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Development and Evaluation of Ramosetron Hydrochloride Transdermal Drug Delivery System



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ABSTRACT

The study was aimed at the development of matrix moderated transdermal drug delivery system of Ramosetron hydrochloride using various polymers. Specific strategies like use of penetration enhancers shall be employed to meet systematic requirement of drug. Different formulation variable shall be studied and optimized to achieve the desired release profile. Formulations were done using different polymers such as Eudragit S100, HPMC K4M in different ratios and combinations. Plasticizer and penetration enhancer were incorporated for getting flexibility for films and improvement of drug absorption respectively. Compatibility between drug and polymers were performed by FTIR Spectral analysis. By FTIR spectral analysis, it was confirmed the absence of interactions. Thickness and flatness of the films were evaluated and the results revealed that the casting mixer was uniformly spread over the mould. Drug content evaluation was done for individual formulations and the values are in the acceptable range. The drug release was found to be increased on increasing the concentration of hydrophilic polymer in the polymer matrix. Formulation A7 containing HPMC K4M: Eudragit S100 (1:1) showed cumulative % drug release of 85.732 ± 1.738 in 24 h, emerging as a best formulation by fulfilling the requirement of better and sustained release which was not possible with HPMC K4M and Eudragit S100 alone. A value of coefficient of determination for the optimized transdermal patch formulation A7 indicates that release of drug follows zero order kinetic model.

INTRODUCTION

Ramosetron hydrochloride is a new selective 5-hydroxytryptamine type 3 (5-HT₃) receptor antagonist that reportedly has more potent antiemetic effects compared with other 5-HT₃ receptor antagonists. The purpose of this study was to evaluate the efficacy of Ramosetron Hydrochloride for the prevention of postoperative nausea and vomiting (PONV) with that of ondansetron or placebo in high-risk patients undergoing gynecological surgery¹.

Transdermal therapeutic systems are defined as a self contained, discrete dosage forms which, when applied to the intact skin, deliver the drug, through the skin at control rate to the systemic circulation. Transdermal formulation maintain drug concentration within the therapeutic window for prolong period of time ensuring that drug levels neither fall below the minimum effective concentration nor exceed the maximum effective concentration. An ideal drug to be formulated as transdermal drug delivery should possess several physicochemical properties, such as short half life, small molecular size, low dose, low oral bioavailability etc².

A recent approach to drug delivery is to deliver the drug into systemic circulation at predetermined rate using skin as a site of application. Transdermal patches are delivered the drug through the skin in controlled and predetermined manner in order to increase the therapeutic efficacy of drug and reduced side effect of drug. Controlled drug release can be achieved by transdermal drug delivery systems (TDDS) which can deliver medicines via the skin portal to systemic circulation at a predetermined rate over a prolonged period of time. TDDS has gained a lot of interest during the last decade as it offers many advantages over the conventional dosage forms and oral controlled release delivery systems notably avoidance of hepatic first pass metabolism, less frequency of administration, reduction in gastrointestinal side effects and improves patient compliance^{3,4}.

The study was aimed at the development of matrix moderated transdermal drug delivery system of Ramosetron hydrochloride using various polymers. Specific strategies like use of penetration enhancers shall be employed to meet systematic requirement of drug. Different formulation variable shall be studied and optimized to achieve the desired release profile.

MATERIALS AND METHODS

Ramosetron hydrochloride gift sample were procured from Clearsynth Labs Ltd., Mumbai, India, Eudragit S100 were procured Research-Lab Industries Mumbai, HPMC K4M and Dibasic sodium phosphate were procured Loba Chemie Pvt. Mumbai, India.

Pre-formulation study

Confirmation of Ramosetron hydrochloride as model drug was done by using melting point determination and Fourier Transform Infra Red spectroscopy. Calibration curves were developed in various solvent systems using UV spectroscopy. Evaluation of the polymer-drug interaction was done by using Fourier Transform Infra Red spectroscopy (FTIR).

Assessment of the drug-polymer interaction using FTIR

FTIR analysis was used to investigate and predict structure characterization of Ramosetron hydrochloride obtained as gift sample and drug-polymer interactions. Therefore it can be applied for selection of suitable chemically compatible excipients. This was used for the confirmation of drug. 2-3 mg of the taster along with 15 mg of KBr used during mortars in addition to triturated which were initially dried. A small amount of triturated samples were taken in addition to reserved into the sample holders along with scanned as of 400cm^{-1} to 4000cm^{-1} (JASCO IR 4100) and was matched and compared with official spectra^{5,6}.

Formulation of Transdermal Patch by using Eudragit S100 and HPMC K4M

In the present study, drug loaded matrix type transdermal films of Ramosetron hydrochloride were prepared by solvent evaporation method. A mould of 5 cm length and 5 cm width with a total area of 25 cm^2 as fabricated was used. The bottom of the mould was wrapped with aluminium foil, 300 mg of the polymer(s) was accurately weighed and dissolved in 5 mL of chloroform: methanol (1:1) and kept aside to form clear solution. Polyethylene glycol (PEG 400) was used as plasticizer and dimethyl sulfoxide (DMSO) was used as permeation enhancer. Ramosetron hydrochloride was dissolved in the above solution and mixed for 10 min. The resulted uniform solution was cast on the aluminium foil and dried at 40°C in the hot air oven for 24 h. An inverted funnel was placed over the mould to prevent fast evaporation of the solvent. After 24 h the dried films were taken out and stored in a desiccator for further studies^{7,8}.

Physical appearance

All the prepared patches were visually inspected for color, clarity, flexibility and smoothness.

Thickness uniformity

The thickness of the formulated film was measured at 3 different points using a digital caliper and average thickness of three reading was calculated⁹.

Weight uniformity

For each formulation, three randomly selected patches were used. For weight variation test, 3 films from each batch were weighed individually and the average weight was calculated¹⁰.

Folding endurance

The folding endurance was measured manually for the prepared films. A strip of film (5 x 5 cm) was cut and repeatedly folded 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 endurance¹¹.

Percentage moisture absorption

The films were weighed accurately and placed in the desiccators containing 100 mL of saturated solution of potassium chloride, which maintains 80-90% RH. After 3 days, the films were taken out and weighed¹². The study was performed at room temperature. The percentage moisture absorption was calculated using the formula:

$$\% \text{ moisture absorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Percentage moisture loss

The films were weighed accurately and kept in a desiccators containing anhydrous calcium chloride. After 3 days, the films were taken out and weighed¹³. The moisture loss was calculated using the formula:

$$\% \text{ moisture loss} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Water vapour transmission rate

Glass vials of 5 mL capacity were washed thoroughly and dried to a constant weight in an oven. About 1 g of fused calcium chloride was taken in the vials and the polymer films of 2.25 cm²

were fixed over the brim with the help of an adhesive tape. Then the vials were weighed and stored in a humidity chamber of 80-90% RH condition for a period of 24 h¹⁴. The vials were removed and weighed at 24 h time intervals to note down the weight gain.

$$\text{Transmission rate} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Time} \times \text{Area}} \times 100$$

Tensile strength

Tensile strength of the film was determined with Universal strength testing machine (Hounsfield, Slinfold, Horsham, U.K.). The sensitivity of the machine was 1 g. It consisted of two load cell grips. The lower one was fixed and upper one was movable. The test film of size (4 × 1 cm²) was fixed between these cell grips and force was gradually applied till the film broke. The tensile strength of the film was taken directly from the dial reading in kg¹⁵. Tensile strength is expressed as follows:

$$\text{Tensile strength} = \frac{\text{Tensile load at break}}{\text{Cross section area}}$$

Drug content uniformity of films

The patches (1cm²) were cut and added to a beaker containing 100 mL of phosphate buffered saline of pH 7.4. The medium was stirred with magnetic bead. The contents were filtered using Whatmann filter paper and the filtrate was examined for the drug content against the reference solution consisting of placebo films (contains no drug) at 300 nm spectrophotometrically. The experiment was repeated to validate the result¹⁶.

***In vitro* drug release studies**

In vitro skin permeation studies were performed by using a modified Franz diffusion cell with a receptor compartment capacity of 20 mL¹⁷. The synthetic cellophane membrane was mounted between the donor and receptor compartment of the diffusion cell. The formulated patches were cut into size of 1cm² and placed over the drug release membrane and 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 37 ± 0.5⁰C. The samples of 1 mL were withdrawn at time interval of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, and 24 h, analyzed for drug content spectrophotometrically at 300 nm against blank. The receptor phase

was replenished with an equal volume of phosphate buffer at each time of sample withdrawal. The cumulative amounts of drug permeated per square centimeter of patches were plotted against time.

***In vitro* drug release kinetic modeling**

The *in vitro* drugs releasing information were investigated in favor of the types of releasing mechanisms follow. To describe the kinetics of drug release from the controlled release transdermal patch, the releasing information be evaluated among the help of arithmetical model such as zero-orders, first-orders, Higuchi as well as Koresmeyer-Peppas models by means of PCP Disso v2.08 software¹⁸.

RESULTS AND DISCUSSION

PREFORMULATION STUDY

The sample of Ramosetron hydrochloride was studied for organoleptic characteristics and showed colorless or white crystalline powder. The melting point of Ramosetron hydrochloride was determined by melting point apparatus using capillary technique and it was found to be 244-246°C which complies with the standard value. Loss on drying of drug sample was calculated and found not more than 0.2 percent.

The drug Ramosetron hydrochloride was identified by U.V spectra and I.R spectra. The interpreted result was presented in the Figure 1 and 2 respectively show that it coincides with standard reference spectra.

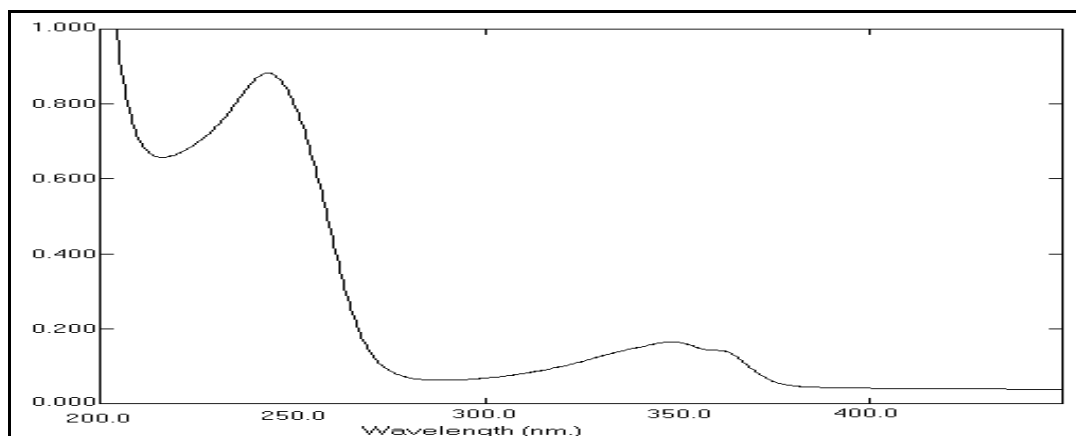


Figure 1: U. V. spectrum of Ramosetron hydrochloride

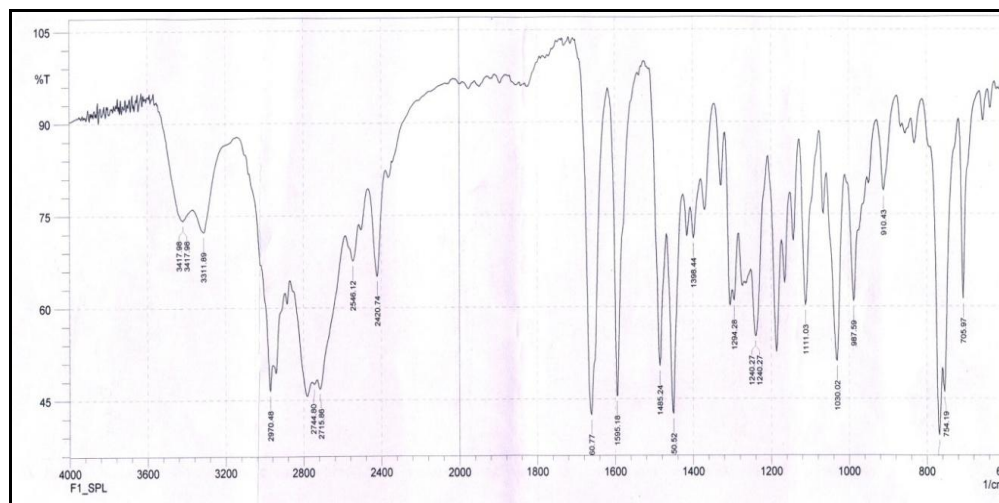


Figure 2: IR spectrum of Ramosetron hydrochloride

Evaluation of transdermal patch

The prepared transdermal patches were evaluated for their physicochemical characteristics such as weight variation, thickness, % moisture loss, % moisture absorption, water vapour transmission rate, folding endurance, tensile strength, drug content and *in vitro* drug release (Table 1). The Cross section area transdermal patches were transparent, smooth, uniform and flexible. The thickness of the patches was varied from 0.195 ± 0.021 mm to 0.204 ± 0.017 mm. Low standard deviation values in the film thickness measurements ensured uniformity of the patches prepared by solvent evaporation.

The weights ranged between 0.379 ± 0.014 g and 0.416 ± 0.015 g, which indicates that different batches patch weights, were relatively similar. The % moisture loss was found to be between 2.76 ± 1.38 to 10.14 ± 1.94 and % moisture absorption was found to be 1.997 ± 1.846 to 5.853 ± 1.827 . The result revealed that the moisture absorption and loss was found to be increased with increasing concentration of hydrophilic polymers. The small moisture loss in the formulations helps the film to remain stable, brittle and free from complete drying. Again low moisture absorption protects the material from microbial contamination and bulkiness of the patches. The patches prepared from HPMC K4M show more tensile strength than the patches prepared from Eudragit S100. As the concentration of hydrophilic polymer HPMC K4M was increased there is increase in tensile strength.

The tensile strength measures the ability of a patch to withstand rupture. Presence of DMSO has shown good tensile strength. The mean value was found to vary between 2.94 ± 0.179 to 3.88 ± 0.297 kg/mm². Folding endurance was found to be >150 that is satisfactory weight of the patches, drug content was found to be 99.25 % to 99.91 %. The cumulative % drug permeated and % drug retained by the individual path in the *in vitro* skin permeation studies were based on the mean amount of drug present in the respective patch.

Table 1. Thickness, Weight, Folding Endurance, % Moisture absorption, % Moisture loss, Water vapour transmission rate of formulations

Formulation code	Thickness (mm)	Weight (g)	Folding Endurance	% Moisture absorption	% Moisture loss	Water vapour transmission rate
A1	0.202 ± 0.025	0.416 ± 0.015	98.06 ± 4.672	4.161 ± 3.073	10.14 ± 1.94	0.0039 ± 0.0002
A2	0.201 ± 0.013	0.382 ± 0.019	69.94 ± 3.731	2.044 ± 2.188	8.74 ± 1.51	0.0029 ± 0.0006
A3	0.203 ± 0.020	0.392 ± 0.011	68.63 ± 5.732	1.997 ± 1.846	8.17 ± 1.43	0.0032 ± 0.0006
A4	0.199 ± 0.015	0.398 ± 0.018	79.12 ± 5.841	2.850 ± 1.714	6.35 ± 2.57	0.0025 ± 0.0003
A5	0.197 ± 0.011	0.386 ± 0.013	91.82 ± 4.961	3.851 ± 1.603	2.76 ± 1.38	0.0037 ± 0.0003
A6	0.204 ± 0.017	0.379 ± 0.014	82.87 ± 4.591	4.263 ± 2.018	5.32 ± 3.64	0.0031 ± 0.0005
A7	0.195 ± 0.021	0.401 ± 0.021	93.74 ± 6.178	5.853 ± 1.827	8.53 ± 1.85	0.0038 ± 0.0005

All values are given in (mean \pm SD) for n = 3.

***In vitro* drug release studies**

Release studies are required for predicting the reproducibility of rate and duration of drug release. The importance of polymer dissolution on drug release from matrices has been known for ensuring the sustained release performance. The result indicated that the release of drug from patches increases with increasing concentration of HPMC K4M. The drug release was found to be increased on increasing the concentration of hydrophilic polymer in the polymer matrix. This is due to the fact that dissolution of aqueous soluble fraction of the polymer matrix leads to the formation of gelaneous pores.

The formation of such pores leads to decrease the mean diffusion path length of drug molecules to release into the diffusion medium and hence, to cause higher release rate. Formulation A7 containing HPMC K4M: Eudragit S100 (1:1) showed cumulative % drug release of 85.732 ± 1.738 in 24 h, emerging as a best formulation by fulfilling the requirement of better and sustained release which was not possible with HPMC K4M and Eudragit S100 alone.

Table 2: Results of tensile strength, drug content and *in vitro* drug release A1-A7

Formulation code	Tensile strength (Kg/mm ²)	% Drug content	% Drug release
A1	3.88 ± 0.297	99.91	66.814 ± 3.262
A2	2.94 ± 0.179	99.66	68.579 ± 2.874
A3	3.10 ± 0.171	99.25	73.823 ± 1.921
A4	3.24 ± 0.148	99.29	74.247 ± 1.347
A5	3.29 ± 0.129	99.83	78.854 ± 2.793
A6	3.38 ± 0.098	99.83	81.082 ± 1.366
A7	3.44 ± 0.173	99.41	85.732 ± 1.738

All values are given in (mean \pm SD) for n = 3.

***In vitro* drug release kinetics**

To understand the mechanism of drug release from the formulations, the data were treated with zero order (cumulative percent of drug release vs. time), first order (log cumulative percentage of drug remaining v/s time), Higuchi model (cumulative percent of drug release v/s square root of time) and Korsmeyer & Peppas (log cumulative percent of drug release v/s log time) equations. When the result was plotted according to the zero order equation, the formulations showed good linearity, when the same data was plotted according to the first order equation, Higuchi's equation and Korsmeyer & Peppas equation, it shown a fair linearity. The results are given in the Table 3 which indicates that the release of drug from the formulations follows zero order release kinetic model.

Table 3: *In vitro* drug release kinetics of optimization batches A7

Batch code	R ² (coefficient of determination) of various Kinetic Models			
	Zero order	First order	Higuchi release	Korsmeyer & Peppas release
A7	0.896	0.735	0.779	0.768

Preformulation study was performed to verify the purity of drug and also to confirm any drug: polymer interaction or change in physical state by various techniques. The melting point of Ramosetron hydrochloride complies with the reported value. FTIR study was performed for Ramosetron hydrochloride to evaluate that no chemical interaction observed between the drug and excipients used. FTIR spectral interpretation confirms all prominent peaks for various functional groups present in the structure of Ramosetron hydrochloride were remains unchanged from their original position indicates no chemical interaction between drug and excipients.

The formulation deals with the matrix diffusional transdermal patch by using HPMC K4M and Eudragit S100 as a controlled release polymers. Various concentrations were used to attain good percentage of drug release at the end of 24 h. The prepared transdermal patches were evaluated for their physicochemical characteristics such as weight variation, thickness, % moisture loss, % moisture absorption, water vapour transmission rate, folding endurance, tensile strength, drug content and *in vitro* drug release. The Cross section area transdermal patches were transparent, smooth, uniform and flexible. Low standard deviation values in the film thickness measurements

ensured uniformity of the patches prepared by solvent evaporation. Which also indicates that different batches patch weights, were relatively similar. A value of coefficient of determination for the optimized transdermal patch formulation A7 indicates that release of drug follows zero order kinetic model.

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