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Design and Evaluation of Transdermal Drug Delivery System of Ivabradine Hydrochlride

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ABSTRACT

Transdermal patches are formulated in such as to deliver the drug substance in a slow but regular way resulting in a prolonged and adequately constant systemic absorption rate after passing through the skin barriers, and it avoid first pass effect. Through a diffusion process, the drug enters the bloodstream directly though the skin. For this studies design the transdermal drug delivery system of Ivabradine hydrochloride with ERS100 and Hydroxy propyl methyl cellulose polymer in various concentrations. Propylene glycol was used as a plasticizer and dimethyl sulphoxides used as permeation enhancer. Characterization of transdermal patch is use to check it's quality, thickness, weight of patch, uniformity & in vitro permeation studies. The market for transdermal products has been in a significant upward trend that is likely to continue for the foreseeable future. It was observed that the formulation containing ERS100:HPMC K100M (4:6) showed ideal higuchi release kinetics. On the basis of in vitro drug release through skin permeation performance, Formulation A2 was found to be better than other formulations and it was selected as the optimized formulation. An increasing number of TDD products continue to deliver real therapeutic benefit to patients around the world.
Keywords: Ivabradine hydrochloride, HPMC, ERS100, Transdermal patch, permeation studies.

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INTRODUCTION

Novel drug delivery is one of the developing friendly dosage forms of various formulations with the ultimate aim of increasing their dosing convenience to the patient. The NDDS may involve a new dosage form e.g., from thrice a day dosage to once a day dosage form or developing a patch forms in place of injections. Today, about 74% of drugs are taken orally and are found not to be as effective as desired. Thus, various forms of NDDS such as transdermal delivery systems, controlled release systems; transmucosal delivery systems etc. emerged (1).

The transdermal route now ranks with oral treatment as the most successful innovative research area in drug delivery, with around 40% of the drug delivery candidate products under clinical evaluation related to transdermal or dermal system. The worldwide transdermal patch market approaches £ 2 billion, based on only ten drugs including scopolamine, nitroglycerine, clonidine, estrogen, testosterone, fentanyl, and nicotine,with a lidocaine patch soon to be marketed (2).

Recently, safety concerns have arisen regarding the continued application of transdermal patches during magnetic resonance imaging (MRI) procedures. Case reports have revealed that serious burns may occur in patients undergoing MRI who have transdermal patches with metallic content applied to their skin. The metallic component of these patches acts as a conductor for the radio frequency pulses of the MRI, inducing an electric current and thereby resulting in intense heat and burns (3).

Objective of the current research study is to design and develop transdermal therapeutic system of a model antihypertensive drug, Ivabradine hydrochloride using matrix devices.

MATERIALS AND METHODS

Ivabradine hydrochloride (Ind-Swift Ltd ,Panchkula) and ethylcellulose- 45 cps (Colorcon Asia pvt Ltd,Goa), were received as a gift samples. Hydroxy Propyl Methyl Cellulose (HPMC) and Eudragit RS 100 were gift samples from Akums Drugs & Pharmaceutical LTD, Haridwar. Propylene glycol & Dimethyl sulfoxide (Qualigens Lab., Mumbai) were purchased. All other reagents used were of analytical grade (AR Grade).

Compatibility studies of Drug and Polymer

The physicochemical compatibility between Ivabradine hydrochloride and polymers used in the films was studied by using fourier transform infrared (FTIR- 8300, Shimadzu Co., Kyoto, Japan) spectroscopy. The infrared (IR) spectra were recorded using an FTIR and spectra were recorded in the wavelength region between 4000 and 400 cm–1. The spectra obtained for Ivabradine hydrochloride, polymers, and physical mixtures of Ivabradine hydrochloride with polymers were compared.

Preparation of transdermal films

In the present study, drug loaded matrix type transdermal films of Ivabradine hydrochloride were prepared by solvent casting method (4) using different ratios of ERS-100 and HPMC K100M polymers (Table 1). The polymers were weighed in requisite ratios by keeping the total polymer weight at 1.0 gm added in solvent mixture (3:2 ratio of methanol, chloroform). Propylene glycol was incorporated as plasticizer and DMSO as penetration enhancer were used. The drug was added slowly to the solution and dissolved by continuous stirring for 30 min. For the formulation of transdermal patch, the aluminum foil was spread uniformly on a glass petri dish. The mould was kept on a horizontal surface. The solution was poured on the foil into a petri dish of about 50 cm2. The rate of evaporation was controlled by inverting a funnel over the mould. Aluminum foil was used as backing film. The solvent was allowed to evaporate for 24 hrs. The polymer was found to be self adhesive due to the presence of Eudragit polymer along with plasticizer. The patches were cut to give required area and used for evaluation.

Physicochemical evaluation

Physical appearance

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

Thickness of the films

Patch thickness was measured using screw gauge at three different places and the mean value was calculated (5).

Weight uniformity

The films of different batches were dried at 60oC for 4 hours before testing. Five patches from each batch were accurately weighed in a digital balance. The average weight and the standard deviation values were calculated from the individual weights (6).

Folding endurance

A strip of film (2× 2 cm) was cut evenly 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 gave the value of the folding endurance (7, 8).

Drug content

Transdermal system of specified area (1 cm2) was cut into small pieces and taken into a 50 ml volumetric flask and 25 mL of phosphate buffer pH 7.4 was added, gently heated to 45oC for 15 minutes, and kept for 24 hours with occasional shaking. Then, the volume was made up to 50 ml with phosphate buffer of pH 7.4. Similarly, a blank was carried out using a drug-free patch. The solutions were filtered and the absorbance was measured at 286 nm (9).

Animals

For the research study white Wistar albino rats were taken and the experiments were conducted according to the protocol approved by the institutional animals ethics committee . The experiments were conducted according to the guidelines of CPCSEA.

***In-vitro* permeation study**

The in-vitro permeation study of fabricated transdermal patches of Ivabradine hydrochloride was carried out by using excised rat abdominal skin as diffusion cell (5). The skin was sandwiched between donor and receptor compartments of the diffusion cell. The patch of per cm2 was placed in intimate contact with the stratum corneum side of the skin; the top side was covered with aluminum foil as a backing membrane. Teflon bead was placed in the receptor compartment filled with 12 ml of normal saline. The cell contents were stirred with a magnetic stirrer and a temperature of 37 ± 0.5°C was maintained throughout the experiment. Samples of 2 ml were withdrawn through the sampling port at different time intervals for a period of 48 h, simultaneously replacing equal volume by phosphate buffer pH 7.4 after each withdrawal. The samples were analyzed spectrophotometrically at 286 nm. Based on the results of in-vitro permeation profiles of preliminary batches of Ivabradine hydrochloride transdermal patches the optimum composition of checkpoint batches of Ivabradine hydrochloride transdermal patch was optimized.

RESULTS AND DISCUSSION

Evaluation of transdermal patch

The prepared transdermal patches were evaluated for their physicochemical characteristics such as appearance, weight variation, thickness, folding endurance, drug content (Table 2) and in vitro drug permeation through albino rat skin (Table 3). The physical appearance of the various formulations in terms of their transparency, smoothness, flexibility, stickiness, homogenicity and opaque properties were recorded. The formulation A-1 was found to be thin, transparent and flexible, formulation A-2 was found to be thin, transparent and flexible, formulation A-3 was found to be thin, opaque and flexible and formulation A-4 was found to be thick, not flexible and opaque. The formulation A-2 gave the most suitable transdermal film with all desirable physico-chemical properties. The thickness of the patches was varied from 0.14±0.068 mm to 0.31±0.034 mm. The weights ranged between 22.61±0.85 mg and 34.92±0.64 mg, which indicates that different batches patch weights, were relatively similar.

Polymers HPMC K100M and ERS-100 were selected on the basis of their adhering property and non toxicity. The result of the finding showed excellent adhering property and controlled release. Result from present study concluded that Ivabradine hydrochloride in combination with HPMC K100M, ERS-100 and with incorporation of PEG 400 (20%) and DMSO (15%) produced smooth, flexible and transparent film. FT-IR studies showed characteristic peaks of Ivabradine hydrochloride, confirming the purity of the drug.

FT-IR spectral studies indicated there was no interaction between Ivabradine hydrochloride and polymers used (Fig. no. 1).

Ivabradine hydrochloride patches were prepared with combination of these polymers and evaluated it for physical parameters such as thickness, drug content, weight variation. From the results, it was observed that thickness, drug content, weight variations were suitable for maximum stability of the prepared formulations. The drug content of TDDS patches ranged from 2.07±0.24 to 2.37±0.33 mg. The cumulative percentage drug release for A2 was found to be 98.45±1.34 % at 48 h and for A4 it was found 92.01±3.47 % at 24 h. The formulation, A2 [ERS100:HPMC K100M (4:6)] is considered as a best formulation, since it shows maximum *in vitro* drug release as 98.45±1.34 % at 48 h shown in figure no. 2.

The drug release kinetics studies showed that the majority of formulations were governed by Higuchi model and mechanism of release was Fickian mediated. Higuchi developed an equation for the release of a drug from a homogeneous-polymer matrix-type delivery system that indicates the amount of drug releases is proportional to the square root of time (10). If the release of drug from the transdermal film, when plotted against square root of time, shows a straight line, it indicates that the release pattern is obeying Higuchi's kinetics. In our experiments, in vitro release profiles of all the different formulations of transdermal patches could be best expressed by Higuchi's equation, for release of drug from a homogeneous-polymer matrix–type delivery system that depends mostly on diffusion characteristics.

From the *in vitro* permeation profile data of all the formulations through rat skin, kinetics of drug release were found for zero-order, first-order, Higuchi-type release kinetics and Korsmeyer-Peppas-type release kinetics. The coefficient of correlation (R2) of each of these release kinetics were calculated and compared (Table no.3). The data revealed that the release pattern of selected formulations was best fitted for Higuchi kinetics, as the formulation coefficient values predominate over zero-order, first-order and Korsmeyer-Peppas-type release kinetics, which again confirmed with Higuchi's equation for the drug release from matrix. Thus, a slow and controlled release as observed is indicating that the drug release mechanism is Fickian model, as proposed by Higuchi.

The regression analysis of the in vitro permeation curves were carried out for in vitro permeation studies in rat skin. Among all these formulations, the formulation A-2 showed the maximum % drug cumulative release i.e. 98.45 % up to 48 hours of the study. All the formulations showed Higuchi-type release kinetics, which was diffusion mediated. Regression analyses of the in vitro permeation curves were carried out. The slope of the straight line obtained after plotting the mean cumulative amount released per Cm. Square patch vs. square root of time was taken as the experimental flux for Ivabradine hydrochloride.

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Table 1 Composition of transdermal patches

Formulation code	Drug (mg)	Polymer	Polymers ratio	DMSO	PEG 400	Solvents ratio (Methanol : Chloroform)
A1	100	ERS:HPMC HPMC	2:8	15%	20%	3:2
A2	100	ERS:HPMCK100M	4:6	15%	20%	3:2
A3	100	HPMCK100M:K15M	5:5	15%	20%	3:2
A4	100	HPMCK100M:K15M	6:4	15%	20%	3:2

Table 2. The drug content uniformity, thickness variations, weight variations and appearance of the various formulations

Formulation Code	A-1	A-2	A-3	A-4
Appearance	+	***	**	*
Thickness (mm)± SD	0.14±0.068	0.19±0.059	0.32±0.081	0.31±0.034
Weight/cm2 (mg)± SD	22.61±0.85	26.40±0.67	31.16±0.83	34.92±0.64
Average drug content (mg)/cm2± SD	2.17±0.30	2.08±0.18	2.07±0.24	2.37±0.33
Comments	Suitable	Very suitable	Suitable	Suitable

Table 3. The regression co-efficient values obtained from different kinetics plots of the formulations

Formulation code	Zero Order (r2)	First order (r2)	Higuchi kinetic (r2)	Korsmeyer kinetic (r2)
A1	0.911	0.997	0.984	0.988
A2	0.904	0.918	0.997	0.994
A3	0.951	0.974	0.991	0.997
A4	0.851	0.990	0.997	0.984

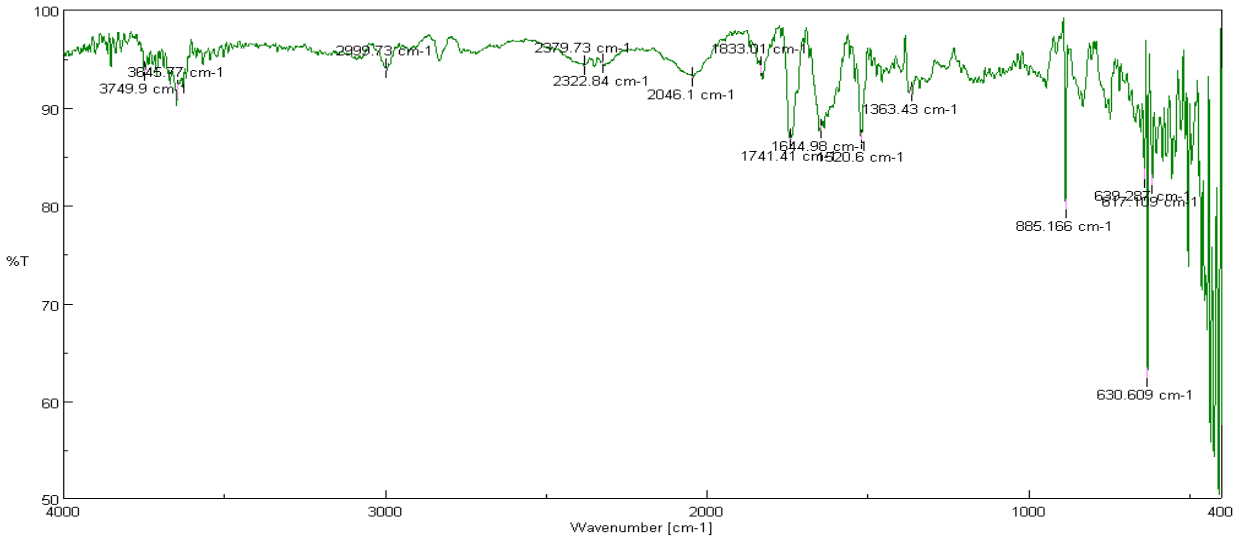

Figure 1 FTIR Spectra of transdermal film of Ivabradine Hydrochloride

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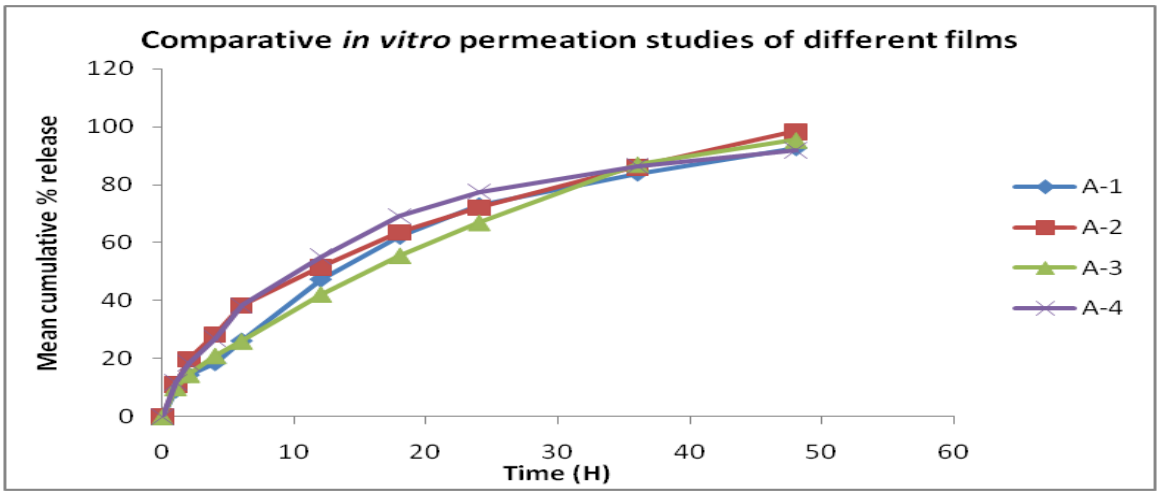

Figure 2 Comparative in vitro drug permeation profile of different film

CONCLUSION

In conclusion, controlled release TDDS patches of Ivabradine hydrochloride can be prepared using the polymer combinations, ERS100:HPMC K100M (4:6) with PEG 400 and DMSO as plasticizer and enhancer, respectively. The release rate of drug through patches increased when the concentration of hydrophilic polymer was increased. Whereas, the mechanism of drug release of all formulations were Fickian. The properties of film did not change during the period of study. Further, in vivo studies have to be performed to correlate with in vitro release data for the development of suitable controlled release patches for Ivabradine hydrochloride.

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