TRANSDERMAL DELIVERY OF PROPRANOLOL HYDROCHLORIDE THROUGH MATRICES OF COMBINED CELLULOSE DERIVATIVES

SUNITA JAIN* AND S.C. JOSHI**

Summary

Cellulose derivatives are the most widely used polymers in the production of hydrophilic matrices hence transdermal drug delivery system (TDDS) of Propranolol Hydrochloride were formulated employing selected ratios of polymers, ethylcellulose (EC) and hydroxypropyl methylcellulose (HPMC) . The ratio of EC and HPMC was kept as (3:1) and (2:2). The matrix diffusion type of system was developed. The potential for drug delivery was evaluated by *in vitro* dissolution studies and *in vitro* skin permeation studies using depilated freshly excised abdominal rat skin. The *in vitro* dissolution study was performed using USP paddle over disk method and *in vitro* skin permeation of drug was studied using modified Franz diffusion cell. The *in vitro* dissolution results showed that the systems followed Higuchi kinetics i.e. cumulative amount of drug was proportional to the square root of time. It was observed that *in vitro* skin permeation of Propranolol Hydrochloride was more in matrices containing ratio EC : HPMC as 2:2 compared to 3:1.Therefore the transdermal matrix with EC : HPMC ratio 2:2 were subjected to *in vivo* release studies, skin irritation studies, SEM studies and accelerated stability study. The *in vivo* release of drug was observed for 24 hrs. through rabbit abdominal skin which was supported by SEM photographs. The prepared matrices were free from any irritating effect on the rabbit skin and stable for 3 months

Key Words: Propranolol Hydrochloride, ethylcellulose, hydroxypropyl methylcellulose, transdermal matrix

Running Title: *Release of Propranolol Hydrochloride through transdermal matrices*.

* Reader, Lal Bahadur Shastri College of Pharmacy,
Udai marg ,Tilak Nagar, Jaipur – 302004 (Raj.) India.
Phone : +91-141- 2295138(R)
+91-141- 2620517(O)
E-mail : sunitajain_30@yahoo.com

For correspondence
** Dy. Director, UGC Academic Staff College and Associate Professor
Department of Zoology, University of Rajasthan, Jaipur - 302004 (Raj.) India
Phone : +91-141- 2710925 (O)
+91-141- 2762525 (R)
Telefax : +91-141- 2740141
E-mail : s_c_joshi2003@rediffmail.com

Introduction

Transdermal drug delivery is a noninvasive means for providing continuous transcutaneous drug infusion to a patient, similar to intravenous administration, except that the drug is delivered from patches applied to the skin, which eliminates the need for vascular access and syringes or pumps [1]. These delivery systems are intended to offer an alternative to oral, injection and infusion pump delivery and to avoid problems associated with these delivery methods.. Potential advantages include reduced administration frequency, enhanced adherence and convenience, reduced toxicity, stable drug concentrations uniform drug effect, decreased cost (occasionally) and decreased daily dosage[2].

Although novel controlled-release drug-delivery systems have been used in other areas of medicine, their application in the treatment of hypertension has been relatively recent Hypertension is an important public health challenge world wide. Its prevalence is high in economically developing countries as compared to economically developed countries [3-6].The prevalence of hypertension in both urban and rural areas in India is very high [6]. This carries a huge economic burden on already over stressed Indian economy. Therefore cost effective approaches to optimally control blood pressure among Indians are very much needed [7-9].

Propranolol Hydrochloride is extensively used antihypertensive drug which antagonizes catecholamines at both β_1 and β_2 adrenoceptors. Both its efficacy in treating hypertension as well as most of its toxic effects result from β -blockade. It is extensively metabolised in liver and hence effective oral doses of Propranolol are greater than effective intravenous doses. The prominent first pass effect partially accounts for the variability in doses required for clinically useful effects. The half life is also 3-6 hrs. [4]. Hence the present work was aimed to develope transdermal devices for Propranolol Hydrochloride (β-blockers) using combined cellulose derivatives and to study their *in vitro* and *in vivo* release patterns.

Material and Methods

PREPARATION OF FREE FILMS

The free films were prepared by employing mercury substrate method [10]. Ethyl cellulose (EC)(Asha Chemicals, India) and hydroxypropyl methylcellulose (HPMC) (Shlesha Pharma Chem, India) were used as polymers for casting films. Dibutyl pthalate (DBP) was used as plasticizer and a blend of chloroform and isopropyl alcohol (IPA) was used as casting solvent(Qualligens fine chemicals (A Division of Glaxo Smithkline Pharmaceutical Ltd.) India).Different ratios of EC and HPMC were dissolved in 10 ml of a blend of chloroform and IPA (8 ml + 2ml) and DBP (30% w/w of polymer) was added into it. The mixture was stirred continuously for 15 minutes on a magnetic stirrer for homogenous mixing. Two ml of this polymeric solution was poured on to the mercury contained in the laboratory fabricated moulds with raised edges. The rate of evaporation of solvent was controlled by placing an inverted funnel over the moulds. The film formation was noted by observing the mercury surface after complete evaporation of the solvent. The dry films were isolated and stored between the sheets of waxpaper and kept in a dessicator until use. The films were evaluated for various parameters like uniformity of thickness, uniformity of weight, physical appearance and water vapour transmission.

PREPARATION OF MATRICES

The free films showing the good characteristics were considered for preparing matrices.The polymeric films containing the selected ratios of EC and HPMC with drug (5 mg/cm^2) were prepared adopting the same method as described in the case of free films [10]. The casting solvent for Propranolol Hydrochloride (a kind gift from Jaipur Pharmaceutical work, India) matrices was Chloroform + IPA + Ethyl alcohol (7 ml + 2 ml + 1 ml) . Ethyl Alcohol was used to solubilise Proporanolol Hydrochloride as it is not completely soluble in high concentration in chloroform. DBP (30% ww of polymer) was added as plasticizer. The prepared polymeric films were evaluated for uniformity of thickness, uniformity of weight, physical appearance uniformity of drug content, water absorption capacity, *in vitro* drug release studies, *in vitro* skin permeation studies, *in vivo*

studies, scanning electron microscopic studies, skin irritation studies and accelerated stability studies.

EVALUATION OF FREE FILMS

Physical appearance, Film Thickness and Uniformity of weight

The free films were evaluated for their physical appearance - opaque/ transparent / smooth/ wrinkled / moist/ dry /tough/ flexible / non flexible sticky / non sticky. The thickness of the dried films were measured at five different places using a thickness gauze (Instrumentation India) and their mean ± S.E.M. values (μm) were calculated. The weight of the dried films were measured for six patches of 1 cm^2 each and their mean ± S.E.M. (mg/cm^2) were calculated.

Determination of water vapour transmission

The method of Utzumi et al, [11]was adopted for the determination of water vapour transmission through free films. The film under investigation was cut, its thickness was measured at five different places and the mean thickness was calculated. The cut film was fixed over the brim of a glass vial (exposed surface area - 2.27 cm^2), containing 3 g of fused calcium chloride as dessicant with an adhesive, the charged vial was kept in a dessicator for about 2 hrs. to attain the equilibrium condition and vial was removed after 2 hrs., weighed and kept in a dessicator containing either saturated solution of potassium chloride or sodium hydrogen sulphate monohydrate to provide the relative humidity of 84% and 52% respectively [12]. The whole assembly was kept on a flat surface without any disturbance. The vial was taken out and weighed at regular time intervals for a period of 72 hrs. The experiment was triplicate and average values were calculated. The water vapour transmission rate was calculated from the plots of amount of water vapour transmitted versus time. The WVT rate ($g.\mu m/cm^2.day$) was calculated using the following equation.

$$WVT\ rate = WL/S$$

where W = g of water / 24 hr;L = thickness of the film in μm.;S = exposed surface area of the film in cm^2.

EVALUATION OF MATRICES

Physical appearance, Matrices Thickness and Uniformity of weight

The matrices were evaluated for their physical appearance - opaque/ transparent / smooth/ wrinkled / moist/ dry /tough/ flexible / non flexible sticky / non sticky.The thickness of the matrices were measured at five different places using a thickness gauze (Instrumentation India) and their mean ± S.E.M. values (μm) were calculated. The matrices were cut into patches of 1 cm^2 each, were weighed and their mean ± S.E.M. (mg/ cm^2) was calculated(n=6).

Uniformity of drug content

Three patches (1 cm^2) were cut from different parts of the matrices and free films. Each were taken in separate stoppered conical flasks containing 25 ml of casting solvent and were stirred vigorously for 4 hrs. on a magnetic stirrer. The above solutions were filtered and their drug content were estimated spectrophotometrically at 290nm using casting solvent of free film as blank.

Water absorption studies

The matrices of each formulation were tested for water absorption capacities according to the method described by Danjo, et al, [13]The matrices (1cm^2) were weighed and hang in a glass chamber containing saturated solutions for different humidity (52%, 58%, 76% and 84% RH) [12]with the help of a glass rod for 4 weeks. Change in weight was noted and percent water absorption capacity was calculated by the formula

$$\text{Percent water absorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial Weight}} \times 100$$

In vitro Drug Release Studies

The developed matrices were analysed for drug release studies using Paddle over disk method [14]of dissolution. The disc assembly holds the system flat and is positioned such that the release surface is parallel with the bottom of the paddle blade. A laboratory fabricated patch holder was employed in dissolution testing. The dry film of known thickness were cut and fixed in patch holder. The patch holder was immersed in a 500 ml phosphate buffer solution (pH 7.4) maintained at a temperature of 37 ± 1°C. The paddle was positioned and regulated to rotate Aliquots of the samples were taken periodically at predetermined time intervals and analysed for drug content after suitable dilution with buffer solution. After each sampling an equal volume of drug free phosphate buffer solution was added to the dissolution medium to maintain a constant volume. Necessary corrections were made in the calculations for the loss of drug due to each sampling. The experiment was done in triplicate and cumulative release (mean ± S.E.M.) (mg/cm^2) was calculated. The release rates were calculated from the linear plots of cumulative amount of drug released versus square root of time.

In vitro skin permeation studies

The *in vitro* skin permeation of drug from the selected films through the rat abdominal skin was tested by using a modified Franz diffusion cell. The full thickness abdominal skin of male Wistar rats weighing 130-160 g were used. Hair on the abdominal area were clipped off by applying depilatory for 10 min and washed with distilled water one day before the experiment. The rats were anaesthesised with ether and the abdominal skin patches were excised. The two edges of abdominal skin were stitched and antiseptic cream was applied for healing. The fatty material adhered to the excised skin was peeled off. The skin was mounted between the two compartments of the diffusion cell with the epidermis facing upward to the donor compartment. The film to be tested was placed on the skin Isotonic phosphate buffer solution (pH 7.4) (15 ml) was used as receptor phase and agitated with a magnetic stirrer at a speed of 600 rpm and the temperature was maintained at 37±1°C. Samples were withdrawn at regular intervals through the sampling port and fresh receptor fluid was added to maintain the constant

volume of the receptor phase. Necessary corrections were made in the calculations for the loss of drug due to each sampling. The samples were analysed as mentioned before and the cumulative amount of drug permeated were plotted against time. The flux values were calculated from the linear portion of the plot.

In vivo Studies

The rabbits (Male New Zealand) weighing between 1.2 – 1.8 kg were used for *in vivo* studies. Animals were housed at 25±1°C in air conditioned room and were provided with water *ad libitum* and standard rabbits feed obtained from Ashirwad Food Industries Ltd. Chandigarh, India. Animals were fasted for 24 hrs prior to administration of drug formulations but had free access to water. One day before the experiment the hair on the abdominal area were clipped off by applying depilatory for 10 minutes and washed with distilled water. Animals were secured in supine position. The rate controlling polymeric film was placed with an pressure sensitive adhesive on the hair free abdominal area and occluded with bandage. The rabbits were housed in neck holder cages. Blood samples were collected at definite interval of time from marginal ear veins and serum was separated by centrifugation. The drugs were extracted from serum and dissolved in mobile phases. The concentration of drugs were estimated from the standard curves prepared in serum by HPLC methods

Scanning electron microscopic study

The surface morphologies of free films and matrices (before and after *in vivo* studies) were examined under a scanning election microscope.

Skin irritation studies

Skin irritation was evaluated after 24 hrs post application of transdermal formulations used for *in vivo* studies by a modified Draize score test [15] . Patches were applied to the intact and to abraded skin of rabbits occluded for 24 hrs and then removed for screening of irritancy, erythema or oedema.

Accelerated Stability Studies

The matrices which were used for *in vivo* performance were subjected to accelerated stability studies.[16] The matrices were kept in petridish and stored in thermostated ovens at a storage condition of 40°C ± 2°C / 75% RH± 5% RH for 3 month. The samples of matrices were withdrawn after 3 months and evaluated for parameters of uniformity of thickness, uniformity of weight, physical appearance and uniformity of drug content.

Results

FREE FILMS

The composition of different films are tabulated in Table I. Formulated films were evaluated for the following physical properties to obtain an optimum ratio of EC : HPMC for the formulation of matrices of selected drugs.All the prepared free films were smooth, dry, flexible and non sticky. The films F_1, F_2, F_4 and F_7 were very fine, F_3 and F_5 were moderately fine and F_6, F_8 and F_9 were thick comparatively . The thickness of the dried films were found in the range of 120-170μm . The film coded as F_1 is finest and film F_9 is thickest. The increase in EC content increased the thickness whereas increase in HPMC content did not show much increase.The weights of the dried films were in the range of 4 - 10 mg.. Individual weight variation was not significantly different. The weights of the free films increased as the content of polymers increased (Table II).

Water Vapour Transmission

The rate of water vapour transmission (WVT rate) at 52% RH was negligible as compared to WVT rate at 84% RH. At the 52% RH, the film coded as F_7 had shown maximum WVT rate (1.369 g.μm/cm^2 day) and film F_3 had shown minimum WVT rate (0.281 g. μm/cm^2 day). At 84% RH, the film F_7 had shown maximum WVT rate (4.389 g. μm/cm^2 day) and film F_1 had shown minimum WVT rate (1.437 g. μm/cm^2 day) (Table 3). The free film F_7 which had shown maximum WVT rate had EC : HPMC ratio as 1 : 3 where as the free film F_3 had ratio as 3:1 and free film F_1 had 1:1 ratio were

showing minimum WVT rate. The free film F_3 and F_5 had shown less WVT rate at 84% RH (2.6 g. μm/cm^2 day and 2.779 g. μm/cm^2 day respectively) and negligible rate at 52% RH (Table III,Fig. 1).

TABLE I: COMPOSITION OF FREE FILMS

CODE	**EC (mg/10ml)**	**HPMC (mg/10ml)**	**DBP (%w/w of polymer)**
F_1	100	100	30
F_2	200	100	30
F_3	300	100	30
F_4	100	200	30
F_5	200	200	30
F_6	300	200	30
F_7	100	300	30
F_8	200	300	30
F_9	300	300	30

TABLE II: PHYSICAL PROPERTIES OF FREE FILMS

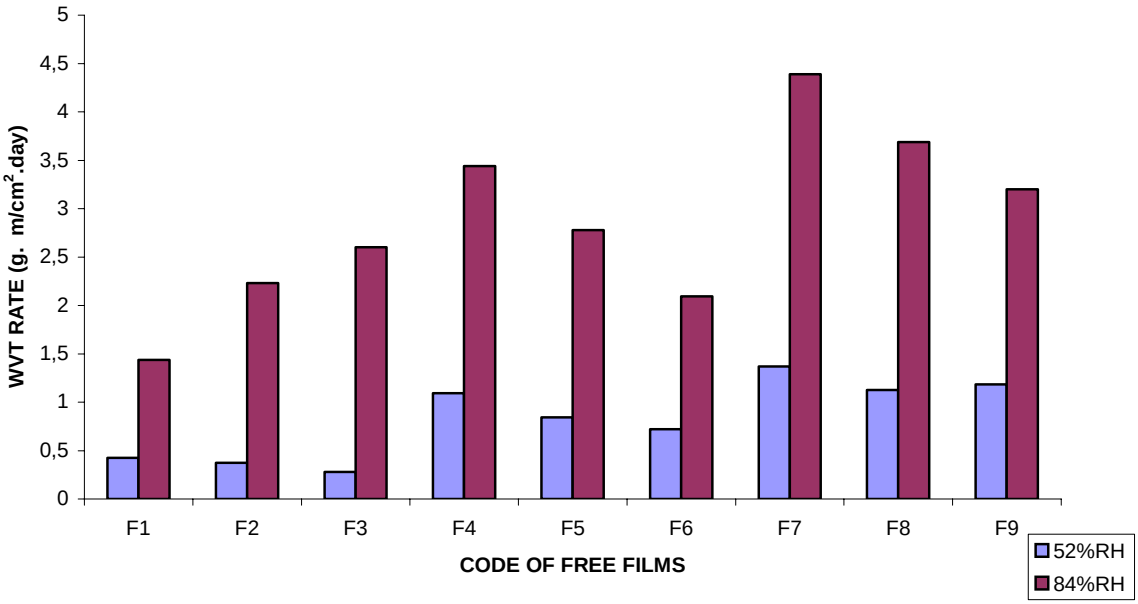
CODE	THICKNESS (n=5) (μm)	WEIGHT (n=6) (mg/cm^2)	PHYSICAL APPEARANCE
F_1	120.8 ± 0.58	4.06 ± 0.02	*
F_2	140.8 ± 0.37	5.04 ± 0.02	*
F_3	159.2 ± 0.37	6.64 ± 0.02	**
F_4	124.2 ± 0.37	5.08 ± 0.02	*
F_5	146.4 ± 0.51	6.66 ± 0.02	**
F_6	163.8 ± 0.58	8.32 ± 0.04	***
F_7	129.2 ± 0.37	6.54 ± 0.02	*
F_8	149.6 ± 0.24	8.66 ± 0.04	***
F_9	168.6 ± 0.24	9.96 ± 0.04	***

MEAN ± S.E.M.
* VERY FINE, SMOOTH, DRY, FLEXIBLE, NON STICKY
** MODERATELY FINE, SMOOTH, DRY, FLEXIBLE, NON STICKY
*** THICK, SMOOTH, DRY, FLEXIBLE, NON STICKY

TABLE III : WATER VAPOUR TRANSMISSION RATE OF FREE FILMS

CODE	**WVT RATE (52% RH) ($g.\mu m/cm^2.day$)**	**WVT RATE (84%RH) ($g.\mu m/cm^2.day$)**
F_1	0.426	1.437
F_2	0.372	2.231
F_3	0.281	2.600
F_4	1.093	3.439
F_5	0.841	2.779
F_6	0.720	2.094
F_7	1.369	4.389
F_8	1.124	3.688
F_9	1.184	3.198

Fig.1 : COMPARATIVE WATER VAPOUR TRANSMISSION RATE OF FREE FILMS AT DIFFERENT HUMIDITY



MATRICES

Based on the results of evaluation of free films, the free films F_3 and F_5 were chosen for preparing matrices. The free film F_3 contains the ratio of polymers EC : HPMC as 3:1 whereas F_5 contains the ratio of 2:2 with DBP (30% w/w of polymer content) as plasticizer. The free films F_3 and F_5 had uniform thickness and uniform weight. The WVT rates for both the films were negligible at 52% RH and very less at 84% RH. Both the free films were also moderately fine, smooth, dry, flexible and non sticky. Hence they were selected for preparing matrices of drugs.

The matrix – diffusion type transdermal matrices were prepared The drug load was kept 5 mg / cm^2 for each drug. The prepared matrices were evaluated for various parameters as described below.

The matrices were found opaque, smooth, dry, flexible. The thickness was found in range of 150-170 μm for all matrices. The SEM value were less indicating that the matrices were uniform in thickness. The matrices were thicker for polymer (EC : HPMC) ratio 3:1 as compared to ratio 2:2. The matrices were having weight approximately 13 mg and they

were all uniform in weight as SEM values were less. The weight of matrices using ratio of EC : HPMC as 3:1 were more as compare to matrices using EC : HPMC as 2 : 2. The matrices (1 cm^2) had uniform distribution of drugs when cut from different parts of film formed in moulds (Table IV) (n=3).

TABLE IV :PHYSICAL PROPERTIES OF MATRICES

CODE	THICKNESS (n=5) (μm)	WEIGHT (n=6) (mg/cm^2)	DRUG CONTENT (n=3) (%)
P_1	168.4 ± 0.24	12.96 ± 0.007	98.78 ± 0.27
P_2	150.8 ± 0.20	12.65 ± 0.004	99.1 ± 0.39

Water absorption studies

Water absorbed by different matrices were lowest at 52% RH. The value increases as relative humidity increases and maximum water was absorbed at 84% RH. The matrices containing EC : HPMC ratio 3 : 1 absorbed less moisture as compare to EC : HPMC ratio 2:2 (Table V).

TABLE V : WATER ABSORPTION CAPACITY (%) OF MATRICES

CODE	52% RH	58% RH	76% RH	84% RH
P_1	2.24 ± 0.05	3.61 ± 0.03	7.19 ± 0.00	8.98 ± 0.15
P_2	2.56 ± 0.07	3.59 ± 0.10	9.33 ± 0.16	11.80 ± 0.09

n=3
MEAN ± S.E.M.
RH RELATIVE HUMIDITY

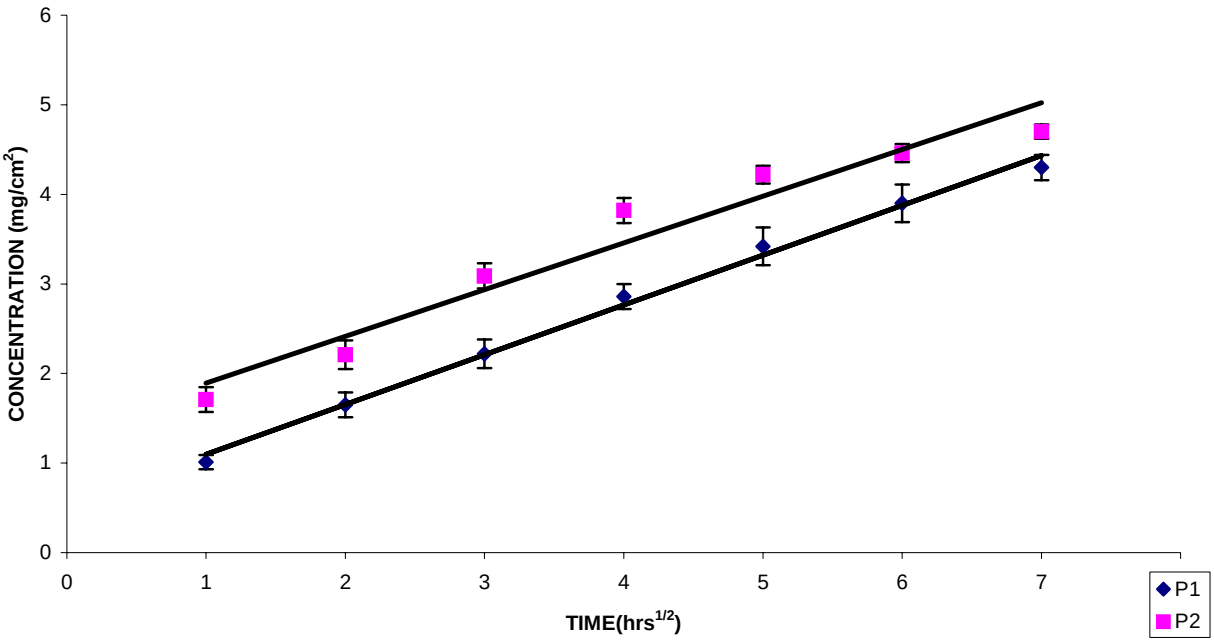
In vitro drug release studies

The release of drug from matrices was observed and the cumulative amount of Propranolol Hydrochloride (Table VI) released from matrices were determined with an interval of 1 hr. in each sampling. The cumulative release of drugs was plotted against square root of time and the release flux were calculated (Fig.2). The release of Propranolol Hydrochloride from P_1 matrices was 20.2%, 33.0%, 44.4%, 57.2%, 68.4%, 78.0% and 86.0% whereas from matrices P_2 it was 34.2%, 44.2%, 61.8%, 76.4%, 84.4%, 89.2% and 94% after 1, 2, 3, 4, 5, 6 and 7 hrs. of study. The matrices P_1 had shown the release flux values of 1.6736 mg / cm^2 $hr^{½}$ and matrices P_2 had shown 1.8556 mg/ cm^2. $hr^{½}$ release flux.The release flux values were higher for the matrices formed with the polymer (EC: HPMC) ratio 2 : 2 as compare to 3 : 1.

TABLE VI : IN VITRO CUMULATIVE DRUG RELEASE FROM PROPRANOLOL HYDROCHLORIDE MATRICES

TIME (hrs)	**P_1 (mg/cm^2)**	**P_2 (mg/cm^2)**
0	0 ± 0	0 ± 0
1	1.01 ± 0.08	1.71 ± 0.14
2	1.65 ± 0.14	2.21 ± 0.16
3	2.22 ± 0.16	3.09 ± 0.14
4	2.86 ± 0.14	3.82 ± 0.14
5	3.42 ± 0.21	4.22 ± 0.10
6	3.9 ± 0.21	4.46 ± 0.10
7	4.3 ± 0.14	4.7 0 ± .08

Fig. 2 : *IN VITRO* CUMULATIVE RELEASE OF PROPRANOLOL HYDROCHLORIDE THROUGH MATRICES



In vitro skin permeation studies

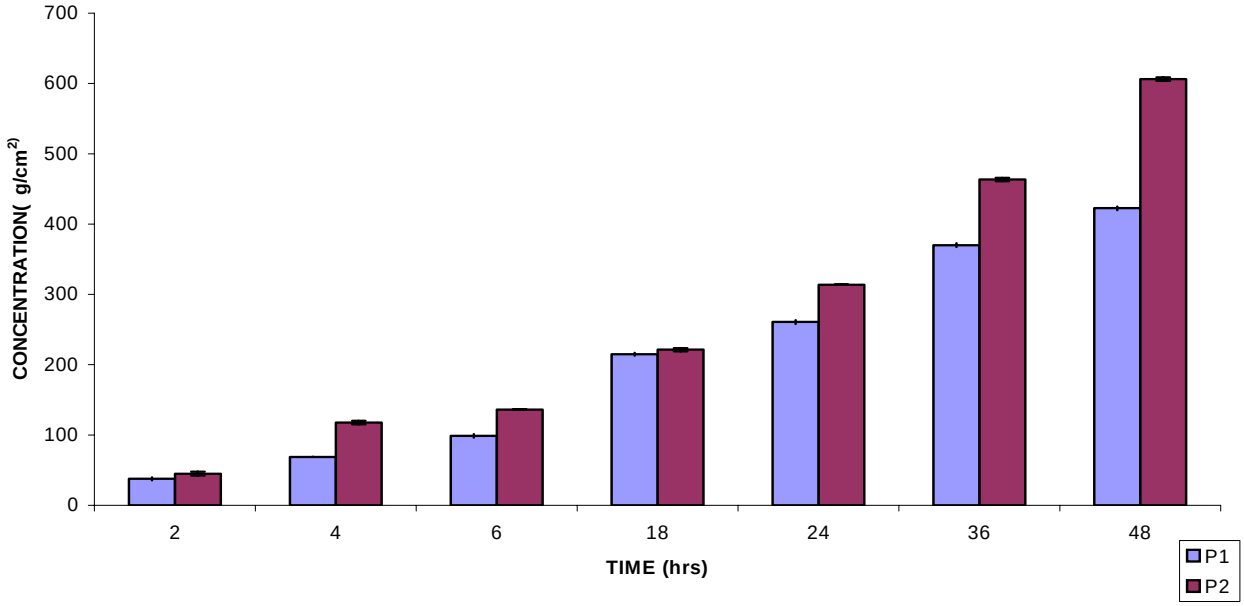
The *in vitro* skin permeation studies were performed on rat abdominal skin and the cumulative release of drugs from matrices were estimated (Table VII). The cumulative release is plotted against time and the permeation flux values were calculated for linear portion of the plot. The skin permeation studies provided that the release of Propranolol Hydrochloride was observed after 2nd hr. of the test. The release of Propranolol Hydrochloride from matrices P_1, was 0.76%, 1.38%, 1.97%, 4.29%, 5.21%, 7.52% and 8.45% and from P_2 matrices 0.90%, 2.35%, 2.72%, 4.42%, 6.27%, 9.27% and 12.12% after 2, 4, 6, 18, 24, 36 and 48 hrs. of study. The permeation flux for P_2 matrices (11.875 µg/cm^2. hr) was more as compared to P_1 matrices (8.85 µg/ cm^2. hr).The matrices containing polymer ratio EC : HPMC 2 : 2 had shown better release as compare to ratio 3: 1 (Fig.3).

TABLE VII: IN VITRO CUMULATIVE SKIN PERMEATION OF DRUG FROM PROPRANOLOL HYDROCHLORIDE MATRICES

TIME (hrs)	P_1 (μg/cm^2)	P_2 (μg/cm^2)
0	0	0
2	37.78 ± 2.25	44.96 ± 2.71
4	68.88 ± 0.32	117.69 ± 2.57
6	98.71 ± 2.40	136.19 ± 0.32
18	214.65 ± 2.08	221.2 ± 2.40
24	260.73 ± 2.59	313.7 ± 0.32
36	376.16 ± 2.57	463.3 ± 2.40
48	422.47 ± 2.57	606.2 ± 2.57

n=3
MEAN ± S.E.M.

Fig.3 : *IN VITRO* CUMULATIVE SKIN PERMEATION OF PROPRANOLOL HYDROCHLORIDE FROM MATRICES



In vivo studies

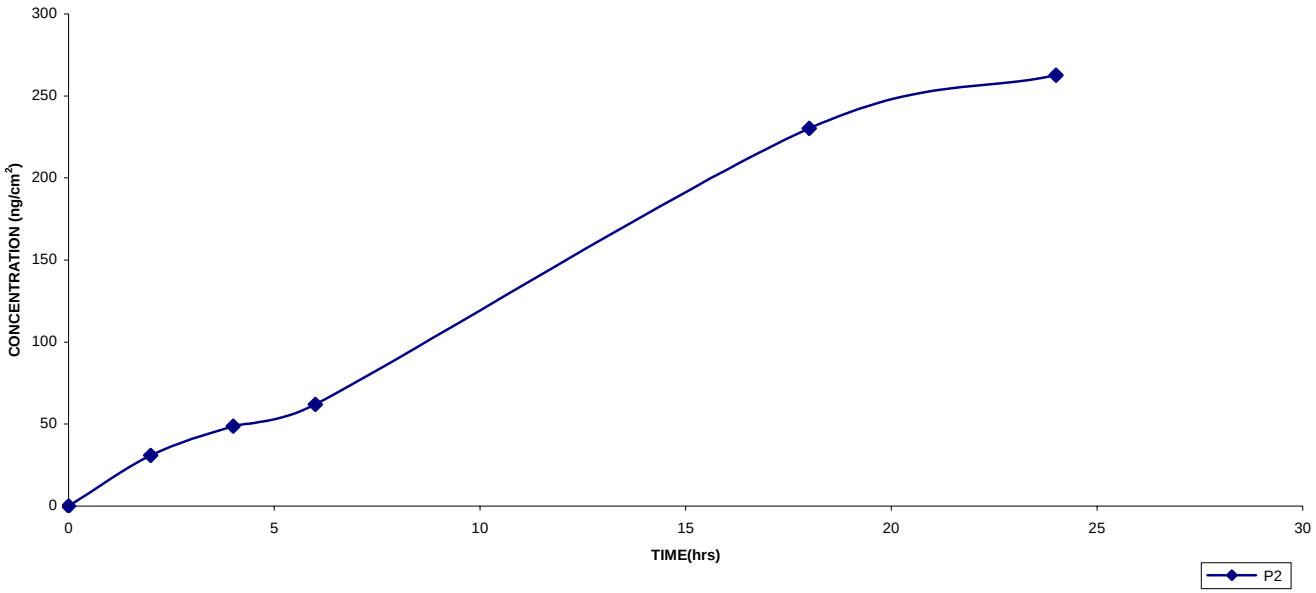
The matrices shown better release flux and permeation flux values (P_2) were considered for *in vivo* studies on male rabbits. Propranolol Hydrochloride was permeated through skin of male rabbits and had shown permeation of 262.7 ng/cm^2 from P_2 matrices after 24 hrs. matrices application(Table VIII,Fig.4). It was observed that all were free from skin irritant effect. None of the matrices had shown any sign of erythema after 24 hrs. application on abdomen of rabbits.

TABLE VIII : IN VIVO DRUG RELEASE STUDY FROM MATRICES

TIME (hrs)	0	2	4	6	18	24
P_2 (ng/cm^2)	0	30.95 ± 1.15	48.68 ± 0.48	61.94 ± 0.38	230.29 ± 0.87	262.7 ± 0.66

n=3
MEAN ± S.E.M.

Fig.4 : *IN VIVO* CUMULATIVE SKIN PERMEATION OF PROPRANOLOL HYDROCHLORIDE FROM MATRICES



Scanning electron microscopic studies

The surface morphologies of the drug dispersed films before and after *in vivo* studies were examined by scanning electron microscopy. A drug free film F_5 was also studied for surface morphology. The study revealed that the free film F_5 (Fig.5) and matrices P_2 (Fig.7) were uniform and smooth in their surfaces. The free film (F_5) did not show any change in surface morphology after application on skin for 24 hrs. (Fig.6). The matrices P_2 observed after 24 hrs. of application on rabbit abdomen skin clearly shown big holes like structure in matrices showing the release of drug from that place(Fig8).

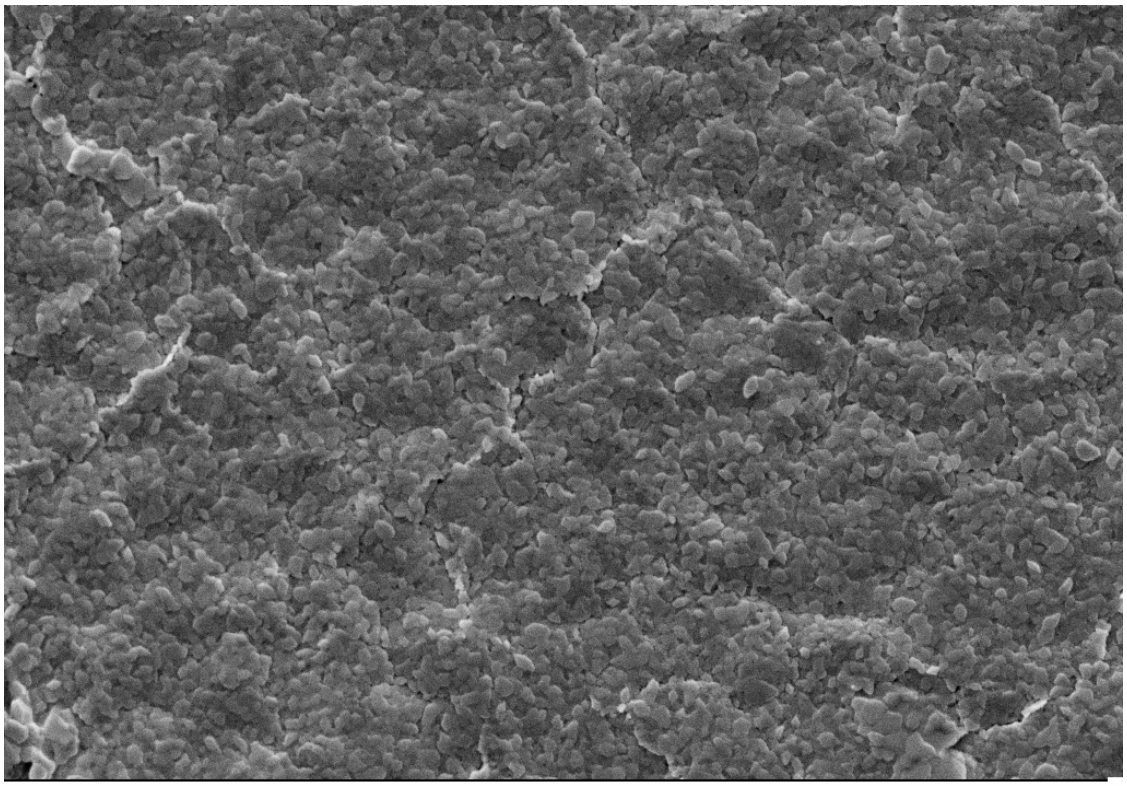


Fig.5: Scanning electron microscopic photograph of free film F_5 showing smoothness of surface before *in vivo* studies.

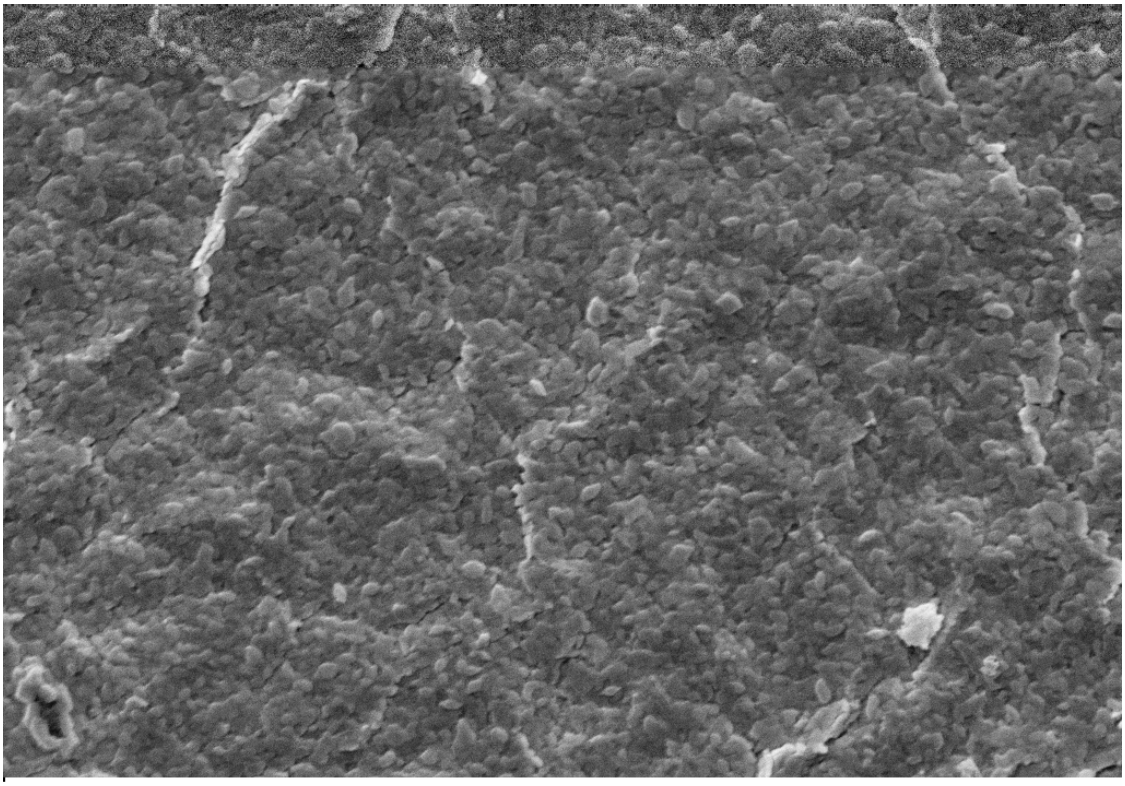


Fig.6: After *in vivo* study the SEM photograph did not show change in morphology of free film F_5. It indicated that the ratio of EC : HPMC as 2:2 for forming matrices will maintain its physical properties even after its application on skin.

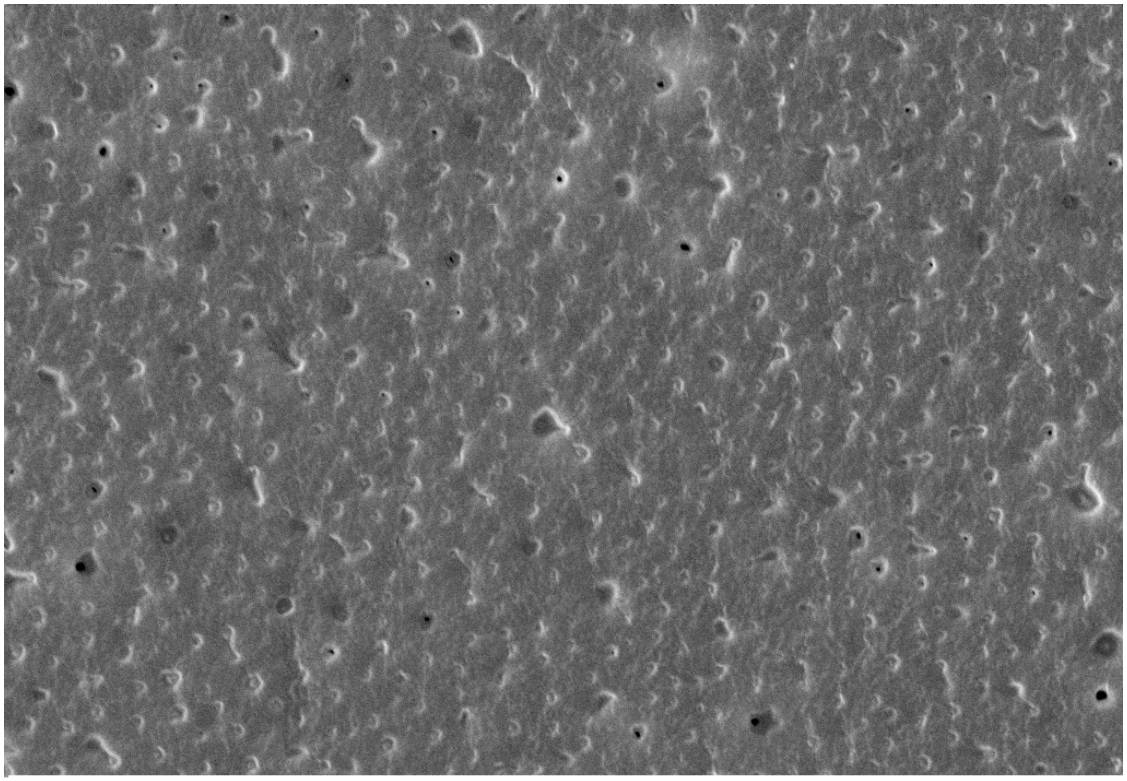


Fig.7: The matrix P_2 is visible as smooth and uniform matrix in SEM photograph before *in vivo* studies.

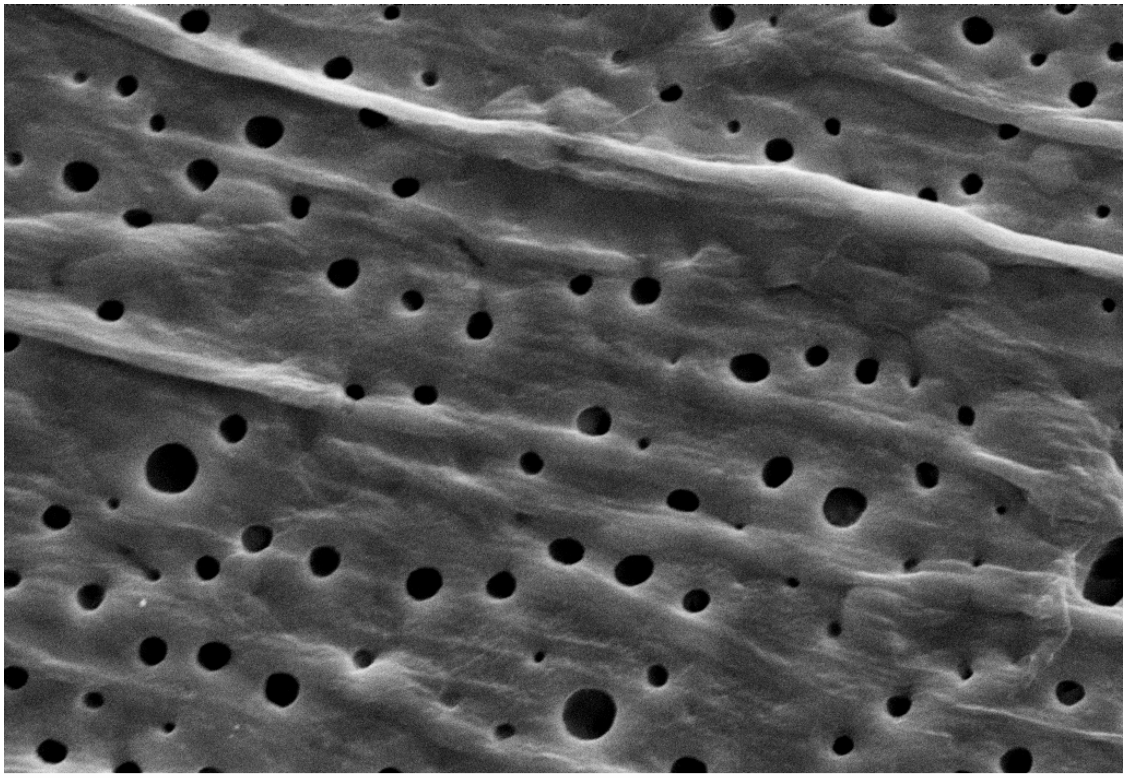


Fig.8: The application of matrix P_2 on abdominal skin of rabbit released the drug into blood stream. The release is visible as the holes in SEM photograph

Accelerated stability studies

The matrices used for in vivo studies (P_2) were also evaluated for their stability as per ICH Guidelines, 2003 (Table IX). The results obtained after 3 months of study revealed that there was no change in thickness as compared to initial thickness. There was very less increase in weight (1.58%). The drug content of matrices had changed to little extent than the initial ones for matrices of all drugs but they were all in the acceptable limits. All the matrices were found uniform in thickness, weight and drug content and hence stable for 3 months.

Discussion

The strategies used by pharmaceutical industry for discovery of a potential new drug delivery system have changed dramatically in recent years. These changes in strategy present new challenges and opportunities for the application of new methodologies in the drug delivery processes. The transdermal patch has become a proven technology, holding the promise that new compound could be delivered in a safe and convenient way through the skin [17].The systemic bioavailability of Propranolol was evaluated following oral and transdermal delivery in rabbits and concluded that the transdermal delivery of Propranolol can significantly increase systemic bioavailability over oral administration [18].

In the present study, Ethyl Cellulose (EC) and Hydroxypropyl methyl cellulose (HPMC) were used for formulating Transdermal Drug Delivery Systems. EC and HPMC were used for developing TDDS of antihypertensive drugs[19-22] Cellulose derivatives are the most widely used polymers in the production of hydrophilic matrices. In particular release rate can be modulated by selecting the appropriate cellulose substitution type. It is reported that Ethyl cellulose (EC) is a non biodegradable polymers which is inert and eliminated or extracted intact from the site of administration and serve essentially as a rate limiting barrier to the transport and release of drug from the device. Hydroxypropyl methylcellulose is a soluble polymer. It can be used alone or in combination with hydrophobic polymers to provide devices that slowly erode over time [23-24]. It is reported that the lipophilic polymers like ethyl cellulose is best plasticized by dibutyl pthalate, diethyl pthalate, dimethyl pthalate etc. hence dibutyl pthalate (DBP) was used in experiments as plasticizer to aid in the formulation of TDDS of antihypertensive drugs [24].

The increase in content of EC increased the thickness of free films whereas HPMC content did not show any significant affect. Free film F_3 was thicker than free film F_5.The water vapour transmission rate was more in free films F_7, F_8 and F_9. It was observed that increase in ratio of HPMC increased the WVT rate. As HPMC is a hydrophillic polymer it may have allowed more water vapours to pass through the films.

This may be attributed to the study by Mosquera et al., [25]who observed that hydrophilic polymers due to moisture uptake increases total porosity and pore diameter. Hence, more water vapours passed through film F_5, as compared to F_3 (WVT rate of F_3 was 0.281 and 2.600 g.μm/cm^2 day at 52% and 84% RH respectively < WVT rate of Free film F_5 was 0.841 and 2.779 g. μm/cm^2 day at 52% and 84% RH respectively). From the above results the free film F_3 and F_5 were selected for the formulation of transdermal devices of Propranolol Hydrochloride.

The matrices formed were uniform in weight, thickness and appearance.When they were stored at different humidity at 20^{o}C, increase in weight was observed at 76% RH and 84% RH while negligible change in formulation weight was observed at 52% and 58% RH. Water absorption studies revealed that moisture uptake was more in matrices having high content of HPMC (P_2) with polymer ratio of EC : HPMC as 2 : 2 as compared to 3 : 1 (P_1). The results were in parallel to the work of Mosquera et al. [25]who had shown that there were significant changes in properties like reduced crushing strength, increased total porosity and increased pore diameter in hydrophilic polymer containing matrices due to moisture uptake. The *in vitro* release studies clearly indicated that the release of a drug from the films followed the diffusion – controlled matrix model, in which the amount of drug released per unit area is proportional to the square root of time. As the amount of HPMC was increased, the release flux and permeation flux values of matrices also increased. The addition of hydrophilic component to an insoluble film former tends to enhance its release rate constants. This may be due to the dissolution of the aqueous soluble fraction of film which leads to the formation of pores and to higher dissolution rates. This may also be attributed to the swelling of the HPMC component which resulted in the formation of pores and thus led to the decrease of mean diffusion path length of the drug molecules to release into dissolution medium and hence to higher release flux values [20]. The abdominal skin of rat was chosen for permeation of drugs through skin as it is easier to obtain in enough amount. Here it is important to state that skin was obtained from anaesthetized rats and not from killed animals. This had two benefits viz. survival of animal and also sacrificing of animal may change the physiologic condition of skin which can effect the release patterns of drugs.

Propranolol Hydrochloride being hydrophilic in nature may have followed transcellular pathway. This pathway is shortest hence concentration was observed in serum after 24 hrs. of application of matrices on skin of rabbit in *in vivo* studies. The SEM photographs obtained for free films and various matrices clearly indicated that the free film and matrices were uniform in their structure. The matrices and free film were also observed after *in vivo* studies. The free film was uniform in its structure after 24 hrs of application. It indicates that there is no change in the polymeric film even after its applications on skin. This suggested that they keep their physicochemical properties as the original one. The matrices of Propranolol Hydrochloride was clearly showing large holes which indicated a large amount was released from that particular place. The SEM photographs were justifying the results of *in vitro* and *in vivo* studies.

Conclusion

From this study, it can reasonably concluded that Propranolol Hydrochloride can be formulated into transdermal polymeric matrices to avoid hepatic metabolism and prolong its release characteristics. The formulation P_2 was found to be best choice for manufacturing transdermal matrices with a polymer combination of EC and HPMC (2:2). They were free from any irritating effect on skin. Also they were found to be stable for 3 months. These may also be used for further pharmacokinetic and pharmacodynamic studies in suitable animal models.

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