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The Pharma Innovation

ISSN: 2277- 7695
TPI 2015; 3(12): 44-49

www.thepharmajournal.com
Received: 06-08-2014
Accepted: 10-09-2014

M. N. Patel
Faculty of Pharmacy, Dharmsinh Desai University, Nadiad – 387001, Gujarat, India

P. D. Bharadia
B. S. Patel Pharmacy College Linch, Dist. Mehsana, Gujarat-382735, India

M. M. Patel
Shankersinh Vaghela Bapu Institute of Pharmacy Vasan, Dist. Gandhinagar-382650, Gujarat, India

Correspondence
M. N. Patel
Faculty of Pharmacy,
Dharmsinh Desai University
Nadiad – 387001, Gujarat, India

Effect of gelling agents & rate controlling membranes on permeability of propranolol hydrochloride through reservoir-type transdermal delivery system

M. N. Patel, P. D. Bharadia, M. M. Patel

Abstract
A Reservoir-type Transdermal Delivery System for Propranolol Hydrochloride was prepared consisting of gel as a drug reservoir in between backing laminates and a rate controlling membrane. The rate controlling membranes used were Nylon (NY), Cellulose Nitrate (CN) and Ethylene Vinyl Acetate (9 % ethoxy content) (EVA, 3M Corporation, COTRAN 9702). The hydrophillic polymers, Hydroxypropyl methyl cellulose (HPMC), Hydroxy Propyl Cellulose (HPC) and Methyl Cellulose (MC) were evaluated for a gel as drug reservoir. 32 full factorial design was adopted to study the effect of independent variables studied. Gel prepared from different polymer for the study, showed desirable physicochemical properties and stability. *In vitro* permeation study revealed that release of Propranolol HCl was maximum (62.98% in 24 hours) in formulation containing HPMC as gel and CN as rate controlling membrane. It was found that cellulose nitrate membrane gives more release and so permeation among all formulation, which might be due to more porosity of CN membrane compared to other membranes. ANOVA study shows that both independent variables had significant effect on selected dependent variable i.e. Flux and Diffusion rate ($P<0.05$).

Keywords: Transdermal, Reservoir-type, Propranolol Hydrochloride, Rate Controlling Membrane.

1. Introduction
The present work aimed to develop reservoir type transdermal delivery system of Propranolol HCl. Reservoir type system consists of a drug reservoir as a gel in between backing laminates and a rate controlling membrane [1]. The rate controlling membrane can be either a microporous membrane or a nonporous polymeric membrane. Propranolol HCl is a nonselective beta-adrenergic blocking agent widely used in the treatment of various cardiovascular disorders. Oral administration of Propranolol has the disadvantage of low bioavailability due to an extensive and highly variable hepatic first-pass metabolism. In addition, Propranolol has a half-life of 2 to 6 hr and requires frequent dosing [2, 3]. Owing to these disadvantages, a transdermal patch of Propranolol was designed and developed. Reservoir type of transdermal systems have been investigated and found to be effective in drug delivery. Drugs like ketorolac [4], bupranolol [5] have been incorporated in the reservoir type TDDS.

The objective of the present investigation was to develop reservoir type TDS of Propranolol HCl using various gel formulation and rate controlling membrane. Now a day variety of gelling agents are used in formulation. Some of them are Hydroxy Propyl Methyl Cellulose (HPMC), Sodium Carboxy Methyl Cellulose (Na CMC), Carbopol, Methyl Cellulose (MC), Hydroxy Propyl Cellulose (HPC) etc. [6] In this investigation the gelling agents used were HPMC (Metolose 90SH 4000SR) [7], Methyl Cellulose and HPC (Nisso HPC-M) [8].
Rate controlling membrane is rate determining membrane that governs the release of drug through membrane. Pore size of rate controlling membrane is rate determining parameter. Variety of Membranes are available that can be used as rate controlling membrane [5]. Among the available membranes, In present study the rate controlling membranes used were Nylon (NY), Cellulose Nitrate (CN) and Ethylene Vinyl Acetate (9% ethoxy content) (EVA, 3M Corporation, COTRAN 9702) [9] membrane.

2. Materials and Methods

2.1 Materials

Propranolol Hydrochloride was received as gift sample from Scion Pharma Pvt. Ltd. Ahmedabad, India. The other material used were Hydroxypropyl Methyl Cellulose (HPMC; Metolose 90SH 4000SR; Shin-Etsu Chemical Co. Ltd., Japan), Hydroxy Propyl cellulose (HPC; Nisso HPC, Japan), Ethylene Vinyl Acetate membrane (EVA; COTRAN 9702; 9% ethoxy content) and Drug impermeable backing membrane (Scotchpak 1109) were provided by 3M Corporation MN, USA. Methyl Cellulose, NY membrane and CN membrane were purchased from S D Fine chem Limited, Mumbai, Pall India Pvt. Ltd., India and Sartorius Stedim Biotech, Germany respectively. Other materials used in the study were of analytical grade.

2.2 Determination of Solubility of Propranolol HCl

The solubility of Propranolol was determined in different solvents. An excess quantity of the drug was added in 10 ml of each solvent in screw capped glass test tubes and shaken for 12 hours at room temperature. The solution was filtered using filter paper and amount of Propranolol HCl solubilized was determined by measuring the absorbance at 290 nm spectrophotometrically [10].

2.3 Determination of Partition Coefficient of Propranolol HCl

The partition coefficient of Propranolol HCl was determined in n-octanol: phosphate buffer pH 7.4 system. An accurately weighed (500 mg) amount of Propranolol HCl was added into 10 ml each of n-octanol and aqueous phase in a screw capped tube. The mixture was shaken for 24 hours until equilibrium was reached. Phases were separated; the aqueous phase was filtered, diluted and the amount of Propranolol HCl solubilized in aqueous phase was determined by measuring the absorbance at 290 nm spectrophotometrically. The partition coefficient of Propranolol HCl was calculated from the ratio between the concentration of Propranolol HCl in organic and aqueous phase using following equation [10, 11].

$$\text{Partition Coefficient} = \frac{\text{Concentration in organic phase}}{\text{Concentration in aquous phase}}$$

2.4 Design of Experiment

A 2-factor 3-level full factorial design 3^2 was used for the formulation and evaluation of TDDS. This design is suitable for statistical analysis by Analysis of variance (ANOVA) & individual responses can be evaluated by F-test. The independent factors used in the design are listed in Table I and Table II shows applied 3^2 factorial design.

Table 1: Independent Factors for Reservoir type TDDS of Propranolol HCl

Independent variable	Factor A Gelling Polymer			Factor B Rate Controlling Membrane		
Coded Levels	-1	0	1	-1	0	1
Actual Levels	HPC	HPMC	MC	EVA	CN	NY

Table 2. 3^2: Full Factorial Design for Reservoir type TDDS of Propranolol HCl

Run	Factor A Gelling Polymer		Factor B Rate Controlling Membrane	
	Coded	Actual	Coded	Actual
1	-1	HPC	-1	EVA
2	-1	HPC	0	CN
3	-1	HPC	1	NY
4	0	HPMC	-1	EVA
5	0	HPMC	0	CN
6	0	HPMC	1	NY
7	1	MC	-1	EVA
8	1	MC	0	CN
9	1	MC	1	NY

EVA – Ethylene Vinyl Acetate membrane, NY – Nylon membrane, CN – Cellulose Nitrate membrane

2.5 Formulation of Transdermal Patch

The reservoir type TDS contains the gelling polymer & rate controlling membrane as shown in above table II. Gel was prepared in water by dissolving Propranolol HCl (300 mg) and adding gelling agent in small portions with continuous stirring. The mixture was stirred continuous for 2 hours at 1000 RPM on magnetic stirrer. The resultant mass gel was kept overnight at an ambient temperature in tightly closed container to allow uniform gelling. Transdermal Systems of Propranolol HCl were fabricated by filling the prepared gel within a shallow compartment made of hollow ring shaped devices and drug impermeable backing membrane (Scotchpak 1109, 3M). The devices were closed by different rate controlling membrane [5]. Prepared TDDS were packed in aluminium foil and stored in desiccators until further use. The composition of transdermal films of Propranolol HCl is shown in Table III.

Table 3: Formulation Compositions for Reservoir type TDDS of Propranolol HCl

Run	Gel Forming Polymer Concentration			Rate Controlling Membrane
	HPC	HPMC	MC	
R 1	4.0 %	---	---	EVA
R 2	4.0 %	---	---	CN
R 3	4.0 %	---	---	NY
R 4	---	1.5 %	---	EVA
R 5	---	1.5 %	---	CN
R 6	---	1.5 %	---	NY
R 7	---	---	1.5 %	EVA
R 8	---	---	1.5 %	CN
R 9	---	---	1.5 %	NY

2.6 Determination of Viscosity of Gel [12]

Viscosity of various gel systems was measured using Brookfield Digital Viscometer Model LVDV-E (Brookfield Engineering Laboratories, USA) with spindle LV-1 at a speed of 25 rpm and the temperature of the solvent systems was maintained at 32 ± 0.5 °C by keeping the container in a water bath.

2.7 Drug Content [13]

A weighed amount gel was reconstituted with phosphate buffer solution (pH 7.4). The volume was adjusted to 100 ml with phosphate buffer pH 7.4 and the solution is filtered with filter paper. Propranolol HCl content of samples was determined by UV analysis at 290 nm.

2.8 Stability Studies

The gel formulations samples were stored in well-sealed glass containers for a period of 60 days at 25 °C, 40 °C. At predetermined time intervals; 0, 15, 30, and 60 days, samples were collected and physical appearance was evaluated. A weighed amount gel was reconstituted with phosphate buffer solution (pH 7.4) and filtered it out with the filter paper and Propranolol HCl content of samples was determined by UV analysis.

2.9 *In vitro* Diffusion Studies [14]

Preparation of skin for permeation studies: Hairless animal skin is generally favored as it is easily obtained from animals of specific age group or sex. Hair on dorsal skin of rat were removed with animal hair clipper, subcutaneous tissue was surgically removed and dermis side was wiped with isopropyl alcohol to remove residual adhering fat. The skin was washed with distilled water. The skin so prepared is wrapped in aluminum foil and stored in a freezer at -20 °C till further use. The skin is defrosted at room temperature when required. In vitro diffusion studies were performed by using a Franz diffusion cell with a receptor compartment capacity of 20 ml. The rat abdominal skin piece was mounted between two compartments of the diffusion cell with the epidermis facing upward into the donor compartment. The reservoir type patch was placed on the skin surface and covered with aluminum foil. The receptor compartment of the diffusion cell was filled with phosphate buffer pH 7.4. The whole assembly was fixed on a hot plate magnetic stirrer, and the solution in the receptor compartment was constantly and continuously stirred using magnetic bead and 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 at each sample withdrawal.

2.10 Data Treatment & Analysis

The following parameters were determined from the in vitro data obtained for the diffusion of Propranolol hydrochloride through rat skin.

Diffusion rate

Diffusion rate is the milligrams of Propranolol HCl diffused through membrane per unit time. It can be determined by dividing the milligrams of Propranolol HCl diffused by time in hour [15].

$$D_r = \frac{Q}{T} \quad (1)$$

The steady-state Flux [16]

Absorption is a passive diffusion process and can be described by Fick's second law equation:

$$J_S = \frac{dQ}{dt} \times \frac{1}{A} \quad (2)$$

Where J_S is the steady-state flux in micrograms/square centimeter per hour, *dQ* is the change in quantity of material passing through the membrane into the receptor compartment expressed in micrograms, *A* is the active diffusion area in square centimeters, and *dt* is the change in time in hours.

The steady-state fluxes of the Propranolol HCl through the skin were calculated from the slope of the linear portion of the cumulative amount permeated through the membrane per unit area versus time plot.

Permeability Coefficient [16]

To determine the permeability coefficient, we used the following equation:

$$K_P = \frac{J_S}{C_d} \quad (3)$$

Where K_P is the permeability coefficient, J_S is the flux calculated at the steady time, and C_d is the donor concentration.

2.11 Kinetics of permeation

For finding out the mechanism of drug release from transdermal system, the diffusion data obtained from the above experiments was treated with different release kinetic equations like Zero order release, Higuchi's square root of time equation [17] and Korsmeyer and Peppas equation [18, 19, 20].

2.12 Statistical Analysis

The selected responses obtained from the various systems were tested for significant differences. Statistical analysis of data was carried out using analysis of variance (ANOVA). The individual response was evaluated using F-test and F value and P value were generated. The diffusion rate and flux were selected for statistical analysis:

2.13 Skin Irritation Study

The rabbit were divided into 3 groups (n=3). On the previous day of the experiment, the hairs on the backside area of rabbit were removed. The animals of group I was served as normal, without any treatment. Transdermal systems (drug loaded) were applied onto nude skin of animals of group II. A 0.8% v/v aqueous solution of formalin was applied as a standard irritant (Group III). The animals were treated with new patch/formalin solution for a day and finally the application sites were graded according to a visual scoring scale, always by the same investigator. The erythema scale was as follows: 0, none; 1, slight; 2, well defined; 3, moderate; and 4, scar formation. The edema scale was: 0, none; 1, slight; 2, well defined; 3, moderate; and 4, severe [21].

3. Result and Discussion

Solubility of Propranolol HCl was determined in different solvents and it shows that the maximum solubility was found in water& ethanol and least in ethyl acetate. Partition coefficient of Propranolol HCl in n-octanol and phosphate buffer pH 7.4 was found to be 3.37. Physical evaluation during the Storage shows that there was no leakage of gel through backing or rate controlling membrane. Viscosity of prepared gel formulations was found in the range of 4800 cp to 6200 cp. Viscosity of 1.5% methyl cellulose gel is more as compare to 1.5% HPMC & 4% HPC gel. Viscosity of prepared HPC & HPMC gels is almost similar. All the formulation shows drug content more than 1.48 mg. Good uniformity in the drug content among the gels was observed and percentage drug recovery ranged from 98.49 to 99.10 %.

Gel samples were subjected to stability study at 25 and 40 °C and drug content was determine at predetermine intervals of 15, 30 and 60 days. Visual inspection of gel Indicates shown that there is no change in physical properties of gel samples, and hence were found to be stable physically.

Drug Content data shows that there was no change in drug concentration even after 60 days. Gel prepared with polymers is stable and can be used in transdermal drug delivery systems. Propranolol HCl has been reported to be stable in various dosage forms. The result indicated that the prepared TDS using the above mentioned polymers is stable and significant drug degradation was not observed.

In vitro permeation experiments were performed at 37 ± 1 ºC with excised rat skin using modified Franz diffusion cell. The Maximum drug diffuse was found in case of R5 i.e. 62.98 ± 0.03 mg in 24 hours of diffusion study whereas R7 shows minimum drug release i.e. 40.91 ± 0.05. Ascending order of cumulative drug permeated was found in following order: R5 > R2 > R8 > R6 > R4 > R3 > R9 > R1 > R7. Diffusion profile of all formulation was subjected to data treatment. Diffusion data were treated with zero order, Higuchi & Peppas equation. Permeation parameters like Diffusion rate, Flux and Permeability coefficient were also determined from permeation profile.

Table 4: Permeation Parameter of Propranolol HCl Permeated through Rat Skin

RUN	Diffusion Rate D_r	Flux J_S	Permeability Coefficient K_P
	mg/hr	mg/cm^{2}hr	cm/hr
R 1	0.076	4.9×10^{-2}	1.15×10^{-2}
R 2	0.102	7.3×10^{-2}	1.72×10^{-2}
R 3	0.084	5.4×10^{-2}	1.27×10^{-2}
R 4	0.090	6.7×10^{-2}	1.58×10^{-2}
R 5	0.112	7.5×10^{-2}	1.76×10^{-2}
R 6	0.096	6.7×10^{-2}	1.58×10^{-2}
R 7	0.072	5.0×10^{-2}	1.18×10^{-2}
R 8	0.097	6.7×10^{-2}	1.58×10^{-2}
R 9	0.078	5.3×10^{-2}	1.25×10^{-2}

3.1 Effect of Gelling Polymer

In vitro permeation data shows that gelling polymer has significant effect on drug release. The diffusion of molecules through gels is also rate limiting step. The release rate of Propranolol HCl from polymer gels of HPMC was much higher than those from polymer gels of HPC and MC. The Maximum average diffusion rate found was 0.112 mg/hr in case of formulation R5 whereas R7 shows minimum drug release with diffusion rate of 0.072 mg/hr.

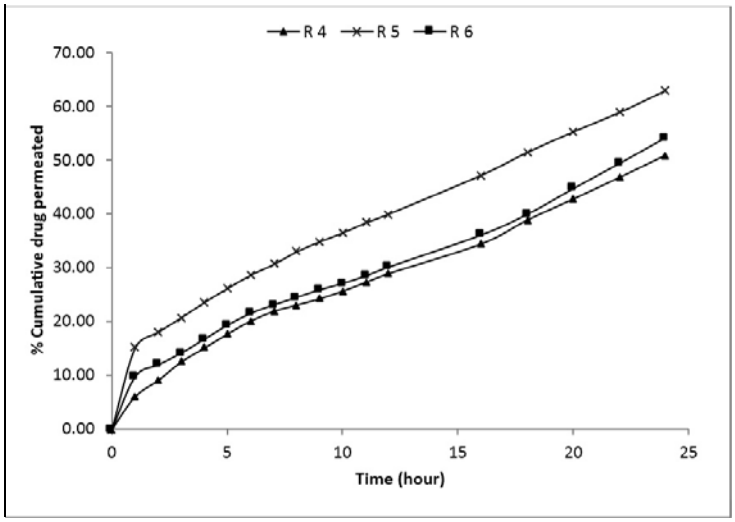

Fig 1: Comparative In vitro Permeation Profile of Propranolol HCl Containing Different Rate Controlling Membrane

Average flux attained for gel system prepared from HPMC, HPC and MC was 0.059, 0.070 and 0.057 mg/cm^{2}hr respectively. Permeation of molecule through gel system might be depends on viscosity of gel. Methyl cellulose gel has more viscosity and so less flux was attained. Highest flux was found in case of formulation R5 i.e. 7.5×10^{-2} mg/cm^{2}hr whereas lowest flux was observed with formulation R7 i.e. 4.9×10^{-2} mg/cm^{2}hr.

3.2 Effect of Rate Controlling Polymer

Rate controlling membrane plays major role in permeation of drugs. Pore size of porous membrane plays major role in diffusion of molecules through rate controlling membrane whereas thickness governs diffusion rate of molecules in case of polymeric membrane.

Drug permeation profile of formulation R4 to R6 prepared with gel of HPMC using different rate controlling membrane is shown in Fig. 1. This indicates that drug molecules easily penetrate through the Cellulose Nitrate membrane as compared to EVA & Nylon membrane. Cellulose Nitrate membrane has more porosity that NY membrane and so TDDS prepared using CN membrane shows higher permeation compare to others.

The diffusion rate of R5 (CN membrane) was more compare to formulation R4 (EVA) and R6 (NY). The device R4 (EVA) showed the lowest drug release among the formulations with HPMC gel.

In this case the rate-limiting step is the diffusion through the polymeric membrane, which is much slower than the diffusion of drug through the gel matrix. Transport through EVAC membranes occurs via a two-step process: partitioning from a reservoir into the EVAC membrane and diffusion through the membrane. So the poor permeation of Propranolol HCl through

EVA membrane might be due to the low vinyl acetate content of the membrane (CoTran™-EVA with 9% vinylacetate). Similar finds were reported by Ocak and Agabeyoglu [22] for isosorbide dinitrate and by Konsil *et al*. [23] for melatonin, by Morimoto *et al.* [24] for nicardipine HCl, where low vinyl acetate content of the EVA membrane was the rate-determining factor for the drug release.

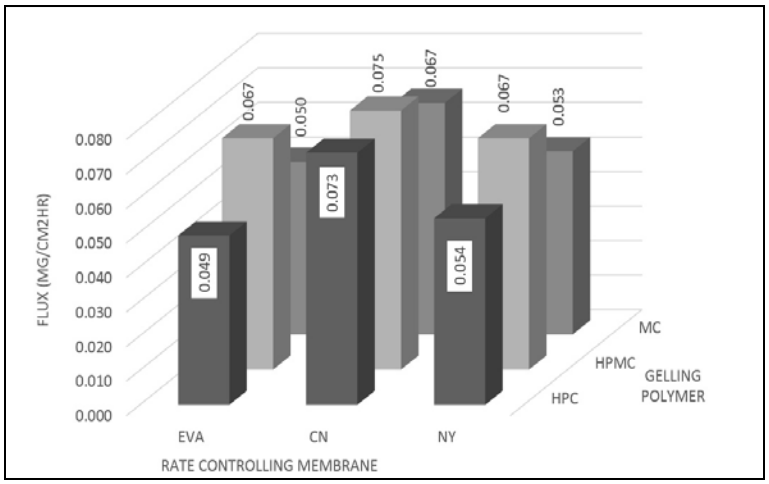

Fig 2: 3-D Chart showing Interaction Effect Gel Polymers and Rate Controlling Membranes on Flux

It can be concluded from kinetics data that Korsemeyer and Peppas model fit the best for all the patches as correlation coefficient value for all the patches were more than 0.9. This is followed by Higuchi and zero order equation. From the n value it can be seen that all the formulations follow anomalous pattern of drug release. This can be supported by the good fit of Higuchi equation. The drug was released by diffusion of the drug from the gel polymer matrix & rate controlling membranes.

Values of "Prob > F" less than 0.0500 indicate model terms are significant. In this case both A and B are significant model terms. Analysis of variance shows that factor A i.e. Gelling polymer and factor B i.e. Rate controlling membrane have significant effect on flux and diffusion rate. From above analysis of variance shows that factor B rate controlling membrane has less Prob>F value and hence is more significant than factor A.

3.3 Skin Irritation Study

The result of skin irritation test showed that no erythma was produced with the prepared patches. The absence of edema indicated that these polymeric films were compatible with skin and hence can be used for the transdermal application.

The skin irritation test of the transdermal formulation showed a skin irritation score (erythema and edema) of less than 1. According to Draize *et al*. [25], compounds producing scores of 2 or less are considered negative (no skin irritation). Hence, the developed transdermal formulations are free of skin irritation.

4. Conclusion

3^2 full factorial design has been adopted to study the effect of independent variables studied. In vitro permeation study shows that release of propranolol hydrochloride was maximum (62.98% in 24 hours) in formulation containing HPMC as gel and CN as rate controlling membrane. It was found that cellulose nitrate membrane gives more release and so permeation among all formulation. This might be due to more porosity of CN membrane compared to other membranes. ANOVA study shows that both independent variables had significant effect on selected dependent variable i.e. Flux and Diffusion rate ($P<0.05$). P-values of both dependent variables shows that factors B (rate controlling membrane) had more significant effect on flux and diffusion rate. The results indicate that the reservoir type TDS made up of 1.5% HPMC gel and CN as a rate controlling membrane was suitable for developing a transdermal drug delivery system for propranolol HCl.

5. Acknowledgments

We are grateful to the 3M, USA for the gift sample of backing membrane and release liner. We are also grateful to Shin-Etsu Chemical Co. Ltd., Japan & Nisso HPC, Japan for the gift samples of polymers. The gift sample of Propranolol HCl by Scion Pharma Pvt. Ltd, Ahmdedabad is highly acknowledged.

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