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COMMUNICATIONS

DRUG CARRIERS FOR TRANSDERMAL PREPARATIONS OF FLURBIPROFEN

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ABSTRACT

Flurbiprofen was incorporated in different carriers like sodium alginate gel, calcium alginate microspheres, gelatin nanoparticles and complex with betacyclodextrin and incorporated in polyethylene glycol bases. Pharmacodynamic and bioavailability studies were carried out in male rats. It was found that drug incorporated in sodium alginate gel and drug complexed with betacyclodextrin were found to be suitable for designing transdermal preparations since they resulted in better therapeutic efficacy.

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INTRODUCTION

The advantages of transdermal route of administration are avoiding first pass effect of oral preparations, reduced gastrointestinal complication and side effects.[1] Drug carriers like sodium alginate gels,[2] gelatin nanoparticles[3] betacyclodextrins and calcium alginate microspheres are some of the carriers used effectively for delivery of drugs to the human systems. Flurbiprofen is a potent nonsteroidal antiinflammatory drug but due to serious side effects[4] on oral administration a need exists for better administration through transdermal route.

MATERIALS AND METHODS

Materials

Flurbiprofen was procured from M/s FDC Limited, Bombay and all other ingredients were of analytical grade.

Methods

Preparations of Transdermal Formulations

Calcium Alginate Microspheres

Sodium alginate - 300 mg, Water - 20 ml,
Calcium chloride - 200 mg in 20 ml water.

The drug and sodium alginate was dispersed in water and added dropwise to a aqueous solution of calcium chloride with gentle agitation. The resulting

microspheres, collected by filtration were then incorporated in 60% w/w Hydroxy Propyl Methyl Cellulose (15 cps) by levigation method. For oral formulation 5% Hydroxy Propyl Methyl Cellulose was used.

Drug Complexed with Beta Cyclodextrin and Incorporated in Polyethylene Glycol 4000 and Polyethylene Glycol 400

For Topical Formulation

Polyethylene glycol 4000 - 7.84 g, Polyethylene glycol 400 -1.96 g, Betacyclodextrin - 0.1 g, Water - 2 ml. The drug and betacyclodextrin were mixed for about 2 hours with little water. PEG 4000 was heated until melted and PEG 400 was incorporated in it. In the above PEG base, the complexed drug was slowly mixed to give a gel like consistency.

For Oral Formulation

Polyethylene glycol 4000 - 1 g, Polyethylene glycol 400 - 0.23 g, Betacyclodextrin - 0.1 g, Water - 8 ml

Gelatin Nanoparticles

Gelatin (1%) - 10 ml, Sodium sulphate (20%) - 2 ml, Isopropanol - 3 to 5 ml, Glutarldehyde (20%) - 1 ml, Sodium metabisulphite (12%) - 0.1 g. The drug was mixed with 10 ml of gelatin solution previously equilibrated at 35°C. 2 ml of sodium sulphate was added to the above gelatin solution containing the

drug. Isopropanol was added until the turbidity disappeared. 1 ml of of glutaraldehyde was added and the mixture was agitated at 35°C for 20 minutes. The hardening process was terminated by adding 1 ml of sodium metabisulphite, frozen overnight and the nanoparticles formed were incorporated in 60% w/w Hydroxy Propyl Methyl Cellulose (15 cps). For oral formulation 0.5% HPMC was used. Drug was also incorporated in 15% sodium alginate gel by levigation. All preparations contain 1% w/w of drug and 0.1% w/w methyl paraben as preservative.

Evaluations

The invitro diffusion studies were carried using Keshary-Chien diffusion cell[5]. The samples withdrawn were analysed at 247nm spectrophotometrically.

Bioavailability of Flurbiprofen in Rats

From separate sets of rats (weighing each about 200 gms) 3 ml of blood samples were collected by cardiac puncture at definite time intervals both after oral administration and topical smearing of the formulation (1 gm) over one square inch area in the interscapular region, the site having been shaved 24 hours prior to the experiment. Minimum of 3 rats were used for each interval and blood collection. Flurbiprofen was analysed spectrophotometrically.[6]

Pharmacodynamic Evaluation

Acute Inflammatory Model - Carrageenan Induced Rat Paw Oedema Method[7]

The rats weighing about 200 gm were divided into different groups each group consisting of 6 rats. Acute inflammation was produced in rat right hind paw by injecting 0.05 ml of 1% carrageenan solution.[8] The animals received the formulation (1 gm) either orally or by topical smearing one hour prior to the carrageenan injection. Paw oedema volume was measured at different time intervals after carrageenan challenge with the help of "plethysmometer".[10] Percentage reduction in paw oedema volume was calculated with reference to control group.

RESULTS AND DISCUSSION

Invitro Diffusion Studies

Drug incorporated in gelatin nanoparticles showed highest rate of release whereas drug incorporated in calcium alginate microspheres showed the lowest. The order of diffusion at the end of sixth hour was as follows.

Gel.N + Drug (70.3%) > CD + PEG + Drug (63.66%) > SA + Drug (60.0%) > Cal.A + Drug (12.55%)

The release of drug from CD + PEG and SA showed uniform, consistent, nearly zero order release pattern.

TABLE - 1

COMPARISON OF PERCENTAGE DECREASE IN PAW OEDEMA VOLUME AFTER ORAL AND TRANSDERMAL ADMINISTRATION OF FLURBIPROFEN FROM DIFFERENT GEL BASES

Carriers	Oral				Transdermal			
	% Reduction of Oedema ± SD (n=6)				% Reduction of Oedema ± SD (n=6)			
	2nd hr.	6th hr.	12th hr.	24th hr.	2nd hr.	6th hr.	12th hr.	24th hr.
60% w/w HPMC	8.0±2.2	6.0±0.45	5.0±2.5	10.35±1.5	3.0±0.4	5.0±0.45	2.05±0.45	24.95±3.05
HPMC+Drug	44.0±1.6	43.0±2.50	50.6±6.4	56.30±8.5	37.0±3.3	30.0±3.50	40.00±2.00	50.00±2.50
CD+PEG+Drug	69.5±3.2	73.3±4.30	58.0±7.2	57.00±3.5	55.0±2.5	75.0±7.0	76.00±3.50	77.00±2.50
CD+PEG	3.5±2.0	12.0±3.7	10.5±1.6	13.30±3.6	11.0±3.5	8.5±2.5	10.50±2.50	17.00±2.30
SA+Drug	74.0±6.3	73.0±2.3	66.0±3.7	69.00±5.3	74.0±3.5	62.0±7.0	63.00±1.50	65.00±3.70
SA	2.5±1.0	10.0±0.0	12.0±3.7	10.00±3.5	7.5±3.5	15.0±3.5	13.30±1.50	18.20±2.00
Cal.A.+Drug	63.0±7.0	45.0±3.5	57.0±7.5	60.00±2.3	43.0±7.3	54.0±5.5	60.00±3.70	60.00±2.30
Cal.A.	5.0±3.5	15.0±2.5	13.0±3.7	3.00±2.5	7.5±2.0	9.5±2.2	3.30±0.50	7.50±2.30
Gel.N.+Drug	37.0±3.5	38.5±5.0	37.0±9.5	36.70±3.5	65.0±3.2	44.0±2.5	44.00±2.50	49.00±3.30
Gel.N.	7.0±2.5	7.0±3.3	11.0±2.3	18.00±9.2	5.0±3.3	13.0±3.3	11.00±3.30	3.50±2.20

Pharmacodynamic Activity (Table 1)

Antiinflammatory activity of transdermal preparation was better when flurbiprofen complexed with betacyclodextrin and incorporated in PEG base and drug incorporated in sodium alginate. However it had poor antiinflammatory activity when it was administered with calcium alginate and gelatin. When the drug was administered orally with calcium alginate and betacyclodextrin complex it had fairly good antiinflammatory activity. Because of inclusion complex formation with betacyclodextrin the solubility and permeation of drug through skin and GI tract may be improved resulting in better efficacy. However in case of calcium alginate microspheres as drug carrier, the permeation of flurbiprofen is not improved. In case of oral administration the drug may be slowly released from calcium alginate microspheres showing prolonged effect, improved bioavailability and antiinflammatory activity.

Bioavailability

The bioavailability parameters are shown in Tables 2. It was evident that T_{max} was higher in case of transdermal preparations (8 to 10 hours) when compared to oral preparations (1 to 2 hours). The C_{max} was less in case of transdermal preparations when compared with that of oral preparations. It was evident that the bioavailability of flurbiprofen was higher when inclusion complex of flurbiprofen was prepared along with betacyclodextrin. However, it was

TABLE - 2

BIOAVAILABILITY PARAMETERS OF FLURBIPROFEN INCORPORATED IN DIFFERENT GEL BASES

Formulation	T_{max} hr	C_{max} mcg/ml	AUC_0 mcg/ml/hr	$AUMC_{0_2}$ mcghr^2/ml	MRT hr	K_{el_1} hr^{-1}	$t_{1/2}$ hr	K_{ss}
				ORAL ROUTE				
CD+PEG+Drug	1	25.47	152.16	1192.23	7.83	0.25	2.76	0.127
SA+Drug	1	16.52	102.40	1045.18	10.20	0.30	2.29	0.098
Cal.A.+Drug	2	15.12	206.46	2753.30	13.30	1.29	0.53	0.075
Gel.N.+Drug	2	23.19	209.50	3949.70	18.85	0.08	8.39	0.053
				TRANSDERMAL ROUTE				
CD+PEG+Drug	10	6.10	531.68	18611.23	35.00	0.0180	38.00	0.028
SA+Drug	10	4.63	153.26	4485.40	29.27	0.1564	4.43	0.034
Cal.A.+Drug	8	2.86	57.25	953.70	16.65	0.2001	3.46	0.060
Gel.N.+Drug	10	3.93	170.60	4925.37	28.87	0.0815	8.49	0.034

low when the same preparation was administered orally. Similarly the bioavailability of drug was better when it was incorporated in sodium alginate and applied transdermally compared to oral administration. When the drug was incorporated in calcium alginate and gelatin the bioavailability decreased after transdermal application when compared to oral administration. The elimination rate constant of drug was lower when preparation was administered transdermally.

CONCLUSION

Flurbiprofen had better bioavailability and antiinflammatory activity when it was incorporated after inclusion complex formation with betacyclodextrin and sodium alginate gel after transdermal application. Though calcium alginate microspheres are good carriers for oral administration of flurbiprofen, it was not suitable for transdermal application.

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