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COMMUNICATION

Transdermal Delivery of Propranolol Using Mixed Grades of Eudragit: Design and In Vitro and In Vivo Evaluation

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ABSTRACT

A matrix-dispersion-type transdermal drug delivery system of propranol was developed using different ratios of mixed polymeric grades of Eudragit. Formulations were evaluated for in vitro dissolution characteristics using a Cygnus' sandwich patch holder. Selected formulations followed zero-order release kinetics. In vivo evaluation was carried out on healthy human volunteers following a balanced incomplete block design (BIBD). In vitro dissolution rate constant k and pharmacokinetic parameters generated from plasma and urine were evaluated statistically. Statistically excellent correlation was found between percentages of drug absorbed from patch versus C_{max}, AUC_{0-24}, and $AUC_{0-\infty}$. A highly significant difference was observed when C_{max} and $AUC_{0-\infty}$ generated from plasma and urine data were compared, but when k_e, $t_{1/2e}$, k_a, and $t_{1/2a}$ were compared, the difference was not significant. Urinary excretion data are suggested as a simpler alternative to blood-level data in studying the kinetics of absorption and deriving the absorption parameter.

INTRODUCTION

Topical administration of therapeutic agents offers many advantages over conventional oral and the more invasive methods of drug delivery. Transdermal delivery not only provides controlled, constant administration of the drug, allowing continuous input of drugs with short biological half-lives, but also can eliminate pulsed entry into the systemic circulation, which often causes undesirable side effects (1). It has the advantage of bypassing hepatic first-pass metabolism, thus achieving higher systemic bioavailability of drugs (2–4).

The present work aimed to develop a matrix-dispersion-type transdermal drug delivery system of pro-

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pranolol, a nonselective beta-adrenergic blocking agent widely used in the treatment of various cardiovascular disorders (4–6). Oral administration of propranolol has the disadvantage of low bioavailability due to an extensive and highly variable hepatic first-pass metabolism (4,7,8). In addition, propranolol has a half-life of 2 to 6 hr (9,10) and requires frequent dosing. Owing to these disadvantages, a transdermal patch of propranolol was designed and developed using mixed grades and ratios of rate-controlling polymers, Eudragit RL100 and RS100, Eudragit RLPO and RSPO, and Eudragit RLPM and RSPM with a plasticizer, dibutyl pthalate.

EXPERIMENTAL

Materials

Eudragits (RL100, RS100, RLPO, RSPO, RLPM, RSPM) were gifts from Rohm Pharma, GmBh Weiterstadt, West Germany. Propranolol was provided by Sarabhai Chemicals, Baroda, India. All solvents and reagents used were of AnalaR grade. The spectroflurometer was a Hitachi fluorescence spectrophotometer model 650-10S, Japan.

Methods

Fabrication of Transdermal Films

The transdermal films of propranolol were made using mixed grades of Eudragits RL100 and RS100, RLPM and RSPM, RLPO and RSPO, each in the ratios of 100:00, 80:20, 60:40, 50:50, 40:60, 20:80, 00:100. Polymer solution (10% w/v) was made by dissolving the respective amounts of polymer in acetone as a casting solvent, except Eudragit RL100 and RS100, for which a mixture of methanol and methylene chloride (in the ratio 80:20) was used. All films were cast from a 10% w/v solution of film former and the plasticizer dibutyl pthalate (10% w/w based on polymer weight). The films were cast on mercury substrate (11). The films were cut into small patches containing the equivalent of 10 mg of the 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 the excitation and emission wavelengths of 315 and 340 nm, respectively (12). For each formulation, 10 films were assayed individually.

Thickness

The thickness of the patch was determined using a traveling microscope at 5 separate points of each patch. For each formulation, 10 randomly selected patches 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 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 (13,14). The dissolution vessel (covered with black paper) contained 500 ml of deaerated water maintained at 32°C ± 0.5°C, the temperature of the skin surface (13). The paddle speed was set at 50 rpm. The patch assembly was carefully placed at the bottom of the vessel and was centered using a glass rod. Sample (5 ml) was withdrawn at 1-hr intervals until the completion of drug release. The withdrawn sample was replenished with fresh media (5 ml). The propranolol content of the sample was estimated spectrofluorometrically (12). Three such determinations were carried out for each formulation. The content of propranolol was computed from the standard curve ($r = 0.999$; $p < .001$) prepared in the dissolution medium. The in vitro dissolution profiles, namely, cumulative drug release and dissolution rate constant, were calculated.

In Vivo Studies

The test formulations were tested for their bioavailability on nine healthy human volunteers (23.67 ± 2.16 years, 58.22 ± 6.15 kg) following a balanced incomplete block design (BIBD). The formulation was applied to the chest 24 hr after hair removal. Blood and urine samples were collected prior to application of film. Thereafter, blood samples were collected at 1, 3, 4, 5, 7, 9, 12, and 24 hr, and urine samples were collected at 1-hr intervals up to 12 hr and then at 24, 28, and 36 hr. Each blood sample (2 ml) was centrifuged for 15 min at 500 rpm 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 analyzed spectrofluorometrically (12). For the purpose of computing the propranolol content of the biological fluids, a standard curve ($r = 0.999$, $p < .001$) in the concentration range 10–100 ng/ml was prepared in the same manner.

The pharmacokinetic parameters 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 $t_{1/2a}$, elimination rate constant k_e, and elimination half-life $t_{1/2e}$ were calculated. The pharmacokinetic data K_a, $t_{1/2a}$, k_e, $t_{1/2e}$, and $AUC_{0-\infty}$ were calculated by a graphical method (15). AUC values (0–12, 0–24, and 0–36) were computed using the trapezoidal rule. Urinary k_a and $t_{1/2a}$ were calculated by the Wagner-Nelson method.

Statistical Evaluation

The relevance of difference in the in vitro dissolution rate profile and pharmacokinetic parameters was evaluated statistically by two-way analysis of variance (ANOVA) and *t* test.

RESULTS AND DISCUSSION

The mixtures of Eudragit RL and Eudragit RS have been reported to provide very hard films, but in the presence of plasticizer, these mixed polymers form films with good elasticity. From the various formulations made, six formulations (A–F) were selected on the basis of drug release pattern. The drug content, thickness, and weight per patch were similar for all grades and ratios of the polymers, but percentage drug dissolved was slightly greater for formulations containing a higher proportion of the RL (permeable) type (Table 1). In vitro release followed zero order as its coefficient of correlation ($r = 0.958–0.994$; $p < 0.001$) predominates over first-order and Higuchi-type release kinetics. The calculated dissolution rate constant showed a significant difference between the test products ($p < .01$), but within the test products, a significant difference was not observed, indicating that the six sets of data differ significantly (Table 1).

Table 1

Characteristics of Transdermal Patch of Propranolol

Test Product	Composition	Drug Content[a] (mg)	Thickness[a] (mm)	Weight[a] (mg)	Percentage Dissolved[b]	Dissolution Rate Constant ($mg.cm^{-2}hr^{-1}$)
A	RLPM:RSPM					
	100:80	9.97	0.605	74.91	99.98	12.267
		(0.026)	(0.001)	(0.034)	(0.00)	(0.059%)
B	80:20	9.95	0.598	74.88	99.58	12.188
		(0.016)	(0.001)	(0.027)	(0.049)	(0.055%)
C	RLPO:RSPO					
	80:20	9.98	0.598	70.38	99.98	12.513
		(0.019)	(0.002)	(0.101)	(0.001)	(0.087%)
D	60:40	9.96	0.599	70.28	99.93	13.207
		(0.017)	(0.001)	(0.048)	(0.049)	(0.045%)
E	RL100:RS100					
	100:00	9.98	0.600	70.12	99.89	11.279
		(0.015)	(0.001)	(0.058)	(0.00)	(0.077%)
F	80:20	9.94	0.596	70.08	99.92	12.403
		(0.016)	(0.002)	(0.047)	(0.050)	(0.090%)
Two-way ANOVA						$p < 0.01$, h.s.

Values in parentheses indicate standard deviation and %CV (coefficient of variation).
h.s. = highly significant.
[a] Mean of 10 readings.
[b] Mean of 3 runs.

Table 2

Pharmacokinetic Characteristics from Plasma Profile of Propranolol from Different Transdermal Films

Test Product	C_{max} (ng/ml)	t_{max} (hr)	k_e[a] (hr^{-1})	$t_{1/2e}$[b] (hr)	k_a[c] (hr^{-1})	$t_{1/2a}$[d] (hr)	AUC_{0-12} (ng hr/ml)	AUC_{0-24} (ng hr/ml)	$AUC_{0-\infty}$ (ng hr/ml)
A	206.336 (1.390)	4	0.1075 (7.248)	6.4722 (8.038)	1.1955 (3.636)	0.5878 (2.369)	1416.027 (1.678)	2085.599 (2.986)	2819.385 (4.029)
B	130.245 (2.143)	4	0.1112 (3.596)	6.2389 (3.187)	1.1607 (6.567)	0.6095 (5.317)	763.515 (2.082)	1172.467 (2.187)	1629.513 (3.197)
C	202.053 (1.859)	4	0.1152 (4.029)	6.0185 (4.055)	1.1994 (4.034)	0.5857 (3.227)	1281.048 (1.049)	1837.288 (1.583)	2484.459 (2.365)
D	148.522 (1.999)	4	0.1046 (1.319)	6.6222 (1.538)	1.1347 (1.845)	0.6131 (2.205)	939.971 (0.144)	1406.560 (0.438)	1957.125 (0.126)
E	181.711 (0.386)	4	0.1205 (0.647)	5.7407 (0.591)	1.1606 (1.265)	0.6000 (1.190)	1140.873 (1.101)	1517.247 (0.585)	2226.652 (0.686)
F	123.668 (0.749)	4	0.1248 (3.013)	5.5733 (3.683)	1.1366 (1.013)	0.6143 (1.745)	698.169 (1.659)	1052.059 (2.257)	1442.397 (1.998)
Two-way ANOVA	$p < .01$ h.s.	—	$p < .01$, h.s.	$p < .01$, h.s.	$p > .1$, n.s.	$p > .1$, n.s.	$p < .01$, h.s.	$p < .01$, h.s.	$p < .01$, h.s.

Values in parentheses indicate %CV; h.s., highly significant; n.s., not significant.

[a] 0.114 ± 0.008 (6.75%).

[b] 6.111 ± 0.411 (6.71%).

[c] 1.165 ± 0.028 (2.38%).

[d] 0.602 ± 0.13 (2.11%).

Hence, it may be suggested that the test products differ in their formulations.

A skin irritation test performed on the six healthy human volunteers showed that neither the polymer nor the drug caused any noticeable irritation or inflammation on or around the patch area. Also, none of the volunteers complained of skin irritation or inflammation after the removal of patches.

The pharmacokinetic parameters C_{max}, t_{max}, k_e, $t_{1/2e}$, k_a, $t_{1/2a}$, and AUC data generated from plasma and urine were taken into consideration for comparative bioavailability. C_{max} values ranging from 123.668 to 206.335 ng/ml were achieved in 4 hr (t_{max}). The variation in the C_{max} may be attributed to the variation in nature and concentration of polymers used in patches. On the basis of C_{max} and AUC values, the test products could be ranked A>C>E>D>B>F (Table 2).

From the urinary profile data (Table 3), the test products (A–F) could be ranked on the basis of C_{max}, AUC_{0-36}, and $AUC_{0-\infty}$ as follows: A>C>E>D>B>F (but F>B in the case of AUC_{0-36}). The time taken to reach maximum concentration t_{max} in urine was found to be 5–6 hr, which is well after the time taken to reach peak plasma concentrations (4 hr). The average values of k_e, $t_{1/2e}$, k_a, and $t_{1/2a}$ were found to be similar to the values obtained using plasma data (Tables 2 and 3). k_a and $t_{1/2a}$ (absorption parameter) were calculated by applying the Wagner-Nelson treatment to the amount excreted during absorption.

On statistical evaluation (two-way ANOVA), pharmacokinetic parameters generated from plasma and urine samples showed significant differences ($p < .01$) among the test products, but did not ($p > .1$) within the test products (Table 2 and 3), except k_a and $t_{1/2a}$ (plasma data), for which a statistically nonsignificant difference ($p > .1$) was observed. Spearman's rank correlation, a nonparameteric statistical test (16) when employed for rank correlation, showed a high degree of positive correlation ($p < .02$, two tail), showing complete agreement in the order of ranks between percentage drug absorbed from patch and C_{max} and AUC values (0–24 and 0–∞). 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 an excellent correlation ($p < .001$) between the percentage drug absorbed and C_{max}, AUC_{0-24}, and $AUC_{0-\infty}$.

The average C_{max} and $AUC_{0-\infty}$ calculated from plasma data were statistically significantly greater ($p < .0005$) than average C_{max} and $AUC_{0-\infty}$ values from urine data (Table 4). There was no significant difference observed when

Table 3

Pharmacokinetic Characteristic from Urine Profile of Propranolol from Different Transdermal Films

Test Product	C_{max} (mcg)	T_{max} (hr)	k_e[a] (hr^{-1})	$t_{1/2e}$[b] (hr)	K_a[c] (hr^{-1})	$t_{1/2a}$[d] (hr)	AUC_{0-36} (mcg hr)	$AUC_{0-\infty}$ (mcg hr)
A	414.086 (0.023)	6	0.1032 (0.185)	6.7286 (0.000)	1.1805 (0.038)	0.5870 (0.037)	5024.740 (1.109)	6109.652 (0.323)
B	323.945 (0.017)	6	0.1452 (1.429)	4.7777 (1.497)	1.1653 (0.050)	0.5947 (0.050)	2502.188 (0.073)	4000.425 (0.8250)
C	386.679 (0.138)	5	0.0959 (1.775)	7.2369 (1.778)	1.2109 (0.123)	0.5723 (0.123)	4428.036 (0.046)	5531.813 (0.598)
D	331.630 (0.032)	5	0.0896 (1.714)	7.7300 (1.469)	1.1367 (0.093)	0.6097 (0.094)	3532.800 (0.142)	4991.317 (0.236)
E	359.006 (0.029)	5	0.1006 (0.385)	6.9000 (0.579)	1.1552 (0.171)	0.5999 (0.171)	4176.364 (0.054)	5023.728 (0.831)
F	281.664 (0.014)	5	0.1333 (0.236)	5.2077 (0.461)	1.1461 (0.114)	0.6046 (0.114)	2638.807 (0.087)	3450.247 (1.889)
Two-way ANOVA	$p < .01$, h.s.	—	$p < .01$, h.s.	$p < .01$, h.s.	$p < .01$, h.s.	$p < .01$, h.s.	$p < .01$, h.s.	$p < .01$, h.s.

Values in parentheses indicate %CV; h.s., highly significant; n.s., not significant.

[a] 0.111 ± 0.023 (20.21%).

[b] 6.4301 ± 1.173 (18.23%).

[c] 1.166 ± 0.027 (2.30%).

[d] 0.595 ± 0.014 (2.27%).

Table 4

t *Test Values*

	C_{max}	AUC	k_e	$t_{1/2e}$	k_a	$T_{1/2a}$
Blood versus urine	7.564	6.097	0.275	0.629	0.076	0.931
Degrees 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[a]	3.169[a]				
Level of significance	$p < .001$, h.s.	$p < .001$, h.s.	$p < .1$, n.s.	$p < .1$, n.s.	$p < .1$, n.s.	$p < .1$, n.s.

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

k_e, $t_{1/2e}$, k_a, and $t_{1/2a}$ data were compared (Table 4). 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 parameter.

CONCLUSIONS

The results of this study indicate the polymeric-matrix-type transdermal films of propranolol prepared with different grades and ratios of Eudragit hold potential for transdermal delivery. A slow and controlled release of drug is indicated by the fact that the percentage cumulative amount of drug release versus time is linear, thus supporting the test products for transdermal films. C_{max} and AUC data were found to be greater than the corresponding values from the urinary profile, whereas no significant difference was observed when k_e, $t_{1/2e}$, k_a, and $t_{1/2a}$ data generated from plasma and urine profiles were compared. Urinary excretion data therefore may be used as a simpler alternative to blood-level data in bioavailability studies.

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