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FORMULATION AND EVALUATION OF MATRIX TRANSDERMAL PATCHES OF RIZATRIPTAN FOR TREATMENT OF MIGRAINE

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ABSTRACT

The objective of the present work was to formulate transdermal patches of rizatriptan in order to improve the half-life and bioavailability of the drug. The patches were prepared using varying the ratio of the matrix polymers methyl cellulose and Eudragit RL100 as well as the plasticizer polyethylene glycol. The patches were prepared by solvent casting method. The patches were formulated using solvent casting method. The results show that increasing the concentration of Eudragit RL100 and PEG causes an increase in the thickness of the patches. The weight variation was found to be around 1% for all the formulations irrespective of the polymer and plasticizer ratios. The folding endurance was lower for patches with high concentration of methyl cellulose and increased with increasing concentration of Eudragit RL10. The concentration of the plasticizer played an important part in the folding endurance. Higher plasticizer improved the foldability of patch. The moisture content was also found to be affected with the polymer and plasticizer. High Eudragit RL100 and high plasticizer presented higher moisture content. All the patch formulations exhibited drug content of more than 90%. The highest drug concentration was found in formulations containing ethyl cellulose and Eudragit RL100 in equal ratio. The best fitting model (Peppas model) exhibits a non-fickian diffusion or anomalous diffusion for RPA7 which depends on erosion controlled release and diffusion release rate together.

KEYWORDS: Rizatriptan, Transdermal patch, Eudragit, Bioavailability, First pass metabolism.

INTRODUCTION

The administration of conventional oral dosage forms like tablets, capsules, liquids orals of drugs suffers a setback due to problem of gastro intestinal tract absorption, local irritation, dilution of drug strength, Liver first pass metabolism, degradation of drug by gastro intestinal tract enzymes, the protein binding of drug at an absorption surface and local toxicity. The bioavailability as well as duration of action is reduced which requires frequent administration, which in turn is associated with the problem of patients compliance to therapy and the economy of the treatment.[1] Transdermal delivery offers a solution to these problems. In recent years, various drug delivery systems have been developed which provide sustained release therapy via a sub-dermal insert. Systems have been disclosed which also provide drug delivery systems suitable for transdermal drug administration. The properties suitable for transdermal delivery include high potency, proper physic-chemical characteristics, good dermal penetration and lack of dermal irritation.

Rizatriptan is a triptan drug used for the treatment of migraine headaches. It is a selective 5-hydroxytryptamine1 receptor subtype agonist.[2] Several transdermal systems have been developed for triptans and other drugs.[3-6] In the proposed research work, we are planning to prepare transdermal patches of a rizatriptan for improving bioavailability of the drug.

MATERIAL AND METHODS

The preformulation studies were carried out in order to identify properties like physical appearance, melting point and FTIR spectroscopy. It also includes solubility profile of drug in various solvent systems, determination of partition coefficient and quantitative estimation of drug.[7]

Calibration curve of rizatriptan

Accurately weighed 50 mg of drug was dissolved in 40 mL of ethanol in a 50 mL volumetric flask and volume was made up to the mark. 1 mL of this solution was pipette out into a 10 mL volumetric flask and volume was made up to the mark. The aliquots of stock solution were diluted to obtain various concentrations of drug sample ranging from 1 to 10 µg/mL and the absorbance of each dilution was observed at 234 nm. A standard curve was plotted between absorbance and concentration.

Preparation of transdermal patches[8]

Transdermal patches were prepared by the use of solvent casting technique. The constituents and their quantities used for preparing the patches are listed in table 1. The polymers were weighed accurately as per their required ratios such that the total polymer weight was 300 mg. They were dissolved in 10 mL of mixture of ethanol: water (1:1) with help of magnetic stirrer. 10 mg of rizatriptan was separately dissolved in the 5 mL ethanol. The mixture was stirred to obtain a clear solution. The plasticizer, polyethylene glycol was added to this solution and mixed with for 30 min on a magnetic stirrer. The prepared solution was poured in a petridish, prelurbicated with Tween 80 and dried at room temperature by covering petridish with inverted funnel for 48 hours. The dried films were removed from the plate and cut into 4 cm^2 area and stored in desiccator for further studies.

Table 1: Constituents of transdermal patch formulations.

S. No	Formulation	Polymer Ratio		PEG (%)	Rizatriptan (mg)
		MC	Eudragit RL 100		
1	RPA1	100	0	10	10
2	RPA2	100	0	20	10
3	RPA3	0	100	10	10
4	RPA4	0	100	20	10
5	RPA5	75	25	10	10
6	RPA6	75	25	20	10
7	RPA7	50	50	10	10
8	RPA8	50	50	20	10
9	RPA9	25	75	10	10
9	RPA10	25	75	20	10

Evaluation of transdermal patches[9]

Weight variation

Five patches from each formulation group were randomly selected, weighed individually and the average weight was calculated. The percent variation in each patch was calculated using the formula

$$\%\ variation = \frac{(Avg\ wt - wt\ of\ patch)}{Avg\ wt}\ x\ 100$$

Thickness

The thickness of randomly selected patches from each formulation group was measured by using vernier caliper at three different positions of the patch and the average thickness was calculated.

Folding endurance

One patch from each batch of the formulations was folded continuously at the same place till it cracked or broke. The number of times the film could be folded from the same place without breaking/ cracking gave the value of folding endurance.

Percentage moisture content

The prepared transdermal patches from each batch were individually weighed and kept in desiccator that contained fused calcium chloride, at room temperature, for duration of 72 hours. After 72 hours, the films were re-weighed and the percentage moisture content was determined by the given formula

$$\%\ moisture\ content = \frac{Initial\ weight - Final\ weight}{Initial\ weigh}\ X\ 100$$

Drug content determination

In order to determining the drug content, an area of 4 cm^2 of the patch was cut into small pieces and dissolved in 25 ml of ethanol. The solution was filtered and the amount of drug in the solution was determined using UV method as described in calibration curve preparation method.

***In-Vitro* release study**

In-vitro permeation studies of the patches were performed using a Franz diffusion cell with a receptor compartment capacity of 30 ml. The formulated patch of surface area of 4cm^2 was placed in between the dialysis membrane and the donor compartment and then dialysis membrane was mounted between the donor and receptor compartment of diffusion cell. The receptor compartment of diffusion cell was filled with 15 mL phosphate buffer saline pH 7.4. The whole assembly was fixed on a magnetic stirrer and the solution in the receptor compartment was constantly and continuously stirred magnetic beads at 50 rpm; the temperature was maintained at 37±0.5ºC. The 1 ml aliquots were withdrawal at different time intervals (1, 2, 4, 6, 8, 10 & 12 hours), diluted with ethanol and analyzed for rizatriptan by UV spectrophotometer. The receptor phase was reimbursed with an equal volume of phosphate buffer (37ºC) after each sample withdrawal. The cumulative amount of drug permeated per square centimeter of patches was plotted against time.

RESULTS AND DISCUSSION

The preformulation studies revealed the procured rizatriptan sample to be white crystalline powder with a melting range of 180-182°C, log P of 1.51 and solubility in methanol, DMF and ethanol. The calibration curve was found to exhibit regression coefficient of 0.991 (Figure 1).

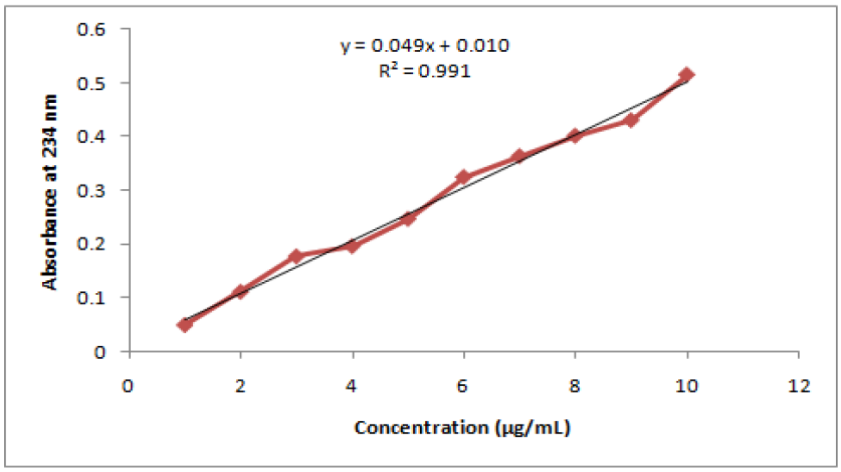

Figure 1: Calibration curve of rizatriptan.

The FTIR spectra of rizatriptan and the physical mixture of rizatriptan, methyl celllose and Eudragit RL 100 was obtained and observed for the prominent peaks. The spectra exhibited the peaks for stretching and bending vibrations of functional groups (C-H, C-C, C=C, N-N, C-N, N-H) in rizatriptan in either case.

Formulation of patches

The transdermal patches were prepared using varying ratio of methyl cellulose and Eudragit RL 100 and two different concentrations of the plasticizer. The method of solvent casting has been the most efficient method for preparation of the patches and hence was used in the present work. Lubrication of the petriplates was done using tween 80 and evaporation of the solvent took 52 hours. The patch was peeled off from the petriplate using tweezers and stored in desiccator.

Evaluation of patches

The results of patch evaluation (Table 2) show that increasing the concentration of Eudragit RL100 and PEG causes an increase in the thickness of the patches. The weight variation was found to be around 1% for all the formulations irrespective of the polymer and plasticizer ratios. The folding endurance was lower for patches with high concentration of methyl

cellulose and increased with increasing concentration of Eudragit RL10. The concentration of the plasticizer played an important part in the folding endurance. Higher plasticizer improved the foldability of patch. The moisture content was also found to be affected with the polymer and plasticizer. High Eudragit RL100 and high plasticizer presented higher moisture content. All the patch formulations exhibited drug content of more than 90%. The highest drug concentration was found in formulations containing ethyl cellulose and Eudragit RL100 in equal ratio.

Table 2: Physicochemical parameters of the formulated patches.

Formulation	Weight Variation (%)	Thickness (mm)	Folding Endurance	% Drug Content	% Moisture Content
RPA1	1.008	0.19	221	93.6	2.08
RPA2	1.041	0.21	263	94.1	2.13
RPA3	0.977	0.17	249	94.2	2.21
RPA4	0.926	0.19	287	94.1	2.36
RPA5	0.949	0.16	228	94.7	2.11
RPA6	0.973	0.17	265	94.9	2.2
RPA7	1.013	0.18	241	96.2	2.15
RPA8	1.022	0.19	277	96.1	2.21
RPA9	0.995	0.19	245	95.8	2.19
RPA10	0.982	0.21	280	95.3	2.25

Release studies were performed to predict the rate and duration of drug release. The importance of polymer dissolution on drug release from matrices has been proven to be ensuring the performance sustained release formulation (Figure 2). The diffusion kinetics of Rizatriptan was assessed by mathematical models employing graphic representation for Zero order, First order, Higuchi and Peppas equation. The R^2 value of model reveals the drug release kinetics of formulations.

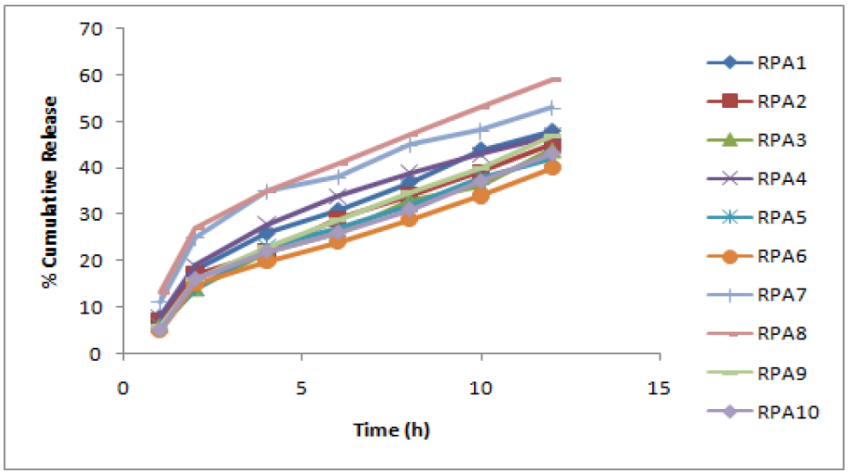

Figure 2: Release of rizatriptan from patches.

The regression coefficient of the formulation RPA7 in all the mathematically modeled graphs were obtained using the software and the values were found to be 0.899, 0.946, 0.962 and 0.799 for zero order, first order, Higuchi and Peppas model respectively. The closeness of regression coefficients in all the models explains mixed order release kinetics from the patches. The best fitting model (Peppas model) exhibits a non-fickian diffusion or anomalous diffusion which depends on erosion controlled release and diffusion release rate together.[10]

CONCLUSION

In the recent years systemic delivery through skin has grabbed lot of interest. Hence in the current investigation an endevour was made to formulate rizatriptan as transdermal patches for the management of migraine. The patches were smooth, aptly thick and were able to provide a prolonged release of drug for more than time duration of 12 h by changing the concentration of the polymeric matrix. The results of release kinetic study exhibited that the patch RPA7 was best amongst the others as they were quite stable physically and exhibited a release of around 53% drug over time duration of 12 h. Furthermore the *in vivo* studies need to be pursued to correlate the data obtained from the *in vitro* release studies in order to develop suitable transdermal patches of rizatriptan.

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