FORMULATION AND EVALUATION OF RESERVOIR TYPE SELEGILINE TRANSDERMAL DELIVERY SYSTEM

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ABSTRACT

The purpose of this research was to design a reservoir type transdermal system for delivering selegiline using a hydrogel-based drug reservoir and a rate-controlling membrane, prepared by solvent casting method by using 2 % w/V of Eudragit RS100 and 0.10% w/V of polyvinyl pyrrolidone K30 (PVP K30) was added in the formulation as pore creating agent. The preparations were evaluated for thickness, drug content, weight variation, tensile strength, folding Endurance. All prepared formulations indicated good physical stability. The in-vitro diffusion studies were carried out using modified Keshery- Chein cell with cellophane as diffusion membrane and the formulations followed Higuchi diffusion mechanism. The formulations containing HEC as polymer showed faster release rate compared to HPMC K4M and the release profile of selegiline followed Higuchi model kinetics in different formulations. However, the release profile of the optimized formulation R4 (r² = 0.9992 for Higuchi) indicated that the permeation of the drug from the patches was governed by a diffusion mechanism. Formulation R4 showed highest flux among all the formulations.

Keywords: Reservoir type transdermal system, Selegiline, Eudragit RS100, In-vitro diffusion studies.

INTRODUCTION

Transdermal drug delivery (TDD) offers several advantages over other routes of drug administration. Besides patient convenience, enhanced and controlled therapeutic responses have been reported.1 Major depressive disorder (MDD) is a highly prevalent and disabling condition. It has a lifetime prevalence of 16% in the US; worldwide, it is the leading cause of a non-fatal disease burden and the fourth leading cause of total disease burden.2,3 Selegiline, an irreversible inhibitor with selectivity for monoamine oxidase type B (MAO-B) at low oral doses, has an established efficacy profile for treating MDD.4 Selegiline also shows potential indications for treating Parkinson’s disease, Alzheimer’s disease, attention deficiency hyperactivity disorder, and cocaine addiction.5 The selegiline transdermal system (STS) recently approved for MDD treatment provides greater systemic delivery of selegiline to the brain with relative sparing of the gastrointestinal MAO type A (MAO-A) enzyme.6 STS avoids the first-pass effect and achieves antidepressant concentrations of selegiline in neuronal tissues with fewer effects on gastrointestinal MAO-A, the principal enzymatic barrier to the ingestion of tyramine.7 It is especially feasible for elderly and Parkinsonism patients since they are known to suffer from swallowing difficulties.8

The aims of the present study were to prepare reservoir type transdermal patches of selegiline using various polymers and study the in-vitro diffusion behavior of prepared reservoir type transdermal patch formulations. The purpose was to provide the delivery of the drug at a controlled rate across intact skin.

MATERIALS AND METHODS

Materials

Selegiline was purchased sample from Themit Medicare Pvt Ltd., Hydroxy propyl methyl cellulose (HPMC K4M), was gifted from Dow Chemicals and Pharma, Mirland. Eudragit RS100 was gifted from Degussa Evonic LTD, Mumbai. Poly vinyl pyrrolidone (PVP) K30, Hydroxy ethyl cellulose (HEC), Menthol, Propylene Glycol, Dichloromethane and Glycerol was procured from S.D. Fine Chemicals, Mumbai. All reagents were analytical grade.

Fabrication of experimental reservoir-type transdermal delivery system

An experimental reservoir-type transdermal delivery system of selegiline was fabricated by encapsulating the selegiline reservoir solution within a shallow compartment molded from a drug impermeable backing laminate and a rate-controlling membrane. Reservoir solution consisted of selegiline saturated in alcohol/ glycerol/ water (1:0.5:8) co solvent systems with Dibutyl phthalate 15 % (w/w of dry polymer composition) as permeation enhancer and gelling agents (HEC and HPMC K4M). Rate-controlling membrane was prepared with 2 % w/V of Eudragit RS100 and 0.10 % w/V of PVP K30 as pore forming agent. To ensure intimate contact of the transdermal patch to the skin, a pressure-sensitive adhesive polymer was coated onto the Eudragit RS100 membrane. The Eudragit RS100 membrane was placed over on the adhesive coated release liner, and then the backing laminate was placed on it. The composite was heat sealed and cut to the appropriate size. The selegiline reservoir solution was dispersed into the device using a disposable syringe. The device was heat sealed again to close the unsealed side of the device ensuring no reservoir leaking out of the device. Then, each patch was kept in a sealed aluminum pouch.9

Preparation of Rate Controlling Membrane

Rate controlling membrane was prepared by solvent casting method, using polymer like, 2 % w/V of Eudragit RS100 and 0.10% (w/V) of polyvinyl pyrrolidone K30 (PVP) was added in the formulation as pore creating agent. Polymer and pore forming agent was added and homogeneously mixed in Propylene Glycol, Dichloromethane and Ethanol in 1:3:7 ratios.5

PHYSICOCHEMICAL CHARACTERIZATION OF FILMS

Thickness

The thickness of patches was measured at three different places using a micrometer (Mitutoyo Co., Japan) and mean values were calculated.

Drug Content Uniformity

Drug content estimation was carried out in triplicates on each formulation. Each patch from different formulations (patch size of 2 cm², equivalent to 5 mg of drug) was transferred into a graduated flask and phosphate buffer pH 7.4 was added up to 100 ml mark for extracting the drug from the patch. The flask was shaken for 4 h in a mechanical shaker. After extraction of the drug, the solution was filtered and diluted suitably with phosphate buffer pH 7.4 and the absorbance was measured at 220 nm, against the placebo patch solution as blank and the drug content was calculated.
Weight Variation

The patches were subjected to mass variation by individually weighing randomly selected patches. Such determinations were carried out for each formulation.\(^1\)

Tensile strength

In order to determine the elongation as a tensile strength, the prepared polymeric patch was pulled by means of a pulley system; weights were gradually added to the pan to increase the pulling force till the patch was broken. The elongation i.e. the distance traveled by the pointer before break of the patch was noted with the help of magnifying glass on the graph paper, the tensile strength was calculated as kg cm\(^{-2}\).\(^2\)

Folding Endurance

This was determined by repeatedly folding one film at the same place till it broke. The number of times the film could be folded at the same place without breaking/cracking gave the value of folding endurance.\(^3\)

In vitro permeation studies

In vitro drug release profiles were carried out by using modified Keshery - Chein diffusion cell with cellophane membrane. The cellophane membrane was soaked in 100 ml of phosphate buffer pH 7.4 for overnight and then cut into pieces of 7 cm\(^2\) area. It was mounted on the diffusion cell and equilibrated with receptor fluid for 15 min and used for the drug release studies. The cell consists of two compartments, the donor and the receptor compartment. The donor compartment was in contact with ambient conditions of the patch. The receptor fluid (5 ml) was withdrawn at predetermined time intervals and replaced immediately with same volume of phosphate buffer pH 7.4.

Permeation Data Analysis

The flux (μg cm\(^{-2}\) hr\(^{-1}\)) of selegiline was calculated from the slope of the plot of the cumulative amount of selegiline permeated per cm\(^2\) of cellophane membrane at steady state against the time using linear regression analysis.\(^4\)

The steady state permeability coefficient (Kp) of the drug through cellophane membrane was calculated by using the following equation:

\[
Kp = \frac{J}{C}
\]

Whereas J is the flux and C is the concentration of selegiline in the patch.

RESULTS AND DISCUSSION

The results of the physicochemical characterization of the patches are shown in Table 2. The thickness of the patches was measured by vernier caliper with three determinations which was found in the range between 290± 1 to 320± 2 μm for the reservoir type patches respectively, which indicate that they are uniform in thickness. The weights ranged between 12.1± 0.3 mg and 14.1± 0.45 mg, which indicates that different batches patch weights, were relatively similar. Good uniformity of drug content among the batches was observed with all formulations and ranged from 4.2 ± 0.93 mg to 4.5 ± 0.97 mg per sq cm patch. The results indicate that the process employed to prepare patches in this study was capable of producing patches with uniform drug content and minimal patch variability.

The tensile testing gives an indication of the strength and elasticity of the film, reflected by the parameters like tensile strength (TS) and elongation at break. The tensile strength was measured by the modified apparatus, and found to be in the range of 3.3± 0.67 to 4.8± 0.81 kg cm\(^{-2}\), respectively. From all the developed and standardized formulations R2 was found to be more tensile strength (Fig 1) because of 200 mg of HPMC K4M due to its viscosity, density, molecular weight etc. From the above results suggested that formulation R2 had a good mechanical strength as compared to the other formulations. The obtained results were shown in Table No. 2.

Table 1: Composition of Reservoir solution.

<table>
<thead>
<tr>
<th>Dibutyl phthalate (%)</th>
<th>Water (ml)</th>
<th>Glycerol (ml)</th>
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<tr>
<td>15</td>
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Note: The above formula gave patch of 2 sq. cm. area

Table 2: Evaluation of Transdermal patches

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Film thickness(μm)</th>
<th>Tensile Strength(kg cm(^{-2}))</th>
<th>Folding Endurance</th>
<th>Drug content mg/film</th>
<th>% Drug release</th>
<th>Flux</th>
</tr>
</thead>
<tbody>
<tr>
<td>R1</td>
<td>310± 1</td>
<td>4.7± 0.49</td>
<td>319± 5.2</td>
<td>4.2 ± 0.93</td>
<td>85.12± 3.5</td>
<td>241.52</td>
</tr>
<tr>
<td>R2</td>
<td>320± 2</td>
<td>4.8± 0.81</td>
<td>302± 4.2</td>
<td>4.5 ± 0.97</td>
<td>84.71± 4.1</td>
<td>277.41</td>
</tr>
<tr>
<td>R3</td>
<td>290± 1</td>
<td>3.5± 0.47</td>
<td>331± 8.3</td>
<td>4.3 ± 0.7</td>
<td>82.96± 3.4</td>
<td>252.62</td>
</tr>
<tr>
<td>R4</td>
<td>300± 1</td>
<td>3.3± 0.67</td>
<td>312± 6.2</td>
<td>4.3± 0.51</td>
<td>79.40± 2.7</td>
<td>279.98</td>
</tr>
</tbody>
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The in-vitro release profile is an important tool that predicts in advance how a drug will behave in vivo. The results of in-vitro permeation studies of selegiline from reservoir type transdermal patches are shown in Figures 2. In the present study hydrophilic polymers are used to prepared patches. Formulation R1 exhibited greatest 85.12± 3.5 % of drug release value, while formulation R4 exhibit lowest 79.40± 2.7 % of drug release value. The cumulative
amount of drug released from formulations containing HEC polymer release drug at faster rate than HPMC K4M polymer. The cumulative amount of drug released from formulations R1 and R2 is much higher than formulations R3 and R4 due to less polymers concentration. In addition to nature of polymer concentration of polymer also affect the drug release. As the concentration of polymer increased drug release decreased. The drug release from the patch is ordered as R1 > R2 > R3 > R4. Unlike the formulations R1, R2, R3 and R4, the formulations R1 achieved a high cumulative amount of drug permeation at the end of 18 hours.

To know the mechanism of drug release from these formulations, the data were treated according to first-order, Higuchi's and zero order pattern. The release kinetics of the patches followed Higuchi's diffusion kinetics ($t^2 = 0.9850$ to $0.9992$). As per Higuchi's release kinetics; the drug release followed diffusion mechanism. Percentage of drug released when plotted against square root of time, the plots showed high linearity. It indicated that release pattern followed Higuchi's diffusion mechanism which states that as the time increases the diffusion path length also increases.

CONCLUSION

Based on the physicochemical parameters and in vitro release studies, it was found that formulations containing low concentration of polymers released faster compared to higher concentration. Results of the present study encouraged that the selegiline reservoir type transdermal patch can be used as controlled drug delivery system and frequency of administration can be minimized.

REFERENCES