matter is to be interpreted merely as illustrative of the disclosure and not as a limitation

Result and Discussion

We Claim,

1. An extended-release dual drug delivery transdermal patch comprising:

a) an impermeable backing layer of ethylene vinyl acetate;

b) a matrix layer comprising:
   - Rasagiline mesylate;
   - Prazosin hydrochloride;
   - A matrix forming polymer combination of *N*,*N*-dimethylmethanamine, 2-methylprop-2-enoic acid (50 mg), hydroxyl propyl methylcellulose (140 mg);
   - 2- ethyl-hexyl acrylate, apolyacrylate pressure sensitive adhesive;
   - A 10 mg protease granules as permeation enhancers;
   - Ethylene vinyl acetate a backing laminate;
   - Polyester foil a release liner of thickness19-125 microns;
   - A combination of polyethylene glycol 400 and dimethyl sulfoxide as plasticizer and enhancer;
   - Chloroform and methanol as solvent, wherein the drugs rasagilinemesylate and prazosin hydrochloride are in 0.3:0.7 ratio; wherein, the transdermal patch shows 50% and 80%drug release for rasagiline mesylate and prazosin hydrochloride respectively in 250 hours; wherein the protease granules are coated with melt-delayed layer(paraffin wax) and melt resistant coating layer (sodium sulfate and talc)along with magnesium sulphate in the core.

2. The transdermal patch as claimed in claim 1, wherein, the patch is highly biocompatible.
3. The transdermal patch as claimed in claim 1, wherein the patch shows no skin irritation.
4. A method for formulating the extended-release dual drug delivery transdermal patch comprising:
   a) The matrix type transdermal patch containing rasagiline and prazosin (50 mg both) prepared by using different ratios of Eudragit RL 100 and hydroxyl propyl methyl cellulose(2:8, 3:7, 6:8, 3.5:6.3, 7:3, 8:2) in amount: 325 mg Eudragit RL 100 and 275 mg hydroxy propyl methyl cellulose;
   b) tHe polymers weighed in requisite ratios by keeping the total polymer weight at 1.0gm and allowed to swell for 2 hours in solvent mixture (8:6) of chloroform and methanol;
   c) The drug solution added to polymeric solution while stirring;
   d) Incorporating polyethylene glycol 400, dimethyl sulfoxide andprotease granules;wherein the protease granules are prepared by the steps

1. 500 parts by volume of liquid medium, containing: 5% defatted soybean meal, 5% glucose, 2% sodium dihydrogen phosphate, and adjusted to pH 7 is fed to fermenter (its capacity being 2000 parts by volume), sterilized, and inoculated with Fusarium sp. S-19-5 followed by inoculation at 28 °C for 5 days under aeration and agitation to prepare seed culture;
2. The culture is inoculated to30,000 parts by volume of a liquid medium having the same components as in above fermenter and is incubated at 25 °C for 144 hours with the aeration rate of 45000 parts by volume per minute under the agitation of 500 r.p.m;
3. During the incubation, foaming is suppressed by the addition ofa suitable amount of soybean oil from time to time;
4. The culture obtained after 144 hours is cooled to about 5 °C and then passed through a filter press with the filter aid hyflo super cel whereby mycelia are removed;
5. To the resulting 20000 parts by volume of the filtrate is added to 0.6 saturated ammonium sulfate and the salted-out precipitate collected by filtration with the filter aid;
6. The resulting ammonium sulfate precipitate containing the filter aid is dissolved in about 6000 parts by volume of cold water and insoluble materials are removed by filtration, 0.6 saturated ammonium sulfate is then added to the filtrate so as to precipitate the enzyme again, which in turn is collected by centrifugation dissolved in 1000, parts by volume of cold water dialyzed against cold water by means of fish skin diaphragm for 4 days and lyophilizedto give a crude enzyme powder with brownish color;
7. Thus the potent protease exhibits a potent activity in the pH range from 8 to 12 which means compatible to skin and is easily absorbed;
8. 500 parts by volume of an aqueous solution containing 100 parts by weight of protease (48500 PU/ml) is blended with a solution of 500 parts by weight of sodium sulfate in 2000 parts by volume of water (37 °C) and while the temperature of the blend is held at 20°-25 °C., 5000 parts by volume of acetone is added, with agitation at 300 r.p.m. the mixture is stirred for further 3 minutes at the same temperature and then allowed to stand for a while whereby the granules are deposited;
9. The mixture is subjected to centrifugation to collect the granules which are washed well with 5000 parts by volume of acetone and dried under reduced pressure at 35 °C.
   a) The solution was poured into glass ring, placed on the surface of mercury and kept in petriplate;
   b) The solvent allowed to evaporate for 24 hours;
   c) the patches cut to give required area and used for evaluation.

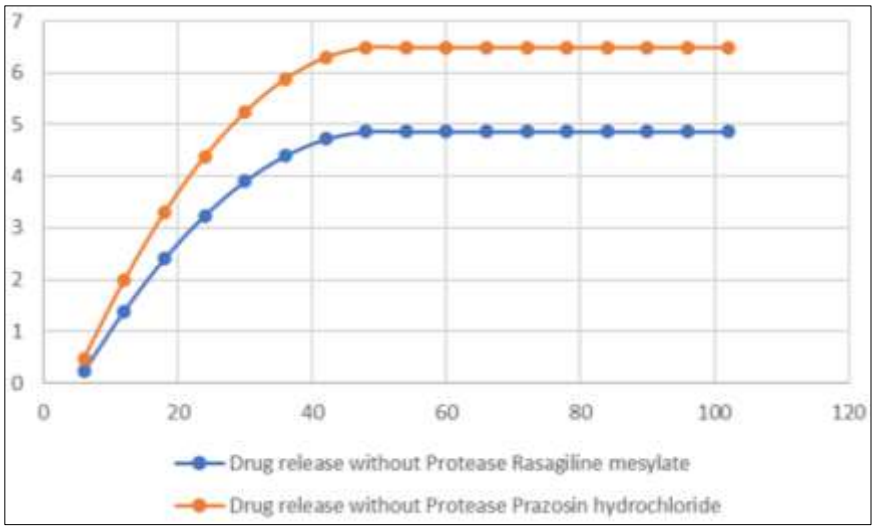

Fig 1: Descibes about drug release without Rasagaline mesylate and prazosin hydrochloride

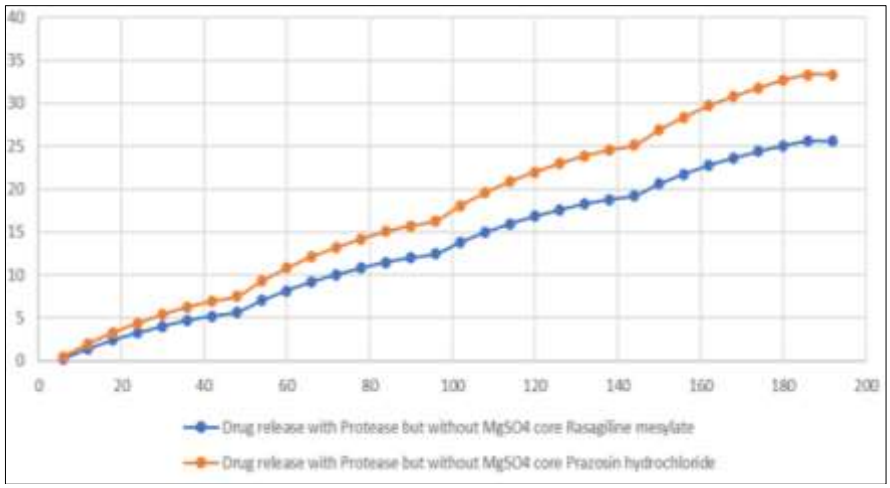

Fig 2: Describes Drug release with Rasagaline and Prazosin with protease but without MgSO4

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