Original Article

Formulation and Evaluation of Transdermal Patch of Rabeprazole Sodium

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Abstract

Aim: The goal of the current study is to design and evaluate transdermal patches of rabeprazole sodium (RPS). **Materials and Methods:** Transdermal patches of RPS were prepared using polymers such as hydroxyl propyl cellulose (HPC-EF), polyvinyl pyrrolidone K-30 (PVP K-30), and polyvinyl pyrrolidone K-90 (PVP K-90) as film formers, polyethylene glycol (PEG-400) as a plasticizer, and Tween-80 and azone as permeation enhancers. The solvent casting technique was employed to develop the patches using aluminum foil as the backing membrane. These patches were evaluated for compatibility using Fourier transform infrared (FTIR) spectrophotometry and for content by ultraviolet (UV) spectrophotometry besides physicochemical properties such as thickness, adhesion, moisture content, moisture loss, and folding endurance. The patches were tested for *in vitro* release in United States Pharmacopoeia (USP) dissolution apparatus V and *ex vivo* permeation across shed snake skin in vertical Franz diffusion cell (FDC). **Results:** The characteristic FTIR spectra of RPS were also evident in the spectra of the patches, indicating drug-excipient compatibility. *In vitro* drug release indicated that the release of the drug was maximum from patches composed of HPC-EF (60.08±1.04%), which was much higher when compared with patches made of PVP K-30 (47.53±0.40%) and PVP K-90 (42.84±0.74%). The *ex vivo* permeation studies suggested that about 116.79±1.99 µg/cm^2 of the drug was permeated in 24 h from formulation patches composed of HPC-EF that resulted in flux of nearly 7.06 µg/cm^2/h. **Conclusion:** The studies indicated that feasibility of transdermal delivery of rabeprazole as a patch of 16 cm^2 is likely to suffice the therapeutic requirement.

Keywords: *HPC-EF, PEG-400, PVP, rabeprazole sodium, transdermal patch*

Introduction

The transdermal drug delivery system (TDDS) is also called as "patches." Conventional dosage forms such as tablets or capsules have limitations like poor bioavailability owing to hepatic first pass metabolism or degradation of drug by enzymatic reactions in gastrointestinal tract (GIT). TDDSs have the ability to enhance bioavailability by preventing the first pass metabolism and enzymatic or acid-mediated degradation.[1] Delivery through the transdermal route is a fascinating and patient-compliant novel drug delivery system and delivers the drug through epidermis in controlled rate within the therapeutic window.[2]

Rabeprazole sodium (RPS), a potent proton pump inhibitor, is a sulfonamide derivative used in the treatment of peptic ulcer. RPS inhibits the H^+K^+ATPase enzyme system in the GIT.[3] The oral bioavailability of the drug is drastically reduced (~52%) owing to extensive first pass metabolism.[4,5] The drug is short-acting and acid-labile too. Considering this, transdermal administration of rabeprazole is advantageous as it has the potential to improve the bioavailability by evading the first pass metabolism and acid-mediated degradation in the stomach. In this context, the aim of the present work is to formulate and evaluate transdermal patches of RPS.

Materials and Methods

Materials

RPS was procured from Yarrow Chem Pvt. Ltd, Mumbai, India. The excipients such as polyvinyl pyrrolidone (PVP) K-30, PVP K-90, hydroxyl propyl cellulose (HPC-EF), polyethylene glycol (PEG)-400, n-octanol, potassium dihydrogen ORTHOPHOSPHATE, AND SODIUM HYDROXIDE PELLETS were procured from Central Drug House Private Ltd, New Delhi, India. Azone was procured from Yarrow Chem Private Limited, Mumbai, India. Tween-80 was procured from Sisco Research Laboratory Pvt. Ltd, Mumbai, India.

Preformulation studies

Estimation of drug by ultraviolet spectrophotometry

Standard solutions having concentrations of 10, 20, 30, 40, and 50 µg/mL in phosphate-buffered

How to cite this article: Soral M, Nanjappa SH, Alayadan P. Formulation and evaluation of transdermal patch of rabeprazole sodium. J Rep Pharm Sci 2021;10:240-6.

Received: 14 Oct 2020
Accepted: 08 May 2021
Published: 17 Dec 2021

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Access this article online

Website: www.jrpsjournal.com

DOI:10.4103/jrptps.JRPTPS_126_20

Quick Response Code:

saline (PBS) pH 7.4, Indian Pharmacopoeia (IP) were prepared. The absorbance of these standards was observed at 283 nm by a UV spectrophotometer using PBS pH 7.4 as blank. The obtained data were plotted in figures and subjected to linear regression in Microsoft Excel.

Melting point determination

The melting point of the drug was determined by Thiele's tube apparatus. The drug was filled in a capillary tube and the melting point was measured with the help of a thermometer.[6] The measurement was done thrice to check repeatability.

Partition coefficient determination

Partition coefficient was determined with equal amount of volume of n-octanol and PBS pH 7.4. An accurately weighed 10 mg of drug was added to 5 mL of PBS pH 7.4 and 5 mL of n-octanol system and mixed intermittently in a separating funnel for 24 h and then left for next 24 h at room temperature. After 24 h, the concentration of RPS was determined using a UV spectrophotometer at 283 nm.[7] The partition coefficient of the drug was determined using equation (1):

$$K = \frac{Concentration\ of\ drug\ in\ organic\ phase}{Concentration\ of\ drug\ in\ aqueous\ phase}. \quad (1)$$

Infrared spectrophotometry

The spectrum of the drug was measured using a Fourier transform infrared (FTIR) spectrophotometer. The drug was placed in the sample holder using IR grade potassium bromide as a blank and scanned between the ranges 400–4000 cm^{-1} to determine the characteristic peaks of the drug.[8]

Development of transdermal patches

The selected polymers were weighed and dissolved in the selected solvent system. The polymeric solution was allowed to stir till a clear solution was obtained. Subsequently, the plasticizer was added to the polymeric solution and stirred. Finally, the drug was added with constant stirring to get a clear solution. The drug containing polymeric solution was casted in an Anumbra petri dish using aluminum foil as a backing membrane to obtain the transdermal patches. The composition of the transdermal patches produced by the solvent casting procedure is outlined in Table 1. The patches were allowed to dry at room temperature for 24 h. The dried patches were stored in a desiccator at 0–4°C and used for further evaluation studies.[9]

Evaluation of transdermal patches

Formulated patches were subjected for the evaluation of physicochemical characteristics such as visual appearance, thickness, uniformity in weight, adhesiveness, content uniformity, *in vitro* drug release, and *ex vivo* permeation.

Visual appearance

The TDDS was evaluated visually for transparency, color, texture, and flexibility.[10] The casted patches were also examined under an optical microscope to detect possible crystallization, if any.

Thickness

The thickness of the transdermal patches was measured at five random sites using a Digimatic caliper (Mitutoyo, Japan). The average of thickness determined for three patches was taken, and values were expressed as mean and standard deviation.[8]

Weight uniformity

Patches randomly selected from each batch were weighed individually on a digital balance and the mean value and standard deviation were calculated.[11] The results were expressed as mean ± standard deviation.

Test for adhesion

The tackiness of the transdermal patches was tested with a rolling ball tack test. A stainless steel ball of diameter 7–16 in was released from the inclined track of angle 22.5° to the horizontal surface. The transdermal patch whose adhesion has to be determined forms the horizontal surface. The distance traveled by the ball on the upper surface of the patch was measured in centimeters. The adhesiveness of the transdermal patch is inversely related to the distance traversed by the ball.[12]

Folding endurance

The transdermal patches were evaluated for mechanical strength by determining the folding endurance. The patch was folded at the same place several times until a crack was visible and the data were reported. The number of times the patches had to be folded until visible crack was observed is considered as folding endurance.[13]

Table 1: Composition of rabeprazole sodium transdermal patches

Formulation code	Polymer quantity		Drug	PEG-400	Permeation enhancer	Quantity
F1	PVP K-30	5%	2.5%	2.5%	—	—
F2	PVP K-30	10%	2.5%	2.5%	—	—
F3	HPC-EF	5%	2.5%	5%	—	—
F4	HPC-EF	10%	2.5%	5%	—	—
F5	PVP K-90	5%	2.5%	5%	—	—
F6	PVP K-90	10%	2.5%	5%	—	—
F7	HPC-EF	5%	2.5%	5%	Azone	1% (v/v)
F8	HPC-EF	5%	2.5%	5%	Tween-80	1% (v/v)
F9	EL-100	5%	2.5%	5%	—	—

Drug content

The drug loaded patch (1 cm^2) was equilibrated with PBS in a volumetric flask. The flasks were agitated on a mechanical shaker for 24 h. Then, 1 mL of the filtered solution was diluted with the buffer up to 10 mL and the absorbance was measured at 283 nm to determine the drug content present in the patch.[14] The measurements were done in triplicate and the results were expressed as mean ± standard deviation.

Percentage moisture uptake

The weighed transdermal patches were kept at 25°C for a day in a desiccator. After a day, the patches were collected and exposed in 84% relative humidity maintained using saturated potassium chloride solution in the desiccator until a constant weight was attained. The initial weight and the weight of patches at predetermined intermittent time intervals were recorded. The % moisture uptake was calculated using equation (2)[10]:

$$\% \text{ Moisture uptake} = \frac{\text{Final weight-Initial weight}}{\text{Initial weight}} \times 100. \quad (2)$$

Percentage moisture content

Accurately weighed patches were kept in a desiccator loaded with fused calcium chloride for 24 h at 25°C. After 24 h, patches were weighed again, and the % moisture content was determined using equation (3)[10]:

$$\% \text{Moisture content} = \frac{\text{Initial weight-Final weight}}{\text{Final weight}} \times 100. \quad (3)$$

In vitro release test (IVRT)

The IVRT of patches was performed using paddle over disc USP dissolution apparatus V. The dissolution media used were PBS (pH 7.4). The patches were pasted on a disc and exposed to the dissolution media taken in a dissolution jar (250 mL). The temperature of water bath was maintained at 32±0.5ºC with a rotating speed of 50 rpm. Samples measuring 1 mL were withdrawn every hour for 8 h, and drug release was determined using UV spectroscopy at 283 nm.[14]

Ex vivo permeation study

Preparation of skin

The shed snake skin was taken and cut according to the Franz diffusion cell (FDC diameter (2 cm^2) and immersed in PBS (pH 7.4) for 1 h before the start of the studies. *Ex vivo* permeation studies were carried out in FDC apparatus with shed snake skin as a barrier. The diffusional area of FDC was 2 cm^2. The skin was carefully sandwiched between the receptor compartment and the donor compartment of FDC. The transdermal patch area was trimmed and positioned over the shed snake skin. The PBS was filled in the receptor compartment as diffusion medium, which was allowed to stir at 600 rpm at a constant temperature (37±1ºC). About 1 mL of the buffer was withdrawn from FDC at time periods (0, 0.5, 1, 2, 3, 5, 8, 24 h); portion of drug permeated was analyzed in a UV spectrophotometer. The withdrawn solution was restored with an equal amount of buffer every time after withdrawal.[14,15] The solutions withdrawn were estimated for the drug content by UV spectrophotometry to determine the amount of drug permeated.

Results and Discussion

Estimation of wavelength

The UV spectrum of RPS in PBS (pH 7.4) was found to display absorption maxima at 283 nm. The absorption maxima was found to correspond well with that reported in the literature.[6] The standard calibration curve of RPS shows linearity with the R^2 value of 0.998 at 283 nm wavelength. The slope of the standard curve was used to determine the drug content in most of the *in vitro* and *ex vivo* samples generated during the studies.

Determination of purity of drug by FTIR

Rabeprazole is known to exhibit its characteristic peaks owing to NH stretching, OH stretching, CH, CH3, C = C, C-N, S = O at positions depicted in Table 2. The characteristic peaks of rabeprazole were quite evident in the spectra of the optimized formulation (F8) at nearly the same positions.[8] The spectral observations suggested the compatibility of drug with various excipients used to develop the transdermal patch of rabeprazole. The observations also suggested the chemical integrity of the drug in the formulation and ruled out the possibility of any possible chemical interaction between RPS and the excipients. The peak of RPS was observed in Figure 1 with FTIR and was stable with optimized formulation shown in Figure 2. The spectral observations are depicted in Table 2 which rules out possible interference and thus shows the compatibility of RPS with excipients used in the formulations.[8,16]

Estimation of melting point

Melting point would determine the ease with which drug would be able to permeate through the skin. Drugs with low melting point would permeate better through the skin. The melting point of RPS was found to be 140±0.5ºC which corresponded well to the standard reference value.[6] In addition, the melting point of the drug being less than 200°C indicated the suitability

Table 2: Interpretation of FTIR studies of rabeprazole sodium

Functional group	RPS	Formulation	Interpretation	Functional group	RPS	Formulation	Interpretation
N-H	3391.21	3504.02	Stretching	CH_3	2365.26	2363.34	Stretching
O-H	3355.53	3076.87	Stretching	C=C	1584.24	1578.45	Stretching
C-H	3143.04	2881.13	Stretching	C-N	1459.85	1454.06	Stretching
CH_2	2968.87	-	Stretching	S=O	1092.48	1092.48	Stretching

of the drug for development of transdermal patch. Drugs with low melting point are known to get easily solubilized in the lipid bilayer and permeate better.[2]

Partition coefficient

Partition coefficient would determine the suitability of the drug for transdermal delivery.[2] The partition coefficient of the RPS in n-octanol and phosphate buffer (pH 7.4) was found to be 90.63 ± 14.9. The log *P* value computed for the partition coefficient was found to be 1.96. The experimental value of log *P* was found to be close to the calculated value for RPS. The partition coefficient study determines the extent of drug penetration through the lipid membrane of the skin.[7] The partition coefficient (log *P*) of RPS according to this study was 1.96, which suggested that the drug was suitable for transdermal delivery. A drug must have both lipophilic and hydrophilic properties to permeate through the intact skin. Log *P* values have been used as a reliable indicator to predict the suitability of drug candidates for transdermal development. Drugs having log *P* value between 1 and 3 are considered to be suitable candidates for transdermal delivery.[2]

Evaluation of transdermal patches of RPS

Physicochemical characterization

The transdermal patches of RPS were found to be clear, colorless, odorless, and transparent. Moreover, the patches developed did not display any signs of precipitation of the drug when observed under an optical microscope. The thickness of the transdermal patches of different batches was found to be uniform ranging from 0.24±0.01 to 0.28±0.02 mm, and thickness of the patches depends on the concentration of polymer and excipients present in the patch.[11] Similarly, the

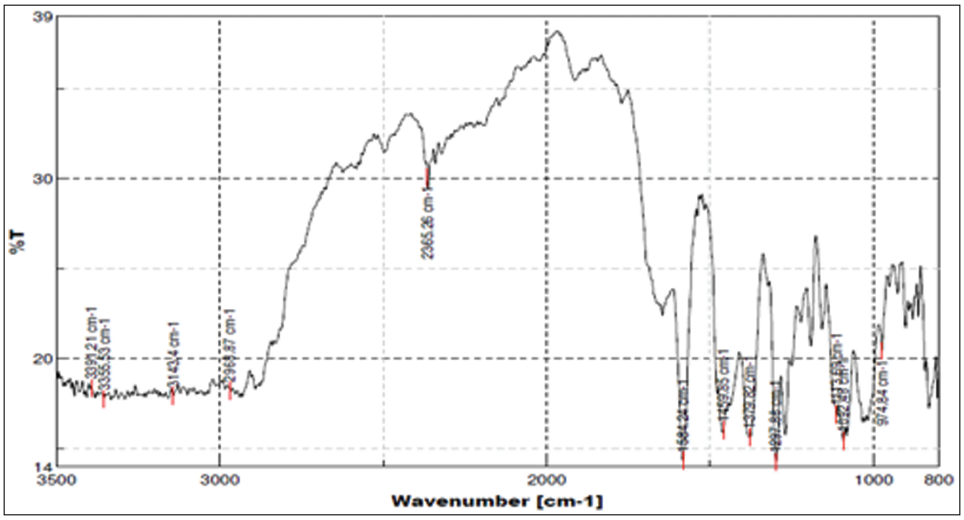

Figure 1: FTIR spectrum of rabeprazole sodium

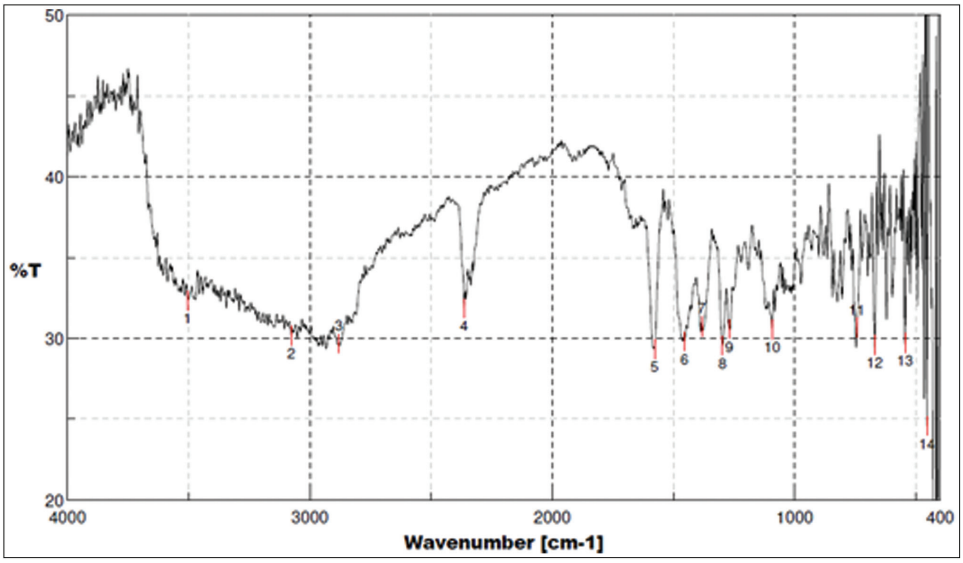

Figure 2: FTIR spectrum of optimized formulation

weight of the transdermal patches was found to be uniform ranging from 0.215 ± 0.04 to 0.230 ± 0.02. Likewise, the content of different batches of transdermal patches was found to be uniform and ranged from 48.02±0.55 to 49.22±0.84 mg/cm^2. The uniformity of the thickness, weight, and content indicated the suitability of solvent casting technique to fabricate transdermal patches of rabeprazole. The solvent casting method continues to be a suitable method of fabrication of transdermal patches. The physicochemical properties of transdermal patches are known to in turn affect the *in vitro* drug release and *ex vivo* permeation.

The folding endurance indicated the mechanical strength of transdermal patches.[14] The folding endurance was found to be in the range of 74.67 ± 4.51 to 91.67 ± 2.08, suggesting that the films produced were found to possess enough mechanical strength.[13] The high value of folding endurance implies that the patch fabricated would maintain its integrity without appearance of any cracks on application of the surface of the skin. The tackiness of the transdermal patches was varying in range from 1.53±0.31 to 3.97±0.15 cm. The tackiness of the transdermal patches is expected to be neither high nor low. Transdermal patches with high tackiness are not desirable as they are known to secure too firmly to the skin surface and pose problems during removal. In contrast, patches with low tackiness are not preferred as they would be easily dissipated from the surface of the skin.[12] The % moisture content was ranging from 5.84±1.06 to 7.92±0.70% and the % moisture uptake was ranging from 11.58±1.95 to 17.68±1.01% at a relative humidity of 84%. The % moisture content and % moisture uptake usually vary due to polymer concentration in the transdermal patches, which are shown in Table 3.

Formulation F9 containing Eudragit L-100 was considered to be unsuitable as patches changed in color to black at room temperature. The interaction of the drug with Eudragit L-100 is the likely reason for the color change noticed in the present study. RPS is prone to instability as it is known to rapidly degrade and get discolored on exposure to acidic media and higher temperature.[17] As the preformulation studies indicated the color change, no formulation of RPS was planned using Eudragit L-100 in the present study.

In vitro release test

The release profile of RPS from varying polymeric patches is shown in Figure 3. Formulation F3 was found to display the highest release (60.08 ± 1.04%), whereas formulation F6 was found to display the least amount of drug release. The studies indicated that HPC-EF readily released the contents from the patch compared with other polymers due to its hydrophilic nature, solubilizing property, and lower molecular weight used in the study.[18,19] The other observation that could be made during the studies was that the % drug release was found to be reduced with the increase in concentration of the film-forming polymer. The formulation F3 that displayed the highest drug release was considered for further evaluation. HPC-EF was not found to hinder the drug release from the matrix unlike other high molecular polymers such as PVP K-90.

Ex vivo permeation studies

Shed snake skin was used as a barrier to test the permeation of drug in vertical FDC. The amount of drug permeated from aqueous solution of the drug and from formulations F3, F7, and F8 was found to be 87.06±3.05, 99.17±2.57, 105.26±2.77, and 116.79±1.99, respectively [Figure 4]. The steady-state flux (J_{ss}) was determined from the drug solution, formulations F3, F7, and F8, which was found to be 5.516±0.028, 4.708±0.088, 4.857±0.132, and 7.064±0.083 µg/cm^2/h, respectively. It was noted that formulation F8 which contains Tween-80 as permeation enhancer displayed the highest flux 7.064±0.083 µg/cm^2/h. Higher penetration of RPS in F8 owing to Tween-80 may be due to change in the barrier properties of the skin and in the vehicle-stratum corneum partition coefficient. It was seen in another work that there was an enhancement in the transdermal flux of hydrocortisone in the presence of Tween-80. It was also reported to enhance the skin permeation of hydrocortisone and lidocaine.[20] Tween-80 belongs to the class of surfactants that has been used as a safe penetration enhancer. Tween-80 has the ability to increase the drug penetration through the skin by micellar solubilization of stratum corneum lipids.[21]

The optimized size of the patch was computed considering the pharmacokinetic parameters of the drug and steady-state flux achieved. The pharmacokinetic parameters that would

Table 3: Physical evaluation of rabeprazole sodium transdermal patch

Formulation	Thickness (mm; *n*=3)	Weight uniformity (g; *n*=3)	Folding endurance (*n*=3)	Drug content (mg; *n*=3)	Tack test (cm; *n*=3)	% moisture content (*n*=3)	% moisture uptake (*n*=3)
F1	0.27±0.001	0.216±0.004	74.67±4.51	48.43±0.71	3.80±0.26	6.16±0.61	15.06±1.13
F2	0.26±0.002	0.228±0.002	89.33±1.53	48.80±0.54	3.97±0.15	6.26±0.76	17.68±1.01
F3	0.24±0.001	0.215±0.004	87.00±4.58	49.18±0.49	2.87±0.31	7.78±1.20	13.80±1.12
F4	0.24±0.001	0.228±0.002	91.67±1.53	48.89±0.38	2.33±0.15	8.10±0.93	14.09±1.27
F5	0.26±0.002	0.219±0.002	82.67±2.08	48.26±0.51	3.47±0.25	6.60±0.23	13.45±1.86
F6	0.28±0.002	0.230±0.002	91.67±2.08	48.02±0.58	1.53±0.31	5.84±1.06	13.75±1.04
F7	0.26±0.002	0.219±0.002	81.67±4.73	49.22±0.84	2.57±0.15	7.69±0.97	11.58±1.95
F8	0.27±0.001	0.227±0.005	85.66±3.51	49.04±1.36	2.60±0.20	7.92±0.70	12.51±1.55

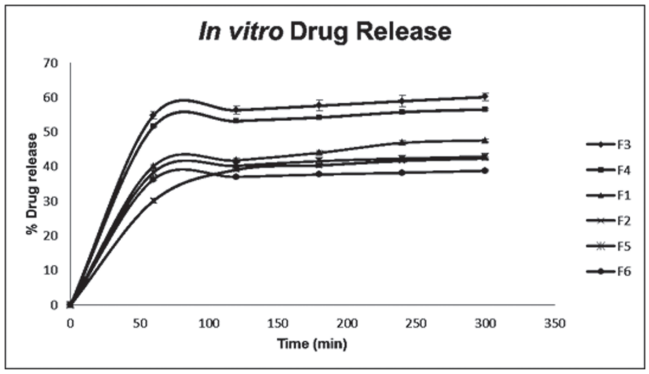

Figure 3: *In vitro* drug release profile of formulation

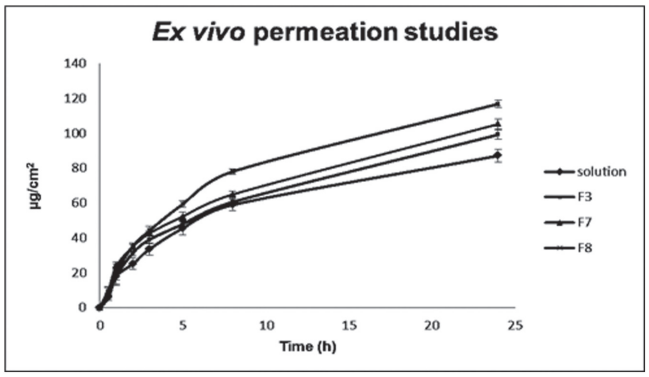

Figure 4: *Ex vivo* permeation of the formulations through shed snake skin

be required for computation such as clearance and effective plasma concentration for rabeprazole were reported to be 4.71± 0.98 mL/(min.kg) and 0.401±0.246 µg/mL.[22] The computation indicated that the transdermal patch of an area of 16 cm^2 could meet the therapeutic requirement in an adult.

Conclusion

Transdermal patches of RPS were successfully developed by the solvent casting technique using bioadhesive polymers and PEG-400 as plasticizer. HPC-EF was found to be the most suitable polymer for the development of transdermal patches as it was found to release most of the drug from the formulation. Tween-80 was found to be the most suitable penetration enhancer for RPS. The studies indicated the feasibility of transdermal delivery of RPS as the patch having an area of 16 cm^2 would most likely be able to deliver therapeutic amounts of the RPS. The transdermal patch of RPS developed has the potential to overcome the first pass metabolism and the gastric degradation of the drug and thereby is likely to enhance the bioavailability as well as patient compliance.

Summary

Transdermal patches of RPS were prepared successfully with the solvent casting technique using various polymers such as HPC-EF, PVP K-30, and PVP K-90. Ethanol was selected as a solvent, PEG-400 as a plasticizer, and Tween-80 and azone as permeation enhancers. The FTIR studies indicated that there was no interaction between RPS and excipients. The transdermal patch containing HPC-EF (5%) as a polymer displayed higher amount of drug release (60.08 ± 1.04%). The *ex vivo* permeation studies performed across shed snake skin in FDC suggested that about 116.79±1.99 µg/cm^2 of the drug was permeated in 24 h from formulation patches composed of HPC-EF that resulted in J_{ss} of nearly 7.06 µg/cm^2/h. The studies indicated that feasibility of transdermal delivery of rabeprazole as a patch of 16 cm^2 is likely to meet the therapeutic requirement.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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