RESEARCH PAPER

Accepted 22 March 2001
Revised 20 February 2000
Received 19 June 2000
Indian J. Pharm. Sci., 2001, 63(3) 200-204

The Effects of Polymers and Permeation Enhancers on Releases of Flurbiprofen from Gel Formulations

V. LOGANATHAN*, S. MANIMARAN, A. JASWANTH, A. SULAIMAN, M. V. SIVAPRASADHA REDDY, B. SENTHIL KUMAR AND A. RAJASESKARAN[1]
Periyar College of Pharmaceutical Sciences For Girls, Trichirapalli-620 021.
[1]Arulmighu Kalasalingam College of Pharmacy, Krishnankoil–626 190.

Flurbiprofen appears to be more active as an antiinflammatory agent than other NSAID products and is usually well tolerated. Gels have gained more and more importance because the gel-based formulations are better percutaneously absorbed than creams and ointment bases. Therefore, flurbiprofen gel formulations were made with different polymers like carbopol 940 (0.6-1.2%) and hydroxy propyl methyl cellulose (HPMC) (1.0-4.0%) containing various permeation enhancers namely sodium lauryl sulphate (SLS) (0.25-1.0%) and dimethyl sulfoxide (DMSO) (5-20%) at different proportions, having 1% concentration of drug. The formulated gels were evaluated for drug content, pH, viscosity and *in vitro* release through the Sigma membrane. Its physical stability was evaluated by freeze-thaw cycling. Selected formulations were evaluated for its antiinflammatory activity using the carrageenin-induced paw edema in rats. The physical stability study revealed that the carbopol 940 gels were highly stable and the gels with HPMC were physically unstable. The carbopol with 15% of DMSO showed best *in vitro* release of flurbiprofen. *In vivo* study for the selected formulation showed significant (P<0.001) antiinflammatory activity in the carrageenin-induced paw edema in rat.

Most of the non-steroidal antiinflammatory drugs (NSAID) have been widely used for the treatment of acute and chronic arthritic conditions[1]. Oral doses often cause gastric irritation leading to ulcer and other systemic side effects. But the topical application of the drug offers potential advantages of delivering the drug directly to the site of action. Creams, gels, ointments and paste are some of the topical semisolids in use for many decades. Out of various semi solid dosage forms, the gels are becoming more popular due to ease of application and better percutaneous absorption than other semisolid preparations. Effectiveness of topical applications mainly depends upon its rate and extent of drug release from the base. Hence a study on formulation of flurbiprofen gels with different polymers and permeation enhancers at various concentrations was selected as a principle objective for antiinflammatory activity. Flurbiprofen appears to be more active as an antiinflammatory agent than ibuprofen and is usually well tolerated[2].

*For correspondence

EXPERIMENTAL

Flurbiprofen was obtained from Boots Pharmaceuticals Limited, Mumbai as a gift sample. Sigma membrane was purchased from Sigma Diagnostics, USA. Other chemicals such as carbopol 940, HPMC, dimethyl sulfoxide, sodium lauryl sulphate, triethanolamine, propylene glycol and alcohol 90% were of laboratory grade, purchased locally and used as received.

Formulation of Carbopol Gels:

Specified amount of carbopol 940 (Table 1) was soaked in water for 2 h and was dispersed with a semi medium mixer. Carbopol was then neutralized with triethanolamine using phenol red as indicator with stirring.

TABLE 1: FORMULATION OF FLURBIPROFEN GELS WITH DIFFERENT OF CARBOPOL CONCENTRATIONS

INGREDIENTS	FPG I	FPG II	FPG III	FPG IV
Flurbiprofen (g)	1	1	1	1
Carbopol (g)	0.6	0.8	1	1.2
Triethanolamine (g)	0.5	0.6	0.7	0.8
Alcohol (ml)	20	20	20	20
Propylene glycol (ml)	10	10	10	10
Purified Water (ml)	67.9	67.6	67.3	67
pH	6.8	7.2	7.1	7.3
Drug Content (mg/g)	9.7	10.2	10.5	10.9
Viscosity (CPS)	32950	37800	44500	49200

Viscosity was determined using Brook field Viscometer model R.VT spindle no. 7

Then required amount of drug was dissolved in specified volume of alcohol and added in divided portions to the carbopol gel.

Preparation of HPMC Gels:

Required amount of the drug (Table 2) was dissolved in propylene glycol by warming at about 40-50°. The polymer HPMC was added with stirring and then the mixture was heated to 90° with constant stirring for 15 min and then cooled to room temperature by stirring for about 15-30 min.

Permeation Enhancers:

The permeation enhancers like sodium lauryl sulphate (SLS)[3,4] and dimethyl sulfoxide (DMSO)[3,4] were incorporated in different concentrations (0.25-1.0%) and (5%-20%) respectively (Table 3) with the selected carbopol formulations.

Evaluation of Gels:

The prepared gels were evaluated for pH, viscosity, drug content, *in vitro* release characteristic and some selected gels were tested for antiinflammatory activity using the carrageenin-induced paw edema in rats. pH measurements were done by using a digital type pH meter by dipping the glass electrode and reference electrode completely into the gel system so as to cover the electrodes. The viscosity of the prepared gels was done with a Brooke Field type of viscometer (model RVT) spindle No. 4 and 7 at various speeds of 10, 20, 50, 100 rpm.

TABLE 2: FORMULATION OF FLURBIPROFEN GELS WITH DIFFERENT CONCENTRATIONS OF HPMC

INGREDIENTS	FPG V	FPG VI	FPG VII	FPG VIII
Flurbiprofen (g)	1	1	1	1
HPMC (g)	1	2	3	4
Propylene glycol (g)	98	97	96	95
pH	7.1	6.9	6.8	6.9
Drug content (mg/g)	10.4	9.5	10.7	9.0
Viscosity (CPS)	310	220	400	670

Viscosity was determined using Brook field Viscometer model R.VT spindle no. 4.

TABLE 3: FORMULATION OF FLURBIPROFEN GELS WITH PERMEATION ENHANCERS

INGREDIENTS	FPG IX	FPG X	FPG XI	FPG XII	FPG XIII	FPG XIV	FPG XV	FPG XVI
Flurbiprofen (g)	1	1	1	1	1	. 1	1	1
Carbopol (g)	0.6	0.8	1	1.2	0.6	0.8	1	1.2
Triethanolamine (g)	0.5	0.6	0.7	0.8	0.5	0.6	0.7	0.8
Alcohol (ml)	20	20	20	20	20	20	20	20
Propylene glycol (ml)	10	10	10	10	10	10	10	10
Sodium Lauryl Sulphate (mg)	250	500	750	1000	-	-	-	-
Dimethyl Sulfoxide (ml)	-	-	-	-	5	10	15	20
Purified Water (ml)	67.9	67.6	67.3	67	62.9	57.6	52.3	47
pH	6.6	7.1	6.9	7.2	7.4	7.1	6.8	7.2
Drug Content(mg/g)	9.7	9.5	10.5	9.8	10.2	9.7	10.7	10.1
Viscosity (CPS)	6150	7150	7900	10000	8100	9300	10400	11700

Viscosity was determined using Brook field Viscometer model R.VT spindle no. 7.

Drug Content Analysis:[5]

A specified quantity (1.0 g) of gel was treated with 10% methanol, the volume was made up to 50 ml and 5 ml of the above solution was further diluted to 50 ml with distilled water. From this stock solution 1 ml was taken, to this 3.5 ml of carbon tetrachloride was added and vortexed. After 5 min the CCl_4 layer was transferred to a clean tube and further extracted with 4 ml of 0.1 N sodium hydroxide solution. The absorbance of the solution was measured at 247 nm using 0.1 N sodium hydroxide as a blank.

***In vitro* Diffusion Studies:**

The diffusion studies of the prepared gels were carried out in an apparatus reported by Zuber *et al.*[6] who developed a simple technique for studying the dissolution release of ointments and creams through a sigma membrane by employing a diffusion cell and membrane assembly. Gel sample (0.5 g) was taken in Sigma membrane and the diffusion studies were carried out at 37±1° using 250 ml of phosphate buffer (pH 7.4) as the dissolution medium. Five milliliters of each sample was withdrawn periodically at 0.5, 1, 2, 3, 4, 5, 6, 7 and 8 h and each sample was replaced with equal volume of fresh dissolution medium. And the samples were analyzed for the drug content at 247 nm by using phosphate buffer as blank.

Pharmacological Screening:

Screening for antiinflammatory activity was carried out by carrageenin-induced paw edema method in rats as reported by Winter *et al.*[7], edema was produced by injecting 0.1 ml of carrageenin solution (1% w/v) in normal saline under the subplantar region of the left hind foot of rats. Paw volume was measured using the volume differential meter after 3 h of carrageenin injection.

RESULTS AND DISCUSSION

Table 4 depicts the *in vitro* diffusion profile of flurbiprofen from gels containing different concentrations (0.6%-1.2%) of carbopol. The total amount of drug released for a fixed period of 8 h was found to decrease with increase carbopol concentration. Even though a good drug release was observed with 0.6% carbopol, as it was too soft and less viscous in nature, and an optimum polymer concentration of 1%, which showed good constancy was selected for further study on drug release. Table 4 also reflects the *in vitro* diffusion profile of flurbiprofen from gels containing different concentrations (1.0%-4.0%) of HPMC. Even though, good release was observed with 1% and 2% HPMC gels, they were found to be less viscous in nature, and an optimum concentration of 3% HPMC was found to be suitable.

On comparing corbopol gels with the HPMC gels, it is obvious that HPMC gels were less efficient in releasing the drug, for example 1% carbopol gel released a maximum of 90.23% of flurbiprofen over a period of 8 h, whereas 3% HPMC gel released only 49.39% of drug.

TABLE 4: *IN VITRO* RELEASE PROFILE OF FLURBIPROFEN FROM DIFFERENT CONCENTRATIONS OF CARBOPOL AND HPMC

TIME (h)	% OF DRUG RELEASEDWITH DIFFERENT CARBOPOL CONCENTRATION				% OF DRUG RELEASED WITH DIFFERENT HPMC CONCENTRATION			
	0.6%	0.8%	1%	1.2%	1%	2%	3%	4%
0.5	37.04	36.09	27.54	27.54	31.34	29.44	24.69	22.78
1	44.64	42.74	36.09	35.14	35.14	33.24	27.54	28.48
2	53.19	50.34	42.74	43.69	37.04	35.14	31.33	30.38
3	62.69	57.94	53.19	49.39	39.89	38.94	34.18	33.2
4	70.28	66.49	58.89	56.99	41.79	40.84	37.04	35.12
5	78.83	76.93	65.54	65.54	44.64	42.74	39.88	37.98
6	85.48	84.53	75.03	73.13	46.54	45.59	44.64	42.72
7	91.17	89.28	82.63	80.73	49.39	47.49	46.54	45.59
8	99.73	91.86	90.23	88.33	53.19	52.24	49.39	47.49

The qualitative stability evaluation of HPMC gels by freeze-thaw cycling had showed that the gels are physically unstable as indicated by the occurrence of syneresis, whereas the carbopol gels showed physically stability under freeze-thaw cycling technique.

Table 5 reveals that SLS release was maximum (90.23%) over a period of 6 h at 0.75% concentration level. Further increase in SLS concentration to 1% level showed no further increase in drug release. In fact, the release was found to be slightly decreased. The incorporation of SLS in higher concentration showed the problem of frothing. Table 5 also depicts that 15% level of DMSO released a maximum of 98.78% of flurbiprofen within a period of 5 h.

In vivo antiinflammatory activity by carrageenin-induced paw edema in rats for the selected flurbiprofen

TABLE 5: *IN VITRO* DISSOLUTION PROFILE OF 1% CARBOPOL GEL WITH AND WITHOUT PERMEATION ENHANCERS

TIME (h)	CONCENTRATIONS OF PERMEATION ENHANCERS									
	SLS					DMSO				
	0 %	0.25%	0.5 %	0.75 %	1 %	0 %	5 %	10 %	15 %	20 %
0.5	27.54	46.54	42.74	56.04	46.54	27.54	32.29	29.44	44.64	41.79
1	36.09	57.94	48.44	64.59	53.19	36.09	40.84	47.99	58.89	55.09
2	42.74	65.54	56.04	72.18	62.69	42.74	54.14	48.44	66.49	65.54
3	53.19	71.23	63.64	77.88	75.03	53.19	65.54	63.64	79.78	73.12
4	58.89	76.93	73.13	88.33	79.78	58.89	82.62	84.53	93.08	85.48
5	65.54	84.53	84.53	94.03	84.53	65.54	94.03	92.13	98.78	95.92
6	75.03	91.17	92.13	99.73	97.83	75.03	97.83	97.83	98.78	99.73
7	82.63	96.88	98.78	99.73	97.83	82.63	97.83	97.83	98.78	99.73
8	90.23	96.88	98.78	99.73	97.83	90.23	97.83	97.83	98.78	99.73

TABLE 6: ANTIINFLAMMATORY ACTIVITY OF FLURBIPROFEN GEL FORMULATIONS

GROUP	FORMULATION	PAW VOLUME (MEAN ± SEM)		
		INITIAL READING'0' m	AFTER 180 m	% INHIBITION AFTER 3 h
CONTROL I	—	5.2 ± 0.94	7.6 ± 0.25	—
II	FPG III with 1% Carbopol	5.8± 0.22	7.5 ± 0.12	35.7
III	FPG XI with 1% Carbopol and 0.75% SLS	5.5 ± 0.12	6.4 ± 0.17	62.0
IV	FPG XV with 1% Carbopol and 15% DMSO	5.7± 0.14	6.3 ± 0.02 *	73.2
V	FPG VII with 3% HPMC	4.9 ± 0.15	6.7 ± 0.10	18.4
VI	Marketed Ibuprofen gel	5.8 ± 0.24	7.5 ± 0.31	34.2

Each value represents the mean ± SEM of (n = 6) observations. Asterisk denotes statistical significance at P<0.001.

gels are shown in the Table 6. Among the four formulations tested FPG XV (1% carbopol with 15% DMSO) showed a maximum of 73.15% inhibition of the edema, whereas other formulations FPG III, FPG XI and FPG VII showed 35.65%, 62.00% and 18.39% respectively. While comparing the HPMC formulation with carbopol, HPMC showed very minimal antiinflamatory activity.

Based on this study the effect of polymer concentration and permeation enhancers on flurbiprofen release, an optimum of 1% carbopol with 0.75% SLS and 1% carbopol with 15% DMSO were found to be more suitable to give a better formulation having good drug release characteristics and consistency. As in *in vitro* study the HPMC formulations showed lesser rate of release than that of the carbopol formulations which reflects in the *in vivo* antiinflammatory study.

All the carbopol formulations showed encouraging *in vivo* results. Hence further formulation studies and clinical evaluations using carbopol formulations should prove more effective for treating acute and chronic inflammatory conditions.

ACKNOWLEDGEMENTS

The authors express their gratitude to M/s. Boots Pharmaceuticals Ltd., Mumbai for their generous gift sample of flurbiprofen for this study.

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