Drug Development and Industrial Pharmacy, 23(7), 633-638 (1997)

RESEARCH PAPER

Drug Development and Industrial Pharmacy Downloaded from informahealthcare.com by Biblioteca Alberto Malliani on 01/30/12
For personal use only.

Transdermal Flurbiprofen Delivery Using HPMC Matrices: Design, In Vitro and In Vivo Evaluation

P. R. P. Verma* and T. E. G. K. Murthy

Department of Pharmaceutical Sciences, Birla Institute of Technology, Mesra, Ranchi 835215, India

ABSTRACT

A matrix-dispersion-type transdermal drug delivery system of flurbiprofen was designed and developed using different concentrations and grades of hydroxypropyl methylcellulose (HPMC). Formulations were selected on the basis of their drug release content and release pattern. These were evaluated for in vitro dissolution characteristics using a Cygnus sandwich-patch holder. The release followed Higuchi kinetics, as its coefficient of correlation ($r = 0.977$–0.990; $p < 0.001$) predominates over the other release kinetics. In vivo evaluation was carried out on healthy rabbits, following the balanced incomplete block design. The in vitro dissolution rate constant and pharmacokinetic parameters were evaluated statistically by two-way analysis of variance (ANOVA). A significant difference was found between the test products ($p < 0.01$), but not within the test products ($p > 0.05$).

INTRODUCTION

The transdermal therapeutic system (TTS) is a discrete dosage form which, when applied to intact skin, delivers the drugs through the skin at a controlled rate to the systemic circulation (1). There has been an increasing interest in TTS during the present decade among pharmaceutical industries, helping to accelerate transdermal drug delivery research activities in the field of pharmaceutics (2,3). In the literature, a number of drugs have been reported for their topical administration, viz., scopolamine (for the prevention and treatment of motion sickness), nitroglycerin (for the treatment of angina and congestive heart failure), clonidine (for the

*To whom correspondence should be addressed.

Copyright © 1997 by Marcel Dekker, Inc.

RIGHTSLINK

treatment of hypertension), nicotine (to reduce cigarette craving and nicotine preference), and estradiol (to control the development and maintenance of sex organs).

The present study aims at the design and development of a matrix-dispersion-type transdermal drug delivery system of flurbiprofen. Flurbiprofen, a potent nonsteroidal anti-inflammatory agent, is a nonselective inhibitor of prostaglandin biosynthesis in human. Upon oral administration, the most frequently reported side effects are abdominal discomfort, dyspepsia, and constipation, along with other gastrointestinal effects (4). Also, it has a short elimination half-life of 3.9 hr (4) and requires frequent dosing. Owing to these disadvantages, a long-term delivery of flurbiprofen at a controlled rate is needed. For this purpose, a matrix-dispersion-type transdermal delivery system of flurbiprofen is developed, using rate-controlling polymers, namely, HPMC K4M, HPMC K15M, and HPMC K100M, together with a plasticizer, glycerine.

EXPERIMENTAL

Materials

HPMC K4M, HPMC K15M, and HPMC K100M were gifts from Colorcon Ltd., U.K. Flurbiprofen B.P. was provided by Boots Pharma Ltd., Bombay, and F.D.C. Ltd., Bombay. All solvents and reagents used were of AnalaR grade. The spectrophotometer was a Beckmann UV-VIS Model 34.

Methods

Fabrication of Transdermal Films

The transdermal films of flurbiprofen 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. These 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 mold (4 cm × 4 cm) fabricated in the laboratory. The casting solvent was then allowed to evaporate overnight to get the dried film. The film was cut into small patches containing amounts equivalent to 10 mg of drug.

Physicochemical Characterization of Transdermal Films

Drug Content

The patch was dissolved in 2 ml of the casting solvent, and volume was adjusted to 100 ml with freshly prepared 0.1 N NaOH. The solution was suitably diluted, and content per film was estimated spectrophotometrically at 247 nm (5). Ten films of each formulation were assayed individually.

Thickness

Thickness of patch was determined using a thickness gauge at 5 separate points of the 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 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 (6,7). The dissolution vessel contained 500 ml of deaerated water maintained at 32° ± 0.5°C, the temperature of the skin surface (6). 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. Five milliliters of sample was withdrawn at 1-hr intervals until the completion of drug release. The withdrawn sample was replenished with fresh media (5 ml). The flurbiprofen content of the sample was estimated spectrophotometrically at 247 nm (5). Three such determinations were carried out for each formulation. 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 16 healthy rabbits weighing 1.31 ± 0.225 kg, following the balanced incomplete block de-

Drug Development and Industrial Pharmacy Downloaded from informahealthcare.com by Biblioteca Alberto Malliani on 01/30/12
For personal use only.

RIGHTSLINK

sign (BIBD). The number of rabbits was fixed so as to keep the variance found for BIBD the same as that in the case of Latin square design. The hair of the back area of animal was removed without damaging the stratum corneum. The formulation was applied on dorsal region 24 hr after the hair removal. Blood samples were collected prior to application of films and then at 1, 2, 4, 6, 8, and 24 hr postapplication of films. With the help of a standard plot ($r = 0.9997$; $p < 0.001$), the amount of drug in each blood sample was estimated spectophotometrically at 247 nm (8,9).

The pharmacokinetic parameters—namely, area under the curve (AUC), maximum plasma concentration (C_{max}), and the time taken to reach the peak plasma concentration (t_{max})—were calculated. AUC was computed using the trapezoidal rule.

Statistical Evaluation

The objective of this study was to evaluate the relevance of difference in the in vitro dissolution rate profiles and the pharmacokinetic parameters. The data were tested by two-way analysis of variance (ANOVA).

RESULTS AND DISCUSSION

Out of the various formulations made using different concentrations and grades of HPMC, 8 formulations (A–H) were selected, on the basis of drug release content and release pattern. The drug content, thickness, and weight of the patches of selected formulations are tabulated in Table 1. Irrespective of the grade and concentration of HPMC used, the drug content per patch is found within 9.876–9.996 mg, but the thickness and weight of patch is found to increase with the increase in polymer content (Table 1).

From the in vitro dissolution profile data, kinetics of drug release were found for zero-order, first-order, and Higuchi-type release kinetics. The coefficient of correlation of each of these release kinetics was calculated and compared (Table 2). The data reveal that the release

Table 1

Characteristics of Transdermal Patches of Flurbiprofen

Test Products	Composition Drug:Polymer	Drug Content[a] (mg)	Thickness[a] (cm)	Weight[a] (mg)	Percent Drug Dissolved[b]
HPMC K4M					
A	1:2.5	9.987	0.827	38.889	99.38
		(0.825)	(0.012)	(0.791)	(0.513)
B	1:3	9.996	0.829	44.978	92.019
		(0.826)	(0.011)	(0.607)	(0.574)
HPMC K15M					
C	1:1	9.867	0.812	23.578	99.966
		(0.131)	(0.013)	(0.248)	(0.198)
D	1:1.5	9.926	0.829	28.576	99.823
		(0.032)	(0.017)	(0.18)	(0.582)
E	1:2	9.918	0.841	34.523	99.557
		(0.028)	(0.024)	(0.214)	(0.473)
F	1:2.5	9.931	0.867	38.579	98.783
		(0.030)	(0.015)	(0.203)	(0.579)
HPMC K100M					
G	1:1	9.912	0.842	25.57	99.898
		(0.029)	(0.009)	(0.130)	(0.129)
H	1:1.5	9.904	0.846	30.715	99.287
		(0.019)	(0.008)	(0.112)	(0.198)

Values in parentheses indicate standard deviation.
[a]Mean of 10 readings.
[b]Mean of 3 runs.

Drug Development and Industrial Pharmacy Downloaded from informahealthcare.com by Biblioteca Alberto Malliani on 01/30/12
For personal use only.

RIGHTSLINK

Table 2

Dissolution Characteristics of Flurbiprofen from Different Transdermal Films

Test Products	Coefficient of Correlation: Zero-Order	First-Order	Higuchi-Type	Dissolution Rate Constant $\mu g \cdot cm^{-2}\ hr^{-0.5}$
A	0.914	0.975	0.986	33.365 (0.377%)
B	0.959	0.958	0.982	32.959 (0.488%)
C	0.892	0.960	0.984	35.981 (0.910%)
D	0.928	0.954	0.990	36.167 (0.486%)
E	0.955	0.955	0.984	35.341 (0.100%)
F	0.968	0.963	0.978	35.784 (0.474%)
G	0.948	0.972	0.977	39.386 (0.064%)
H	0.947	0.961	0.985	33.106 (0.074%)
Level of significance			$p < 0.001$ HS	
Two-way ANOVA				$p < 0.01$ HS

Values in parentheses indicate % CV. HS: highly significant.

Table 3

Pharmacokinetic Characteristics of Flurbiprofen from Different Transdermal Films

Test Product	C_{max}, μg/ml	AUC_{0-24}, μg hr/ml	t_{max}, hr
A	5.509 ± 0.230 (4.175)	113.243 ± 4.437 (3.918)	6.00
B	5.961 ± 0.20 (3.355)	121.951 ± 4.545 (3.727)	6.00
C	4.483 ± 0.285 (6.357)	92.408 ± 5.302 (5.738)	6.00
D	4.885 ± 0.195 (3.992)	101.364 ± 4.698 (4.635)	6.00
E	4.945 ± 0.356 (7.20)	103.856 ± 6.919 (6.662)	6.00
F	5.552 ± 0.265 (4.773)	115.372 ± 4.563 (3.955)	6.00
G	5.577 ± 0.253 (4.536)	113.432 ± 4.807 (4.238)	8.00
H	5.711 ± 0.325 (5.691)	116.061 ± 6.005 (5.174)	8.00
Two-way ANOVA	$p < 0.01$ HS	$p < 0.01$ HS	

Values in parentheses indicate % CV. HS: highly significant.

Drug Development and Industrial Pharmacy Downloaded from informahealthcare.com by Biblioteca Alberto Malliani on 01/30/12
For personal use only.

RIGHTSLINK

Drug Development and Industrial Pharmacy Downloaded from informahealthcare.com by Biblioteca Alberto Malliani on 01/30/12
For personal use only.

Table 4

Two-Way Analysis of Variance of Pharmacokinetic Parameters

Source of Variation	Sum of Squares		*df*	Mean Sum of Square		*F* Calculated		Probability	
	C_{max}	AUC_{0-24}		C_{max}	AUC_{0-24}	C_{max}	AUC_{0-24}	C_{max}	AUC_{0-24}
Between samples	6.99	2607.344	7	0.998	372.478	17.207	16.914	$p < 0.01$	$p < 0.01$
Within samples	0.516	201.781	3	0.172	67.260	2.965	3.054	$p > 0.05$	$p > 0.05$
Residual	1.222	462.469	21	0.058	22.022				
Total	8.728	3271.594							

RIGHTSLINK

pattern of selected formulations is best fitted for Higuchi kinetics, as the formulations' coefficient of correlation values predominate over zero-order and first-order release kinetics. A significant linear correlation (0.977–0.990; $p < 0.001$) is found for Higuchi-type release kinetics. This conforms with Higuchi's equation for the drug release from matrix. Thus, a slow and controlled release was observed indicating that the drug release mechanism is by diffusion, as proposed by Higuchi.

On dissolution rate constant data, two-way ANOVA was employed to find out if the 8 sets of in vitro dissolution profile data of the test products are the same or different from each other. A significant difference was observed between the test products ($p < 0.01$), while the same was not observed within the test products ($p > 0.1$) (Table 2), indicating that the 8 sets of data differ significantly. Hence, it may be inferred that the test products are not the same but different in their formulations.

The pharmacokinetic parameters, AUC_{0-24}, C_{max}, and t_{max} are shown in Table 3. Statistical analysis (two-way ANOVA) of the C_{max} and AUC_{0-24} showed a significant difference between the test products ($p < 0.01$) but did not ($p > 0.05$) within the test products (Table 4), thus differentiating the test products in their formulations. The t_{max} values of the test products A–F are found the same except for the test product made with HPMC K100M (Table 3). On the basis of C_{max} and AUC_{0-24}, the 8 test products could be ranked as B > H > F > G > A > E > D > C, except for when F = G in the case of C_{max}. Also, on the basis of the AUC profile, the test products A, B, F, G, and H showed very good profiles as compared to the rest.

CONCLUSION

The results of this study indicate that among the polymeric-matrix-type transdermal films of flurbiprofen, prepared with the different grades and ratios of HPMC and evaluated, the test products A, B, F, G, and H are better in their in vitro dissolution and pharmacokinetic characteristics, and thus hold potential for transdermal delivery. A slow and controlled release of drug is indicated by the fact that the percent cumulative amount of drug release versus square root of time is found to be linear, thus supporting that the test products are suitable for transdermal films. Further, the selected formulations, which have been duly screened, may be evaluated for their pharmacokinetic and pharmacodynamic profiles in humans to the best of their advantage.

ACKNOWLEDGMENTS

The authors wish to thank Dr. B. K. Razdan, dean, Postgraduate Studies and Research, Birla Institute of Technology; and Dr. A. K. Sharma, professor and head, Department of Pharmaceutical Sciences, BIT, for providing required facilities and encouragement throughout this work. One of the authors (T. E. G. K. Murthy) gratefully acknowledges financial support in the form of a Junior Research Fellowship provided to him during the period of this study by the University Grants Commission, New Delhi.

REFERENCES

1. D. C. Monkhouse and A. S. Huq, Drug Dev. Ind. Pharm., 14, 183 (1988).
2. T. Kurihara-Bergstrom, W. R. Good, S. Feisullin, and C. Signor, J. Controlled Release, 15, 271 (1991).
3. R. H. Guy and J. Hadgraft, Int. J. Pharm., 32, 159 (1986).
4. R. N. Brogdon, R. C. Heel, T. M. Splight, and G. S. Avery, Drugs, 18, 417 (1979).
5. British Pharmacopoeia, Vol. 1, HMSO, London, 1993, p. 922.
6. V. P. Shah, N. W. Tymes, L. A. Yamamoto, and J. P. Skelly, Int. J. Pharm., 32, 243 (1986).
7. M. M. Connic Chang, P. H. Lee, C. T. Bromah, and G. W. Cleary, J. Controlled Release, 27, 59 (1993).
8. G. Seetharaju and N. Udupa, Indian Drugs, 26, 585 (1980).
9. U. V. Singh, S. Pandey, and N. Udupa, Drug Dev. Ind. Pharm., 20, 1811 (1994).

Drug Development and Industrial Pharmacy Downloaded from informahealthcare.com by Biblioteca Alberto Malliani on 01/30/12
For personal use only.

RIGHTSLINK