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Research Article

FORMULATION AND EVALUATION OF ANTIPARKINSON'S DRUG INCORPORATED TRANSDERMAL FILMS

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ABSTRACT

Objective: Ropinirole suitable for transdermal delivery due to its small molecular size (260.37 g/mol), optimum log p (2.3), and low oral bioavailability (50%) due to first-pass metabolism, the short elimination half-life of 4–6 h. Dose of drug is 6 mg/day. Hence, in the present study, an attempt was made to deliver antiparkinson's drug through transdermal route in the form of transdermal film to attain sustained release using different concentration of drug, polymers stabilizers.

Methods: Among the different formulations of matrix type (F1 to F5), F2 and F4 formulations were optimized based on crystallinity. These formulations were carried out for *in vitro* permeation studies. Out of these two formulations, F4 formulation showed target drug release.

Results and Discussion: The formulation F4 containing 2 mg drug, 600 mg hydroxypropyl methylcellulose E15 and 50 mg of Eudragit RS 100 was selected as optimized formulation, after considering its microscopic examination throughout stability, % drug content (98.4%), drug permeated through the cellophane membrane at the end of 72 h, and evaluation of physicochemical characterization parameters such as thickness, weight variation, flatness, folding endurance, moisture content, and tensile strength.

Conclusion: The results of physicochemical characterization were ensured the stability of the films. The drug permeation profile was also found to follow Higuchi kinetic model.

Keywords: Ropinirole, Transdermal film, Permeation studies, Cellophane membrane.

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INTRODUCTION

Transdermal drug delivery systems allow delivery of a drug into the systemic circulation through permeation through skin layers at a controlled rate. The skin poses an extremely good barrier to drug penetration, and it is usually necessary to employ enhancement strategies [1,2]. For transdermal products, the goal of dosage design is to maximize the flux through the skin into the systemic circulation and simultaneously minimize the retention and metabolism of the drug in the skin [3]. The drug input can be terminated at any point of time of removing transdermal patches [4,5]. The simplified medication regimen leads to improved patient compliance and reduce inter- and intra-patient variables [6]. It is possible that an equivalent therapeutic effect can be elicited through transdermal drug delivery with a lower daily dose than that is required by oral route [7,8].

Ropinirole is used to treat Parkinson's disease drug influences striatal neuronal firing rates through activation of dopamine receptors in the striatum and the *Substantia nigra*, the site of neurons that send projections to the striatum, improves motor function [9-11]. Ropinirole is a non-ergoline dopamine agonist with high intrinsic activity at the D_2 and D_3 dopamine receptor subtypes; it binds with higher affinity to D_3 than to D_2 or D_4 receptor subtypes [12]. It is weakly active at the 5-HT_2, and α_2 receptors and is said to have virtually no affinity for the 5-HT_1, benzodiazepine, gamma-aminobutyric acid, muscarinic, α_1, and β-adrenoreceptors [13,14].

The model drug was chosen as the suitable for formulating a transdermal drug delivery system: Because of the conventional multidose therapy leads to fluctuations in serum levels of drug, and low oral bioavailability due to first-pass metabolism, shorter half-life. The rational strategy to overcome this drawback is to minimize the fluctuations by fabricating sustained-release formulations. Model drug suitable for transdermal delivery due to its molecular size (260.37 g/mol), optimum logP (2.3), and low oral bioavailability (50%) due to first-pass metabolism. The short elimination half-life of 4–6 h dose of drug is 6 mg/day. Hence, in the present study, transdermal film for drug was designed and developed to achieve sustained release using different concentration of polymers.

METHODS

Ropinirole was procured from Mylan Laboratories Ltd., India. Hydroxypropyl cellulose was procured from Colorcon Asia Pvt., Ltd., India. Eudragit RS 100 was procured from Evonik Pharma, India. Other materials used in the study were of analytical grade.

Preformulation study

Preformulation involves the application of biopharmaceutical principles to the physicochemical parameters of drug substance is characterized with the goal of designing an optimum drug delivery system. Preformulation studies relate to pharmaceutical and analytical investigation carried out proceedings and supporting formulation development efforts of the dosage forms of the drug substance. Preformulation yields basic knowledge necessary to develop suitable formulation. It gives information needed to define the nature of the drug substance and provide framework for drug combination with polymers in the dosage form. Hence, the following preformulation studies were carried out [15,16].

1. Identification of drug
   - Standard calibration curve
   - Solubility analysis.
2. Partition coefficient.

Identification of drug

Determination of λ_{max}: 25 mg of pure drug was taken and known concentration of drug solution was prepared by diluting drug solution in methanol. The solutions were scanned from 200 to 400 nm against the reagent blank to fix absorption maxima. Spectrum of the model drug was obtained and λ_{max} of model drug was found to 249 nm. Hence, all further investigations were carried out at the same wavelength.

Standard calibration curve

Standard stock solution

Transfer an accurately weighed amount of about 25 mg of drug and working standard into a 50 ml volumetric flask. Dissolve and make up the volume with methanol [17].

Standard preparation

Pipette 5 ml of the standard stock solution into a 50 ml volumetric flask, make up the volume with methanol.

Solution: (a) Std. stock solution 500 µg/ml in methanol and (b) working stock 50 µg/ml in methanol.

From the stock solution, different aliquots were taken in series of 10 ml volumetric flasks and volume made up with buffer to get a series of working standard solutions of concentrations, 5 µg/ml, 10 µg/ml, 15 µg/ml, 20 µg/ml, and 25µg/ml. The absorbance of samples was obtained spectrophotometrically against the reagent blank at 249 nm. The calibration curves were constructed by plotting drug concentration versus the absorbance value at 249 nm and the regression equation was computed.

Solubility studies

The solubility of drug is an important physicochemical property because it affects the bioavailability of the drug, and hence the therapeutic efficiency of the pharmaceutical product. The solubility of the molecules in various solvents is determined as a first step. This information is valuable in developing a formulation. Solubility was determined in organic solvents [18].

Solubility study of model drug in different media

Solubility studies were performed by taking required quantity of drug in 1 ml of different organic solvents (methanol, ethanol, ethyl acetate, isopropyl alcohol, heptane, and water) separately up to its saturation and subjected to mechanical shaking at 100 rpm for 24 h. The resultant dispersions were collected and subjected to centrifugation and the concentration of drug was determined from absorbance at 249 nm.

Partition coefficient

The partition coefficient is the ratio of concentrations of a compound in the two phases of a mixture of two immiscible solvents at equilibrium. Normally, one of the solvents chosen is phosphate buffer (pH 7.4), while the second is hydrophobic such as octanol. Standard solution of drug was prepared in phosphate buffer (pH 7.4). The classical and most reliable method of log p determination is the shake-flask method, which consists of dissolving some of the solute in question in a volume of octanol and phosphate buffer (pH 7.4), then measuring the concentration of the solute in each solvent [19].

Experimental method

Preparation of ropinirole transdermal film

Transdermal film containing ropinirole was prepared by the solvent casting technique using aluminum foil as a backing layer. The two independent factors were hydroxypropyl methylcellulose E15 and Eudragit RS 100. The mixture of solvent casting method consisted of solvent (Ethanol), permeation enhancer (Tween 80, 5% of total weight of drug+polymer), and plasticizer (polyethylene glycol, 2.5% of total volume of solvent). Dose of drug was adjusted in such a way that square patch (2 sq. cm) consisted of 2 mg of ropinirole. The films were stored between sheets of wax paper in a desiccator. The formulation chart of transdermal films is depicted in Table 1.

Physicochemical characterization of films

Drug content

Films of a specified area (1 cm^2) were dissolved in 5 mL of dichloromethane, and the volume was made up to 10 mL with phosphate buffer pH 7.4, dichloromethane was evaporated using a rotary vacuum evaporator at 45°C. A blank was prepared using a drug-free film treated similarly. The solutions were filtered through a 0.45 µm membrane, diluted suitably and absorbance were read at 249 nm in a double beam ultraviolet (UV)-visible spectrophotometer.

Thickness

The thickness of films was measured at three different places using a digital micrometer (Mitutoyo Co., Japan) and mean values were calculated [20].

Weight variation

The films were subjected to mass variation by individually weighing randomly selected films. Such determinations were carried out for each formulation [20].

Flatness

Three longitudinal strips were cut out from each film: One from the center, one from the left side, and one from the right side. The length of each strip was measured and the variation in length because of non-uniformity in flatness was measured by determining percent constriction, with 0% constriction equivalent to 100% flatness [21].

Folding endurance

Folding endurance was determined by repeatedly folding one film at the same place until it broke. The number of times the film could be folded at the same place without breaking/cracking gave the value of folding endurance [22].

Tensile strength

To determine the elongation as a tensile strength, the polymeric film was pulled by means of a pulley system; weights were gradually added to the pan to increase the pulling force until the film was broken [21]. The elongation, i.e., the distance traveled by the pointer before break of the film was noted with the help of magnifying glass on the graph paper, the tensile strength was calculated as $kg\text{-}cm^{-2}$.

Percentage of moisture content

The films were weighed individually and kept in a desiccators containing activated silica at room temperature for 24 h. Individual films were weighed repeatedly until they showed a constant weight. The percentage of moisture content was calculated as the difference between initial and final weight with respect to final weight [23].

In vitro skin permeation studies

In vitro skin permeation studies were performed using a Franz diffusion cell with a receptor compartment capacity of 22.5 mL. The excised rat abdominal skin (Wistar albino) was mounted between the donor and receptor compartment of the diffusion cell. The formulated

Table 1: Formulation chart of transdermal films

Ingredients	F1	F2	F3	F4	F5
Ropinirole base	2	2	2	2	2
hydroxypropyl methylcellulose E15 (mg)	100	150	200	250	50
Eudragit RS100 (mg)	200	150	100	50	250
Tween 80 (%w/w)	5	5	5	5	5
Polyethylene glycol (%w/w)	2.5	2.5	2.5	2.5	2.5
Ethanol (ml)	2.5	2.5	2.5	2.5	2.5

films were placed over the skin and covered with paraffin film. The receptor compartment of the diffusion cell was filled with phosphate buffer pH 7.4. The whole assembly was fixed on a magnetic stirrer, and the solution in the receptor compartment was constantly and continuously stirred using magnetic beads at 50 rpm; the temperature was maintained at 32±0.5°C. The samples were withdrawn at different time intervals and analyzed for drug content spectrophotometrically. The receptor phase was replenished with an equal volume of phosphate buffer pH 7.4 at each sample withdrawal. The cumulative percentages of drug permeated per square centimeter of films were plotted against time [24,25].

Kinetic modeling of drug release

To analyze the mechanism of drug release from the films, the release data were fitted to the following equations [26]:

Zero-order equation:

$$Q=k_0 t$$

Where Q is the amount of drug released at time t, and k_0 is the release rate.

First-order equation:

$$\ln(100-Q)=1n\ 100-k_1 t$$

Where Q is the percent of drug release at time t, and k_1 is the release rate constant.

Higuchi's equation:

$$Q = k2\sqrt{t}$$

Where Q is the percent of drug release at time t, and k_2 is the diffusion rate constant.

RESULTS AN DISCUSSION

Identification of drug

Calibration curve

Determination of λmax: UV-spectra of ropinirole are shown in Fig. 1. The linear equation in methanol was y=0.0416×concentration (mcg/ml). Different standard concentration and their absorbance values were shown. At all the concentration levels, the standard deviation was low. Goodness-of-fit of regression equation was supported by high regression value (0.9998). Hence, the developed method can be used for routine analysis of the drug in pharmaceutical formulations studies. Calibration curve data of the ropinirole in methanol are depicted in Fig. 2.

Solubility analysis

Solubility studies showed that the ropinirole shows organic solubility. It showed maximum solubility in ethanol, methanol, and minimum solubility in isopropyl alcohol and water. The comparison solubility profile of ropinirole in different solvents is depicted in Fig. 3.

Partition coefficient

In the present study, pH 7.4 phosphate buffer was used as *in vitro* study fluid and the solubility drug in pH 7.4 buffer was found to be 0.456 mcg/ml. The logarithmic value of the partition coefficient (log p) was found to be 2.1. The results indicated that the drug has optimum log p value, which fulfilled the requirements of formulating it into a transdermal patch. The calibration curve of model drug in pH 7.4 buffer is shown in Fig. 4.

Physicochemical characterization of films

Drug content (Assay): The drug content of different formulations (F1-F5) was ranged between 93.2 and 98.4%. The drug content was nearly the same as the dose of the drug in all the patches. The cumulative percentage drug permeated and percentage drug retained by individual patch in *in vitro* permeation studies were based on the mean amount of drug present in the respective patch. The drug content of different formulations (F1-F5) is shown in Table 2.

Table 2: Drug content (Assay)

S. No.	Formulation code	Drug content %
1	F1	95.8
2	F2	93.2
3	F3	96.9
4	F4	98.4
5	F5	94.1

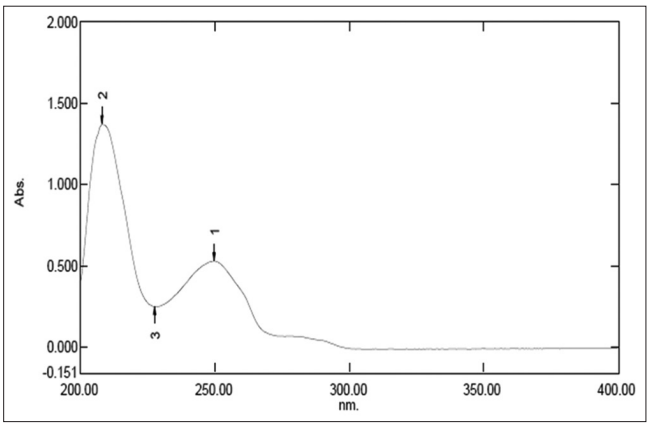

Fig. 1: Ultraviolet -spectra of drug

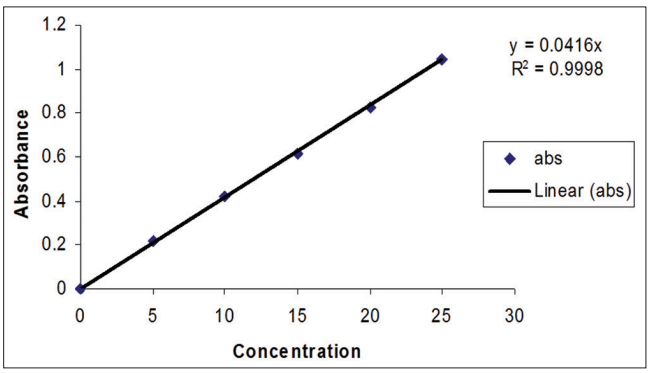

Fig. 2: Calibration curve data of the atmospheric pressure ionization (ropinirole) in methanol

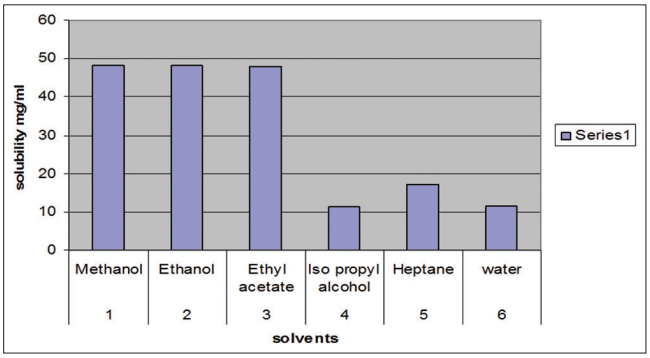

Fig. 3: Comparison of solubility profile of atmospheric pressure ionization in different solvents

Table 3: Physicochemical characterization of prepared transdermal films

Formulation code	Thickness (µm)	Weight variation (mg cm^{-2})	Folding endurance	Tensile strength (kg cm^{-2})	Moisture content (%)
F1	112±2.4	13.58±0.62	76.21±1.08	3.82±0.068	2.73±0.44
F2	127±6.5	12.46±0.39	69.76±1.12	2.65±0.093	1.95±0.85
F3	141±7.3	15.19±0.32	82.94±2.54	2.99±0.064	2.81±0.14
F4	133±1.8	12.25±0.87	88.56±1.96	3.86±0.019	2.84±0.58
F5	140±3.4	14.26±0.54	74.35±1.89	3.07±0.094	1.94±0.69

Table 4: Regression coefficient values of different kinetic models

Formulation code	Higuchi kinetics (R^2)	Peppas plot (R^2)	Zero-order kinetics (R^2)	First-order kinetics (R^2)
F1	0.9894	0.9124	0.9014	0.9129
F2	0.9865	0.9308	0.9333	0.9308
F3	0.9834	0.9266	0.9246	0.9266
F4	0.9877	0.9126	0.9059	0.9126
F5	0.9926	0.9515	0.9536	0.9515

The results of the physicochemical characterization, i.e., thickness, weight variation, folding endurance, tensile strength, and moisture content of the films are shown in Table 3. The thickness ranged between 112±2.4 and 141±7.3 µm, which indicated that the prepared films were uniform in thickness. The weights ranged between 12.25±0.87 mg and 15.19±0.32 mg, which indicates that different batches film weights were relatively similar. The results indicated that the process employed to prepare transdermal films in this study was capable of producing films with uniform drug content and minimal film variability. The flatness study showed that all the prepared film formulations had the same strip length before and after their cuts, indicated 100% flatness. Thus, no amount of constriction was observed; all films had a smooth, flat surface and that smooth surface could be maintained when the film was applied to the skin. Folding endurance test results indicated that the films would not break and would maintain their integrity with general skin folding when applied. The moisture content of the prepared formulations was low, which could help the formulations remain stable and reduce brittleness during long-term storage.

In vitro skin permeation studies

In the *in vitro* drug permeation studies, the cumulative amount of drug permeated per sq. cm from different formulations having different concentrations of drug and polymers showed variable permeation patterns. The process of drug permeated in most of the controlled/sustained release devices including transdermal patches is governed by diffusion. The mean cumulative amounts of drug permeated (*In vitro* permeation) from different concentrations up to 72 h were analyzed. Out of all these different formulations F4 formulation showed targeted drug permeation. Studies revealed that the maximum drug permeation was found (97.5%), as the concentration of drug increases, amount of drug permeated also increases. The *in vitro* permeation studies data have shown that drug release from the patch formulation has been affected by types of polymer and concentration of polymer, concentration of drug. The *in vitro* drug permeation profile of cumulative amount permeated formulations (F1-F5) is depicted in Fig. 5.

Kinetic modeling of drug release

To analyze the mechanism of drug release from the films, the release data were fitted to the various kinetic models, i.e., Higuchi model, Peppas plot, zero-order, and first-order kinetics. The obtained results are shown in Table 4. From the results, Higuchi kinetic model was showed good regression coefficient (R^2) for all prepared formulations.

CONCLUSION

In the present research, ropinirole transdermal films were prepared by solvent casting technique using different polymer ratio. All film formulations were checked for physicochemical properties such as thickness, weight variation, and drug content, flatness, folding endurance, and moisture content and showed good results. The

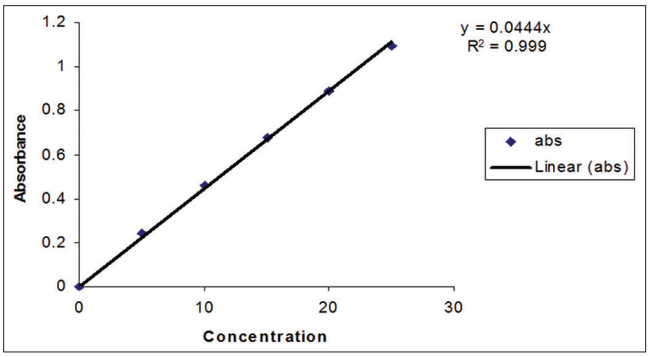

Fig. 4: Calibration curve of model drug in pH 7.4 buffer

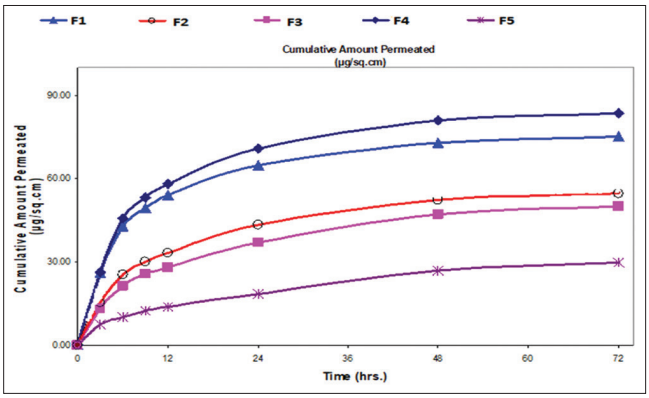

Fig. 5: *In vitro* drug permeation profile of cumulative amount permeated formulations

in vitro drug permeation data showed that drug release from the films formulations has been affected by types of polymer and concentration of polymer. Drug release data were fitted to various kinetic models, and Higuchi model showed good regression coefficient. The finding of this result revealed that the problems of ropinirole on oral administration such as dissolution rate-limited absorption and gastric side effects can be overcome by applying ropinirole topically in the form of transdermal film.

AUTHORS' CONTRIBUTIONS

All authors contributed equally to the paper.

CONFLICTS OF INTEREST

The authors have none to declare

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