DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 19(7), 843-852 (1993)

FORMULATION AND EVALUATION OF ORAL AND TRANSDERMAL PREPARATIONS OF FLURBIPROFEN AND PIROXICAM INCORPORATED WITH DIFFERENT CARRIERS

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ABSTRACT

Flurbiprofen and piroxicam were incorporated in carriers like niosomes, albumin microspheres and beta-cyclodextrin. The bioavailability and anti-inflammatory activity of drugs after oral and transdermal administration in rats were studied.

INTRODUCTION

Dose dumping results in more side effects due to conventional therapy of anti-inflammatory drugs. In view of

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this, formulation of suitable transdermal delivery systems of flurbiprofen and piroxicam are attempted.

Flurbiprofen and piroxicam are having analgesic, anti-inflammatory and antipyretic activities.[1-4] For controlled transdermal delivery of drugs to the systemic circulation, drugs like clonidine, scopolamine, estradiol and nitroglycerine with many advantages over their conventional therapy were tried.[5] In the present study an attempt is made to improve the therapeutic efficacy of flurbiprofen and piroxicam in transdermal preparations by incorporating drug entrapped niosomes, albumin microspheres and drug beta-cyclodextrin complex.

Niosomes which are the nonionic surfactant vesicles can be used as drug carriers with modified tissue distribution characteristics.[6,7] Similarly drug entrapped albumin microspheres can be used for sustained release of drugs.[8,9] Inclusion complex with beta-cyclodextrin increased the absorption pattern of many drugs.[10,11]

MATERIALS AND METHODS

1% w/w flurbiprofen/0.5% piroxicam were incorporated in semisolid gel bases of guar gum (10% w/w, GG), methyl cellulose (4% w/w, MC), hydroxy propyl methyl

cellulose (60% w/w, HPMC), carboxy methyl cellulose (5% w/w, CMC) and sodium alginate (14% w/w, SA); each base containing 0.1% w/w methyl paraben (MP) as preservative.

Niosomes of Flurbiprofen

Niosomes of flurbiprofen were prepared using Span 60 (71.25 mg), cholesterol (71.25 mg) and dicetyl phosphate (7 mg) to get a ratio of 47.5 : 47.5 : 5 respectively. The lipids were dissolved in diethyl ether (10-15 ml) and 50 mg of flurbiprofen was added to the solution. The solvent was evaporated using a rotary flash evaporator, leaving a thin layer of solid mixture deposited on the wall of the round bottom flask. This film was hydrated by adding 5 ml of water in divided quantities and intermittently mixing on a vortex until a good dispersion of the mixture was obtained. The free drug was separated by dialysis method, using 0.9% sodium chloride solution. The percentage entrapment of flurbiprofen was 65% w/w.

Albumin Microspheres

2 ml of 20% egg albumin solution was taken, 100 mg of drug was added and mixed well. Then 8.5 ml of arachis oil was added followed by 0.1 ml of sodium lauryl sulphate (0.5% in n-heptane) and temperature was raised to 80°C and was

maintained for 10 minutes and cooled to room temperature with stirring. Then 0.02 ml of formaldehyde and 4 ml of n-hexane were added and filtered using Whatman filter paper, washed with 10 ml of n-hexane and dried under vacuum for 12 hours.

Beta-cyclodextrin Drug Complex

100 mg of flurbiprofen/piroxicam and 100 mg beta-cyclodextrin were taken in 100 ml beaker and 10 ml of water was added, kept for stirring on a magnetic stirrer for about 2 to 3 hours and finally incorporated in HPMC base.

Preparation of Transdermal Ointments

The prepared niosomes, albumin microspheres and beta-cyclodextrin complex were incorporated in the HPMC semisolid base with 10% of glycerine by levigation method. The preparations were then filtered in the collapsible tubes, sealed and labelled. The preparations contain 1% of flurbiprofen or 0.5% of piroxicam.

Bioavailability Study of Flurbiprofen/Piroxicam in Rats

In separate sets of rats (weighing about 200 gm) 3 ml of blood samples were collected by cardiac puncture at intervals of 0,15,30,60,90,120,180,240,300 and 360 minutes

after administering orally 1 ml of dispersion (1% flurbiprofen/0.5% piroxicam) by gavage and topically by uniform smearing of 1 gm of flurbiprofen (1%)/piroxicam (0.5%) ointment over one square inch area in the inter-scapular region. Collected blood samples were centrifuged and plasma samples were separated and kept at -20°C until analysis. The above studies have been conducted for 3 types of preparations mentioned above. Flurbiprofen[13] and piroxicam[15] were analysed in plasma spectrophoto-metrically, measuring absorbance at 247 nm and 354 nm respectively.

Pharmacodynamic Studies

(Acute inflammatory model, carrageenan induced rat paw oedema method)

The rats weighing about 200 gm were divided into 10 groups, each group containing 6 rats. Acute inflammation was produced in rat right hind paw by injecting 0.05 ml of 1% carrageenan solution. Animals of a group received either 2% HPMC vehicle orally, semi-solid ointment base topically, flurbiprofen/piroxicam in different forms orally and ointments topically, one hour prior to the carrageenan injection. The dose of flurbiprofen given both orally and topically 1 ml suspension and 1 gm of ointment each containing 1% of drug. Then the percentage reduction in paw volume was calculated.[14] Similarly piroxicam preparations

with and without beta-cyclodextrin were administered orally and topically (1 ml or 1 gm containing 0.5% drug) and percentage reduction in paw volume was calculated.

RESULTS AND DISCUSSION

Pharmacokinetic Studies

From the pharmacokinetic studies of flurbiprofen using transdermal preparations in rats, it was evident that sufficient amount of drug was percutaneously absorbed to systemic circulation. The bioavailability of flurbiprofen from transdermal administration was higher than with oral administration (Table 1). By incorporating drug entrapped niosomes, albumin microspheres and drug beta-cyclodextrin complex the bioavailability of flurbiprofen improved both in case of oral as well as transdermal preparations. By incorporating above drug entrapped carriers in HPMC gel a sustained release pattern of drug was observed (Table 1). However, in case of piroxicam the bioavailability was better when it was administered orally compared to transdermal preparation. Bioavailability of piroxicam improved in presence of beta-cyclodextrin both after oral and transdermal administration (Table 1).

TABLE 1.

BIOAVAILABILITY PARAMETERS OF FLURBIPROFEN AND PIROXICAM IN TRANSDERMAL AND ORAL DRUG DELIVERY SYSTEMS

Type of Preparation	Transdermal			Oral		
	T max (hrs)	C max (mcg/ml)	AUC 0-24 hrs (mcg/ml/hr)	T max (hrs)	C max (mcg/ml)	AUC 0-24 hrs (mcg/ml/hr)
Plain flurbiprofen ointment/suspension	4.0 ± 0.6	10.0 ± 1.5	152.0 ± 18.0	1.5 ± 0.2	28.00 ± 2.3	80.62 ± 11.0
Flurbiprofen niosomes	12.0 ± 0.8	18.0 ± 2.0	320.0 ± 24.0	2.0 ± 0.2	42.30 ± 3.5	246.43 ± 21.0
Flurbiprofen albumin microspheres	18.0 ± 1.2	23.0 ± 2.2	364.0 ± 26.0	0.5 ± 0.1	28.67 ± 2.4	155.77 ± 19.0
Flurbiprofen with beta-cyclodextrin	2.0 ± 0.2	18.0 ± 2.0	359.0 ± 25.0	1.0 ± 0.1	60.64 ± 4.5	312.94 ± 22.0
Piroxicam in HPMC	2.0 ± 0.2	9.3 ± 1.2	86.2 ± 11.2	2.0 ± 0.2	17.00 ± 2.0	178.00 ± 20.0
Piroxicam with beta-cyclodextrin in HPMC	1.0 ± 0.1	13.6 ± 1.3	130.1 ± 12.0	1.0 ± 0.1	23.00 ± 2.2	192.90 ± 19.5

Significance of difference in transdermal preparation by Mann Whitney method $p < 0.05$ compared to oral administration

Significance of difference in case of drug with carriers $p < 0.05$ compared to drug in vehicle alone (both in transdermal and oral)

TABLE 2.

COMPARISON OF PERCENTAGE DECREASE IN PAW OEDEMA VOLUME AFTER ORAL AND TRANSDERMAL ADMINISTRATION OF DIFFERENT FORMS OF FLURBIPROFEN AND PIROXICAM IN HPMC SEMISOLID BASE (DOSE 1 gm OF OINTMENT)

Type of Preparation	Activity in % reduction of oedema ± SD (n = 6)					
	Transdermal			Oral		
	3rd hr	12th hr	24th hr	3rd hr	12th hr	24th hr
HPMC vehicle	3.00 ± 4.0	2.05 ± 4.45	24.95 ± 3.05	36.00 ± 0.0	5.00 ± 2.50	10.35 ± 1.5
Flurbiprofen in HPMC vehicle	32.00 ± 2.0	40.00 ± 2.00	50.00 ± 2.50	44.00 ± 1.6	20.60 ± 6.40	56.30 ± 8.5
Flurbiprofen niosomes	22.00 ± 2.2	36.20 ± 2.00	96.90 ± 1.00	44.00 ± 8.0	55.90 ± 5.90	71.90 ± 9.4
Flurbiprofen microspheres	24.00 ± 4.0	89.65 ± 4.00	95.10 ± 1.80	20.00 ± 3.3	75.00 ± 1.50	65.65 ± 3.1
Flurbiprofen with beta-cyclodextrin	35.00 ± 6.0	98.20 ± 2.00	100.00 ± 0.00	46.65 ± 2.6	92.65 ± 4.45	93.75 ± 6.2
Piroxicam in HPMC vehicle	50.00 ± 4.0	70.10 ± 0.00	96.90 ± 3.00	58.00 ± 6.0	67.60 ± 2.90	68.70 ± 3.1
Piroxicam with beta-cyclodextrin in HPMC vehicle	12.00 ± 6.0	95.00 ± 1.50	98.50 ± 1.60	62.00 ± 1.0	92.70 ± 1.5	98.50 ± 1.5

Significance of difference in transdermal preparation by Mann Whitney method $p < 0.05$ compared to oral administration

Significance of difference in case of drug with carriers $p < 0.05$ compared to drug in vehicle alone (both in transdermal and oral)

Pharmacodynamic Evaluation.

Significant decrease in oedema was observed in case of transdermal preparations of flurbiprofen when it was incorporated with carriers like niosomes, albumin microspheres and drug beta-cyclodextrin complex ($p < 0.05$). Even in case of orally administered flurbiprofen the anti-inflammatory activity significantly increased when the drug was entrapped in different carriers ($p < 0.05$). Both in case of oral and transdermal preparations containing beta-cyclodextrin complex of flurbiprofen and piroxicam, the anti-inflammatory activity significantly improved ($p < 0.05$). Compared to oral administration of drug, transdermal preparation had shown better anti-inflammatory activity for longer duration in case of flurbiprofen. In case of piroxicam, oral preparation was better than transdermal preparation (Table 2).

CONCLUSION

The bioavailability and anti-inflammatory activity of flurbiprofen can be improved by incorporating it in niosomes, albumin microspheres and beta-cyclodextrin both in case of oral and transdermal preparations. The bioavailability of piroxicam can be improved by incorporating with beta-cyclodextrin to form inclusion complex.

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