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Controlled Transdermal Delivery of Propranolol Using HPMC Matrices: Design and In-vitro and In-vivo Evaluation

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Abstract

To improve bioavailability and achieve a smoother plasma-concentration profile as compared with oral administration, a matrix-dispersion-type transdermal delivery system was designed and developed for propranolol using different ratios of hydroxypropylmethylcellulose (HPMC) K4M, K15M and K100M. Formulations were evaluated for in-vitro dissolution characteristics using a Cygnus' sandwich-patch holder.

Drug release followed Higuchi rather than zero-order or first-order kinetics. In-vivo evaluation was carried out on healthy volunteers ($21 \pm 1{\cdot}41$ years; $60{\cdot}89 \pm 5{\cdot}35$ kg) following the balanced incomplete block design. The dissolution rate constant (k) and data generated from plasma and urine (C_{max}, maximum plasma concentration; t_{max}, time to reach peak plasma concentration; AUC, area under the curve; k_e, elimination rate constant; $t_{\frac{1}{2}e}$, elimination half-life; k_a, absorption rate constant; $t_{\frac{1}{2}a}$, absorption half-life) were evaluated statistically by two-way analysis of variance. Statistically excellent correlation was found between the percentage of drug absorbed and C_{max}, AUC_{0-24} and $AUC_{0-\infty}$. A highly significant difference ($P < 0{\cdot}001$) was observed when C_{max} and $AUC_{0-\infty}$ generated from plasma and urine were compared, but k_e, $t_{\frac{1}{2}e}$, k_a and $t_{\frac{1}{2}a}$ did not differ significantly ($P > 0{\cdot}1$).

We conclude that urinary excretion data may be used as a simpler alternative to blood level data in studying the kinetics of absorption and deriving the absorption parameters.

The transdermal therapeutic system is a discrete dosage form which, when applied to intact skin, delivers the drug through the skin at a controlled rate to the systemic circulation. The advantages of delivering drugs across the skin for systemic therapy are well documented and transdermal drug delivery on its own merit, has now become one of the fastest growing areas in drug development (Monkhouse & Haq 1988). This route of administration is perhaps one of the most successful controlled-release technologies available today (Guy 1996). Topical administration of drugs avoids many of the problems that arise with conventional oral administration and the more invasive methods of drug delivery. It has the advantage of not only by-passing hepatic first-pass metabolism, but also can maintain a constant, prolonged and therapeutically effective drug level in the body (Chien 1983; Loftsson et al 1987; Wiechers 1989; Corbo et al 1990). Transdermal delivery is being extensively investigated as a viable alternative to deliver drugs with improved bioavailability.

The present study is aimed at the design and development of a matrix-dispersion-type transdermal drug-delivery system for propranolol. Propranolol, a non-selective beta-adrenergic blocking agent has been widely used in the treatment of various cardiovascular disorders such as angina pectoris, cardiac arrhythmia and hypertension (Riddell et al 1987; Reynolds 1989; Corbo et al 1990). Oral administration of propranolol has the disadvantage of low bioavailability due to an extensive and highly variable hepatic first-pass metabolism (Gomeni et al 1977; Corbo et al 1990; Barnwell et al 1992; Ademola et al 1993). Furthermore, propranolol has a half-life of 3–6 h (Reynolds 1989) and requires frequent dosing. To avoid these disadvantages, a transdermal patch was developed where polymers play an important role. Rate-controlling polymers (hydroxy-propylmethylcellulose (HPMC) K4M, HPMC K15M and HPMC KI00M), together with plasticizer (glycerin), were

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used in the design and development of a matrix for long-term delivery of propranolol.

Materials and Methods

Materials

HPMC (K4M, K15M, K100M) were gifts from Colorcon Ltd, UK. Propranolol was provided by Sarabhai Chemicals, Baroda. All solvents and reagents used were of analytical reagent grade. The spectrofluorometer was a Hitachi Fluorescence spectrophotometer, Model 650–10S.

Fabrication of transdermal films

Transdermal films of propranolol were made using varying concentrations of HPMC K4M, K15M and K100M, keeping the drug concentration constant (10 mg per patch). The drug : polymer ratios used were 1 : 1, 1 : 1·5, 1 : 2, 1 : 2·5 and 1 : 3. The required amounts of drug and polymer were dispersed separately in alcohol as casting solvent. The two were then mixed and glycerine (150% w/w based on polymer content) was incorporated as plasticizer. This solution was then poured into a glass mould (4 cm × 4 cm) fabricated in the laboratory. To control the rate of evaporation of solvent, the mould was covered with a funnel of suitable size. The casting solvent was then allowed to evaporate overnight to obtain the dried film. The films were cut into small patches containing the equivalent of 10 mg of drug, and were stored between sheets of wax paper in a desiccator.

Physicochemical characterization of transdermal films

Drug content. The patch was dissolved in 2 mL of the casting solvent and the volume was adjusted to 100 mL with distilled water. The solution was suitably diluted and fluorescence was measured at excitation and emission wavelengths of 315 and 340 mn, respectively (Trivedi et al 1986). Ten films of each formulation were assayed individually.

Thickness. The thickness of the patch was determined using a travelling microscope at 5 separate points of each patch. Ten randomly selected patches of each formulation were tested for their thickness.

Weight variations. The patches were subjected to weight variation by individually weighing 10 randomly selected patches. Such determinations were carried out for each formulation.

In-vitro dissolution studies. To ensure the patch-to-patch in-vitro release reproducibility of the transdermal films, a newly developed Cygnus' sandwich-patch holder, a slightly modified Food and Drug Administration (FDA) sandwich-patch holder, was employed in dissolution testing (Shah et al 1986; Connic Chang et al 1993). The dissolution vessel (covered with black paper), containing 500 mL of de-aerated water, was maintained at $32 \pm 0{\cdot}5^{\circ}C$, the temperature of the skin surface (Shah et al 1986). The paddle speed was set at 50 rev min^{-1}. The patch assembly was carefully placed at the bottom of the vessel and was centered using a glass rod. Samples (5 mL) were withdrawn at 1-h intervals until the completion of drug release. The withdrawn sample was replenished with 5mL of fresh media. The propranolol content of the sample was estimated spectrofluorometrically at an excitation wavelength of 315 nm and an emission wavelength of 340 nm (Trivedi et al 1986). Three such determinations were carried out for each formulation. The content of propranolol was calculated from the standard curve ($r = 0{\cdot}999$, $P < 0{\cdot}001$) prepared in the dissolution medium. The in-vitro dissolution profiles, namely, cumulative drug release and dissolution rate constant, were calculated.

In-vivo studies

The formulations were tested for their bioavailability in nine healthy volunteers, following the balanced incomplete block design. Volunteers with a mean age of $21{\cdot}00 \pm 1{\cdot}41$ years and a weight of $60{\cdot}89 \pm 5{\cdot}35$ kg were selected. The hair of the chest area of volunteers was removed without damaging the stratum corneum. The patch was applied to the chest 24 h after hair removal. Blood and urine samples were collected before application of the film. Thereafter, blood samples were collected at 1, 3, 4, 5, 7, 9, 12 and 24 h and urine samples were collected at 1-h intervals up to 12 h and then at 24, 28, and 36 h. Each blood samples (3 mL) was centrifuged for 15 min at 500 rev min^{-1} and 20°C. The supernatant plasma sample (1 mL) and collected urine sample (5 mL) were stored in well-closed test-tubes under refrigeration for the analysis of propranolol. The plasma and urine samples were analysed spectrofluorometrically at an excitation wavelength of 315 nm and an emission wavelength of 340 mn (Trivedi et al 1986). For the purpose of calculating the propranolol content of the biological fluids, a standard curve ($r = 0{\cdot}999$, $P < 0{\cdot}001$)

was prepared for the concentration range of 10–100 ng mL^{-1}, in the same manner.

The following pharmacokinetic parameters were calculated: area under the curve (AUC), maximum plasma concentration (C_{max}), time to reach peak plasma concentration (t_{max}) absorption rate constant (k_a), absorption half-life ($t_{\frac{1}{2}a}$), elimination rate constant (k_e) and elimination half-life ($t_{\frac{1}{2}e}$). The pharmacokinetic data k_a, $t_{\frac{1}{2}a}$, k_e, $t_{\frac{1}{2}e}$ and $AUC_{0-\infty}$ were calculated by a graphical method (Ritschel 1984). AUC values (0–12, 0–24, and 0–36 h) were calculated using the trapezoidal rule. Urinary k_a and $t_{\frac{1}{2}a}$ values were calculated by the Wagner–Nelson method.

Statistical evaluation

The relevance of differences in the in-vitro dissolution rate profile and pharmacokinetic parameters was evaluated statistically. The data were tested by two-way analysis of variance and *t*-test.

Results and Discussion

Of the various formulations made using different concentrations and grades of HPMC, six formulations (A–F) were selected on the basis of drug content and the release pattern. The drug content, thickness and weight of the patches of the selected formulations are shown in Table 1. Irrespective of the grade and concentration of HPMC used, the drug content per patch was within 9·97–10·01 mg, but the thickness and weight of the patch increased with increase in polymer content (Table 1).

From the in-vitro dissolution profile data, kinetics of drug release were found for first-order, zero-order and Higuchi-type release kinetics. The coefficient of correlation of each of these kinetics was calculated and compared (Table 2). The release pattern of the selected formulations were best fitted for Higuchi kinetics, with a significant linear correlation ($r = 0{\cdot}991–0{\cdot}997$; $P < 0{\cdot}001$) being found for Higuchi-type release kinetics. This complies with Higuchi's equation for drug release from a matrix: a slow and controlled release was observed, indicating that the drug-release mechanism was by diffusion, as proposed by Higuchi. The dissolution rate constant was calculated for the six test products and compared (Table 2). When examined by two-way analysis of variance, the data showed a significant difference between the test products ($P < 0{\cdot}01$), but not within the test products ($P > 0{\cdot}1$), indicating that the six sets of data differ significantly. Hence, it may be suggested that test products differ in their formulations.

A skin-irritation test was performed on six healthy volunteers. The studies indicated that neither the polymer nor the drug caused any noticeable irritation or inflammation on or around the patch area during the period of study. Also, none of the volunteers complained of skin irritation or inflammation after the removal of patch.

For a comparative bioavailability study, plasma data and urinary data were considered. The pharmacokinetic parameters, C_{max}, t_{max}, k_e, $t_{\frac{1}{2}e}$, k_a, $t_{\frac{1}{2}a}$ and AUC data from plasma and urine are shown in Tables 3 and 4 . C_{max} values, ranging from 140·492–195·094 ng mL^{-1}, were achieved in 4 h (t_{max}). The variation in C_{max} may be attributed to the variation in the concentration and grades of HPMC used in the patches. On the basis of plasma C_{max} and AUC values, the test products could be ranked as follows: C > A > D > E > B > F (Table 3).

Table 1. Characteristics of transdermal patches of propranolol.

Patch formulation	Composition (drug : polymer)	Drug content* (mg)	Thickness* (mm)	Weight* (mg)	% Dissolved**
HPMC K4M					
A	1 : 2·5	9·97 (0·016)	3·505 (0·016)	37·25 (0·037)	99·92 (0·001)
B	1 : 3·0	10·01 (0·013)	4·106 (0·014)	42·96 (0·055)	99·93 (0·050)
HPMC K15M					
C	1 : 2·0	9·97 (0·017)	2·935 (0·010)	33·09 (0·018)	99·92 (0·001)
D	1 : 2·5	9·99 (0·015)	3·601 (0·014)	38·16 (0·029)	99·91 (0·00)
E	1 : 3·0	9·97 (0·011)	4·216 (0·013)	43·63 (0·034)	99·92 (0·001)
HPMC K100M					
F	1 : 2·0	9·97 (0·016)	3·146 (0·022)	34·47 (0·078)	99·99 (0·001)

Figures in parentheses indicate standard deviation. *Mean of 10 readings. **Mean of 3 runs.

Table 2. Dissolution characteristics from different transdermal films.

Patch formulation	Coefficient of correlation			Dissolution rate constant ($mg\,cm^{-2}\,h^{-\frac{1}{2}}$)
	First order	Zero order	Higuchi	
A	0·906	0·916	0·993 (0·007)	35·682 (0·008)
B	0·859	0·937	0·997 (0·004)	33·062 (0·021)
C	0·855	0·917	0·992 (0·006)	34·237 (0·013)
D	0·771	0·921	0·991 (0·007)	32·592 (0·022)
E	0·841	0·939	0·996 (0·004)	32·227 (0·049)
F	0·702	0·926	0·991 (0·009)	32·461 (0·047)
Level of significance			$P < 0·001$	
Two-way analysis of variance				$P < 0·01$

Values in parentheses indicate % CV.

The values of k_e, $t_{\frac{1}{2}e}$, k_a and $t_{\frac{1}{2}a}$ were $0·109 \pm 0·007\,h^{-1}$, $6·345 \pm 0·389\,h$, $1·157 \pm 0·013\,h^{-1}$ and $0·644 \pm 0·008\,h$, respectively (Table 3).

From urinary profile data (Table 4), the test products could be ranked on the basis of their C_{max} and AUC values as follows: C > A > D > E > B > F. The time (t_{max}) to reach maximum concentration in urine was found to be 5–6 h, which is well after the time taken to reach peak plasma concentration (4 h). The average values of k_e ($0·112 \pm 0·014\,h^{-1}$) and $t_{\frac{1}{2}e}$ ($6·299 \pm 0·795\,h$) coincide with those obtained from plasma data. By Wagner–Nelson treatment, average k_a and $t_{\frac{1}{2}a}$ (absorption parameter) values were found to be $1·155 \pm 0·013\,h^{-1}$ and $0·600 \pm 0·007\,h$, respectively. These values also coincide with those obtained from plasma data (Table 3).

Upon statistical evaluation (two-way analysis of variance), a significant difference ($P < 0·01$) was observed between the test products but not within the test products ($P > 0·1$), when C_{max}, AUC, k_e, $t_{\frac{1}{2}e}$, k_a and $t_{\frac{1}{2}a}$ data generated from plasma and urine (Tables 3 and 4) were taken into consideration, except for k_a and $t_{\frac{1}{2}a}$ (plasma), where no statistically significant difference ($P > 0·1$) was observed. Spearman rank correlation, a non parametric statistical test (McClave & Benson 1990), demonstrated a high degree of positive correlation ($P < 0·02$; two tail), showing a complete agreement in the order of ranks between percentage of drug

Table 3. Pharmacokinetic characteristics from plasma profile of propranolol from different transdermal patches.

Patch formulation	C_{max} ($ng\,mL^{-1}$)	t_{max} (h)	k_e[1] (h^{-1})	$t_{\frac{1}{2}e}$[2] (h)	k_a[3] (h^{-1})	$t_{\frac{1}{2}a}$[4] (h)	AUC_{0-12} ($ng\,h\,mL^{-1}$)	AUC_{0-24} ($ng\,h\,mL^{-1}$)	$AUC_{0-\infty}$ ($ng\,h\,mL^{-1}$)
A	190·735 (0·486)	4	0·1024 (1·514)	6·7889 (1·724)	1·1543 (0·967)	0·6038 (1·125)	1309·687 (0·286)	1939·800 (0·420)	2454·689 (1·089)
B	151·198 (0·087)	4	0·1103 (2·048)	6·2778 (2·194)	1·1495 (0·833)	0·6048 (1·364)	1023·104 (0·623)	1474·727 (0·818)	1917·133 (1·709)
C	195·094 (0·378)	4	0·1014 (1·489)	6·8222 (1·716)	1·1569 (3·262)	0·6083 (3·539)	1358·133 (0·161)	2004·764 (0·375)	2481·182 (0·877)
D	178·652 (0·340)	4	0·1104 (1·205)	6·2833 (1·506)	1·1403 (0·740)	0·6167 (0·885)	1169·206 (0·169)	1724·069 (0·509)	2154·835 (0·550)
E	173·528 (0·076)	4	0·1140 (0·912)	6·0250 (2·075)	1·1698 (1·451)	0·5952 (0·916)	1131·237 (0·127)	1626·450 (0·456)	2086·586 (0·772)
F	140·492 (0·339)	4	0·1179 (2·918)	5·8750 (2·909)	1·1735 (1·970)	0·5952 (0·916)	944·045 (9·199)	1341·526 (0·811)	1689·718 (0·774)
Two-way analysis of variance	$P < 0·01$		$P < 0·01$	$P < 0·01$	$P > 0·1$	$P > 0·1$	$P < 0·01$	$P < 0·01$	$P < 0·01$

Values in parentheses indicate % CV. [1]$0·109 \pm 0·007$ (5·94%); [2]$6·345 \pm 0·389$ (6·12%); [3]$1·157 \pm 0·013$ (1·08%); [4]$0·604 \pm 0·008$ (1·35%).

Table 4. Pharmacokinetic characteristics from urine profile of propranolol from different transdermal patches.

Patch formulation	C_{max} (ng mL^{-1})	t_{max} (h)	k_e[1] (h^{-1})	$t_{\frac{1}{2}e}$[2] (h)	k_a[3] (h^{-1})	$t_{\frac{1}{2}a}$[4] (h)	AUC_{0-36} (ng h mL^{-1})	$AUC_{0-\infty}$ (ng h mL^{-1})
A	366·176	5	0·1026	6·7615	1·1445	0·6055	4225·034	5104·675
	(0·242)		(2·163)	(2·238)	(0·265)	(0·264)	(0·329)	(1·543)
B	289·718	6	0·1244	5·5818	1·1477	0·6038	2997·993	3898·840
	(0·215)		(1·109)	(1·124)	(0·172)	(0·171)	(0·059)	(1·386)
C	388·277	5	0·0931	7·4500	1·1570	0·5990	4701·814	5953·291
	(0·159)		(1·861)	(2·325)	(0·035)	(0·035)	(0·057)	(1·821)
D	321·771	5	0·1031	6·7429	1·1395	0·6082	3702·833	4429·394
	(0·083)		(0·494)	(0·485)	(0·119)	(0·118)	(0·080)	(0·453)
E	304·978	6	0·1220	5·6800	1·1662	0·5943	3198·431	4166·282
	(0·104)		(0·430)	(0·403)	(0·143)	(0·146)	(0·052)	(1·374)
F	269·932	6	0·1244	5·5750	1·1721	0·5912	2823·194	3719·968
	(0·199)		(0·422)	(0·311)	(0·104)	(0·104)	(0·225)	(1·289)
Two-way analysis of variance	$P < 0·01$		$P < 0·01$	$P < 0·01$	$P < 0·01$	$P < 0·01$	$P < 0·01$	$P < 0·01$

Values in parentheses indicate % CV. [1]0·112 ± 0·014 (12·18%); [2]6·299 ± 0·795 (12·61%); [3]1·155 ± 0·013 (1·11%); [4]0·600 ± 0·007 (1·11%).

Table 5. *t*-Test values.

	C_{max}	AUC	k_e	$t_{\frac{1}{2}e}$	k_a	$t_{\frac{1}{2}a}$
Blood vs urine	7·372	6·595	0·355	0·599	0·395	0·844
Degree of freedom	10	10	10	10	10	10
t_{tab} (two tail)	4·587	4·587	1·812	1·812	1·812	1·812
(one tail)	3·169*	3·169*				
Level of significance	$P < 0·001$	$P < 0·001$	$P > 0·1$	$P > 0·1$	$P > 0·1$	$P > 0·1$

*Average value of C_{max}/AUC for blood was significantly greater than for urine.

absorbed from the patch and AUC_{0-24} and $AUC_{0-\infty}$. The increase in the amount of drug absorbed was thus associated with the increase in peak blood level (rate of absorption) and area under the plasma curve (extent of absorption). This was further quantitatively confirmed by regression analysis showing a good correlation between percentage of drug absorbed and C_{max} and AUCs.

A highly significant difference was observed when C_{max} and $AUC_{0-\infty}$ data generated from plasma and urine were compared. The average C_{max} and $AUC_{0-\infty}$ calculated from plasma data were statistically significantly greater ($P < 0·0005$) than average C_{max} and $AUC_{0-\infty}$ values calculated from urine data (Table 5). There was no significant difference ($P > 0·1$) between k_e, $t_{\frac{1}{2}e}$, k_a and $t_{\frac{1}{2}a}$ data generated from plasma and and those from urine (Table 5). This study indicates that urinary excretion data may be used as a simpler alternative to blood level data in studying the kinetics of absorption and deriving the absorption parameters.

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