DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 20(15), 2459-2465 (1994)

TRANSDERMAL DELIVERY OF PROPRANOLOL

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ABSTRACT

Three transdermal formulations containing propranolol hydrochloride in a hydrophilic polymer matrix were prepared - one without a rate controlling membrane(H-1), one with a 20μ thick Ethylene Vinyl Acetate(EVA) rate controlling membrane (H-2) and one with a 65μ thick EVA membrane.These patches were evaluated for their *in-vitro* performance.Cumulative % permeated across excised hairfree rat skin were 79.2% from H-1, 65.53% from H-2 and 53.44% from H-3. Increase in thickness of EVA lead to greater retention of drug in device and a zero order profile was seen with patches H-2 & H-3. Matrix diffusion profile was observed with H-1 patch.

INTRODUCTION

Beta receptor antagonists are invaluable in the treatment of hypertension and a host of other cardiovascular diseases (1). However , they are used in multiple dosage schedules and suffer from high "first pass" metabolism. Transdermal delivery offers obvious advantages of bypassing first pass metabolism , reduction in dose and the advantages and convenience of rate controlled drug therapy. For this reason many beta blockers have been the focus of transdermal delivery reasearch.

Propranolol was chosen as the model candidate for this study since it possesses the near ideal characteristics that a drug must have in formulating a TDDS- a low molecular weight , high lipid solubility , effective in low plasma concentration as well as it suffers from a high degree of first pass metabolism.It also means multiple daily administration with a subsequent lack of patient compliance(2).The aim of this study was to formulate propranolol hydrochloride in a hydrophilic polymer matrix of hydroxy propyl methyl cellulose (HPMC) and to study the effect of two different thicknesses of EVA rate controlling membrane , evaluate the films for physico-mechanical integrity and *in-vitro* permeation profile across excised hairfree rat skin ,and to conduct skin irritation studies of the best patch in rats .

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MATERIALS

Propranolol HcL was a gift from Cipla Ltd, Bombay ,India. Ethylene Vinyl Acetate(40% vinyl acetate) was obtained from duPont Chemical Co, Wilmington, Dalware , USA and Hydroxy Propyl Methyl Cellulose from G.S Chemical Testing Lab & Allied Industries , India. Male albino rats were obtained from Zoological Emporium Pvt.Ltd, Varanasi , India.

METHODS

Preparation of Patches

3% polyvinyl alcohol was used as the backing membrane.The polymer was dissolved in distilled water with slight warming and poured onto a glass substrate and dried at 60°C for 6 hours.The H-1 patch was prepared by dissolving 600 mg of HPMC in distilled water(10 ml) and adding 78 mg of propranolol hydrochloride(in 5 ml distilled water) followed by mixing on a magnetic stirrer.The resulting solution was poured on the backing layer as prepared earlier and oven dried at 45 °C for 6 hours.The H-2 and H-3 patches were prepared similarly except that a 3% w/v of EVA in chloroform was poured over the drug reservoir to get a 20 μ film in H-2 and a 65μ film in H-3(Table 1).

Evaluation of Patches

The patches were evaluated for thickness (screw gauge) , weight uniformity , moisture vapour transmission , moisture absorption / loss , and drug content uniformity.

Moisture Vapour Transmission

The MVT is defined as the quantity of moisture transmitted through unit area of film in unit time .Glass cells (length, 3.5 cm & diameter 1.25 cm) were filled with 2g of anhydrous calcium chloride and a film of specified area was affixed on the rim of the cell.The assembly was accurately weighed , placed in a constant humidity chamber containing ammonium chloride (RH 79.5% , RT) in a oven maintained at 27 ± 2 °C for 24 hours and 1 week and again weighed .

Moisture Absorption/Loss of Films

Conditioned films of specified dimensions were suspended in two constant RH chambers(one with a RH 51% at 37 °C and the other at an RH 79.5% at RT). Films were weighed accurately before and after this treatment when placed for 24 hours & 1 week.

Drug Content Uniformity

Films of specified area were cut and weighed accurately. The pieces were taken into a 100 volumetric flask and 40 ml phosphate buffer pH 7.4 added & kept in a shaker for 12 hours.A blank was carried out using a drug free patch treated similarly.The solutions were filtered , centrifuged and absorbances read at 290 nm in a Beckman UV spectrophotometer(9).

In-vitro Permeation Studies

A modified Franz diffusion cell was fabricated in our laboratory with a receptor volume of 24 ml.The magnetic stirrer was set at 500 rpm , pH 7.4 phosphate buffer was used as the receptor solution and the whole assembly maintained at 37 ± 2 °C. Hair from the abdominal region of a healthy albino rat was carefully removed and skin excised. The dermal side of the skin was thoroughly cleaned of any adhereing tissues or blood vessels and equilibrated for an hour in pH 7.4 buffer before running the experiment. 2.5 cm diameter transdermal discs were placed in intimate contact with the stratum corneum side of the skin and were placed in between two halves of the diffusion cell. The amount

Table 1 - Formulation of Transdermal Films

Formulation	Backing Layer	Drug Reservoir	Rate controlling membrane
H-1	3% PVA	4%HPMC	-
H-2	3% PVA	4%HPMC	3% EVA (20 μ)
H-3	3% PVA	4%HPMC	3% EVA (65 μ)

Table-2 -Skin Irritation Studies with H-1 Patch

Sl.No.	Rat No.	Propranolol Patch		Formalin Control	
		Erythema	Edema	Erythema	Edema
1	1	1	0	3	4
2	2	0	1	3	3
3	3	2	0	2	3
4	4	2	0	3	4
5	5	0	0	2	4
Mean Combined Score		1.2(mild)		6.2 (Severe Irritation)	

of drug permeated was determined by removing 1 ml samples at hourly intervals for 10 hours and then at 24 hours.The volume was replaced with an equal volume of fresh prewarmed buffer. The absorbances were read at 290 nm in a Beckman U-24 model UV spectrophotometer(9).After the diffusion study residual drug content was determined in the skin and patch by extacting the homogenised fractions and using a blank.

Skin Irritation Test

The patches were tested for their potential to cause skin irritation / sensitization in rats. A modification of the method followed by Vlasses *et al* (8) was used.The abdominal areas of five healthy rats were shaved carefully avoiding peripheral damage and the patch applied onto the nude skin using a peripheral adhesive (Leucoplast™).Each site of patch application was rated with regard to the presence and severity of flare and wheal. A 0.8% aqueous solution of formalin was applied as a standard irritant and its effects compared with test.Animals were observed for any sign of flare and wheal for a period of 7 days.**(Table 2)**

RESULTS & DISCUSSION

Table 3 summarises the data obtained from tests of film integrity like MVT and moisture absorption as well as *in - vitro* permeation studies.Hydroxy propyl methyl cellulose of such grade used which has 8% hydroxypropyl and 22% methoxy content , is a hydrophilic polymer and a commonly used popular matrix forming material for oral drug delivery systems. The kinetics of oral drug release has been extensively studied and matrix diffusion controlled release profile has been suggested(4,5). The mechanism of drug release from polymer matrix has been attributed to swelling and erosion. We started this study with a working hypothesis that when a film of HPMC matrix is placed as a patch on the skin , it

Table-3 Summary of the data obtained from evaluation of film integrity and in-vitro permeation profile across excised hairfree rat skin.

Test Parameter	H-1 TDDS	H-2 TDDS	H-3 TDDS
1*Moisture vapour transmission, g(cm^2)$^{-1}$(h)$^{-1}$*			
1 day	3.77 x 10^{-5}	3.34 x 10^{-5}	3.3 x 10^{-6}
7 days	2.93 x 10^{-5}	5.7 x 10^{-6}	3.8 x 10^{-6}
2*Assay (mg/cm2)*	1.053	0.916	1.027
3.*Thickness(mm ±0.01 mm)*	0.12	0.14	0.185
4.%Moisture absorbed *(a) at 51% RH - 1 day*	1.72	0.072	0.060
-7 days	1.95	0.088	0.074
(b)at 79.5% RH - 1 day	2.06	0.076	0.0334
-7 days	2.92	0.094	0.041
5.*Weight Of 2.5 cm dia. discs(g)*	0.033	0.041	0.037
6.*In-vitro permeation studies (a)amount in patch(mg)*	5.215	4.538	5.087
(b)amount permeated,24h,(mg)	4.130	2.924	2.718
(c)cumulative % permeated	79.2	65.53	53.44
(d)Residual Drug Content (i)patch	0.928	1.337	1.945
(ii)skin	0.097	0.218	0.423

causes occlusion and accumulation of dermal secretions reulting in a swelling of the polymer at a microscopic level with an increase in porosity causing a thrust in drug release.Therefore we chose to use the propranolol as the hydrochloride itself. As control and in order to prove that thickness of rate controlling membrane plays a major role in drug release , we prepared HPMC based patches containing EVA in two thicknesses as rate controlling membrane.Tests from MVT indicated that moisture was transmitted through the film greatest in H-1 , intermediate in H-2 and least in H-3.An increased thickness in EVA resulted in a reduction in MVT value and moisture absorption. As the relative humidity was increased from 51% to 79.5% the percentage moisture also increased. The % moisture absorbed also

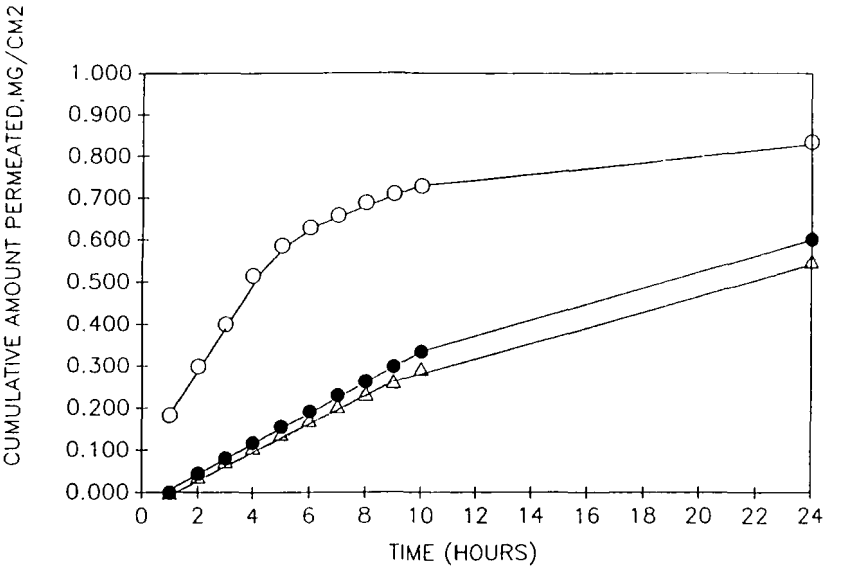

Fig.1: Cumulative amount of propranolol permeated across excised hairfree rat skin (open circles-H-1; closed circles-H-2; and open triangles-H-3 patches)

increased as exposure period was extended from 1 day to 7 days. In - vitro permeation studies indicate that 79.2% of drug permeated from H-1 patch at the end of 24 hour study(Fig.1). H-1 showed an initial high permeation rate with about 60% permeated at the end of 6th hour (104.83μg/cm^2/hr) but at the end of the 24th hour the rate had fallen down to 34.75 μg/cm^2/hr.The permeation profile was observed to be of matrix diffusion type (Fig.2). However the relationship was seen to be "quassi-linear". The reasons for this could be due to a time-dependent change in polymer porosity altering therefore the permeation rate.The rapid rise in permeation rate could be attributed to an accumulation of drug particles on the periphery of the device.H-2 and H-3 showed cumulative % permeated values of 65.53% and 53.44% respectively. Both showed initial lag times of one hour.The permeation profile was zero order.In these devices the drug reservoir exists as a saturated system with excess drug particles (confirmed by microscopic observations) , sandwitched between the backing layer and the rate controlling membrane.Since the concentration of the material in equilibrium with the inner surface of the enclosing membrane is constant and since the driving force for diffusional drug release is constant, we could observe zero order permeation profile(Fig.3).Therefore as long as excess solid is maintained in the reservoir constant drug release is assured.Once the device nears exhaution of drug , concentration gradient falls and a deviation from zero order release occurs (as noted at the 24th hour).Drug permeability is also dependent on thickness of rate controlling membrane since an increase in path resistance (in H-3) reduces drug

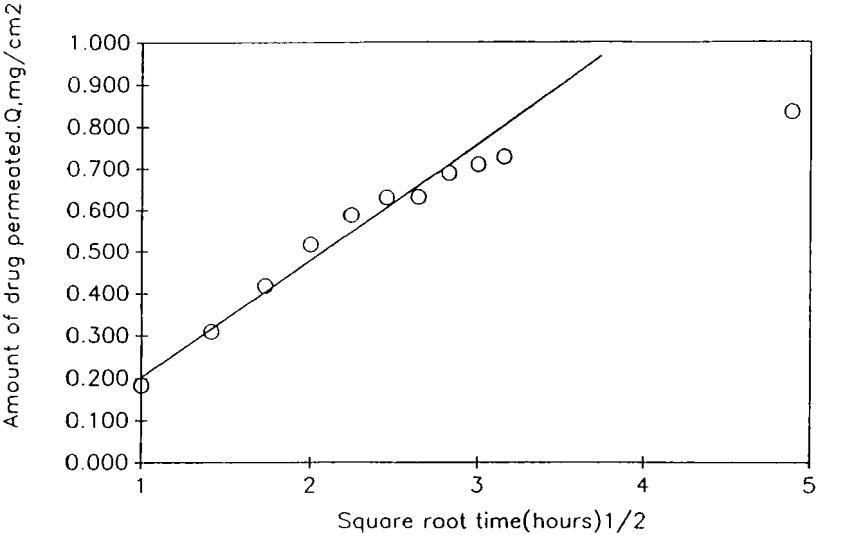

Fig.2: Matrix diffusion type permeation profile across excised hairfree rat skin from H-1 patch

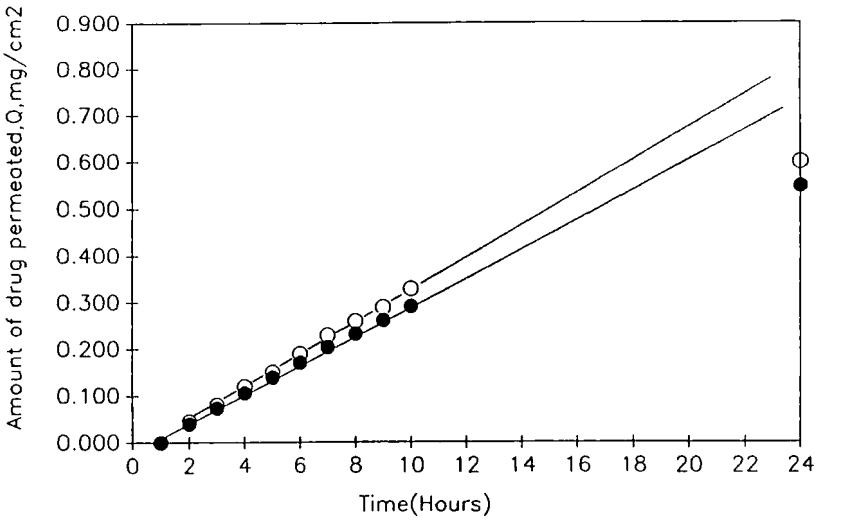

Fig.3: Zero order permeation profile across excised hairfree rat skin from H-2(open circles) and H-3(closed circles) patches.

permeation rate appreciably. Since the fabricated transdermal discs H-2 and H-3 were used in *in-vitro* studies immediately after preparation , the device requires some time to establish a concentration gradient within the rate controlling membrane. This might explain the lag times seen with H-2 and H-3 patches..The rabbit pinna skin has shown to be an excellent model for in-vivo studies(6,7).The pinna is also hairfree and so no disturbance, mechanical or chemical , was given. Skin irritation studies demonstrated that H-1 patch evoked only a mild response.Results of an in-vivo study comparing oral, intravenous and transdermal delivery is reported elsewhere(9).

ACKNOWLEDGEMENTS

The authors would like to thank M/s Cipla Ltd, Bombay , India for providing with the free pure propranolol hydrochloride and Prof.(Dr.) S.P.Wahi , Head , Department Of Pharmaceutics , BHU for the facilities..Mr.Rajesh Krishna was a recepient of the UGC Junior Research Fellowship.

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