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EVALUATION OF TOPICAL NON-STEROIDAL ANTI-INFLAMMATORY DRUGS USING PENETRATION ENHANCERS

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Summary Several topical formulations of piroxicam (1% w/w) and ibuprofen (5% w/w) were prepared. Various penetration enhancers were incorporated in these formulations and evaluated for antiinflammatory activity using carrageenin induced rat paw edema model. The maximum effect was seen when piroxicam and ibuprofen were combined with 3% azone and 5% N-methyl-2-pyrrolidone as enhancers, respectively.

Key words Topical NSAIDs penetration enhancers antiinflammatory activity

The antiinflammatory drugs like aspirin, ibuprofen and piroxicam have an established use in the treatment of arthritis. The current concern of serious and potentially fatal side effects such as gastric irritation has emphasised the importance of developing a topical dosage form of these drugs. This paper is an attempt to study the effect of various enhancers on the antiinflammatory activity of piroxicam and ibuprofen.

MATERIALS AND METHODS

Piroxicam,, ibuprofen, white petroleum, stearyl alcohol, sodium lauryl sulphate, propylene glycol, sodium metabisulphite, parabens and glycerine were all of i.p. grade. Carbopol 940 and carrageenin (phlogistic agent) were of pharmacopoeia1 grade and were used without further purification. Azone (1-dodecylazacycloheptan-2-one), N-methyl-2-pyrrolidone (NMP), dimethylsulphoxide (DMSO) and urea were all of analar grade.

Several formulations were prepared and enhancers such as Azone, urea, NMP and DMSO incorporated in them in different concentrations. The details are given in table 1.

Young adult male albino rats weighing between 125 165 g were taken for the study. They were divided into control and the study groups. The study group was further divided into 10 groups (four groups for the study of piroxicam and six groups for the study for ibuprofen formulations) comprising of six rats in each group. Four rats from each group were exclusively used for studying the effect of plain base i.e. unmedicated formulation. The test sample (100 mg) was weighed and spread uniformly over a butter paper and placed on the back of each rat of the study group. The control group did not receive any application. The treatment was given an hour before the injection of a phlogistic agent into the rat foot. Carrageenin induced rat hind paw edema model was used for the evaluation of antiinflammatory activity of the formulations.

Student's t test was applied to determine the level of significance.

RESULTS

The data given in table 1 shows that piroxicam (1%) and ibuprofen (5%) are almost equipotent (SI. Nos. 1 Vs 5; 3 Vs 7). The gel base formulation is better than Canadian formulary cream or hydrophilic oinment base formulation (SI.Nos.1 Vs 3; 5 Vs 7,9).

The maximum antiinflammatory effect was seen when piroxicam and ibuprofen were combined with 3% azone and 5% NMP as enhancers, respectively. The combination of piroxicam with azone as enhancer produced better effect than its combination with urea (SI.Nos.2 Vs 4). Similarly the combination of ibuprofen with NMP or DMSO produced better effect than its combination with urea (SI.Nos.6,10 Vs 8).

There was statistically no significant difference in percentage of edema inhibition (after 6 hrs) by plain bases between study group and control group (Table 2) indicating that the base *per se* did not exert any antiinflammatory effect.

DISCUSSION

Ibuprofen and piroxicam are lipophilic in nature and hence unlikely to permeate the skin easily, especially the viable epidermis which provides a more

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Table 1. Inhibition of carrageenan induced rat paw edema by piroxicam and ibuprofen in different formulations

Sl. No.	Formulation (as % w/w)"	% edema inhibition after 6 hours
1	Piroxicam (1%) with gel base	41 ± 3..2
2	Piroxicam with gel base and Azone (3%) as enhancer	66 ± 2.7'
3	Piroxicam (1%) with Canadian formulary cream base	27.5 ±1.3
4	Piroxicam with Canadian formulary cream base and urea (5%) as enhancer	34.5± 3.3*
5	Ibuprofen (5%) with gel base	39 ± 1.9
6	Ibuprofen with gel base and NMP (5%) as enhancer	51 ± 3.1'
7	Ibuprofen (5%) with Canadian cream base	22 ± 1.7
8	Ibuprofen with Canadian formulary cream base and urea (5%) as enhancer	32.5± 2.5'
9	Ibuprofen (5%) with modified hydrophilic ointment base USP	25.5 ±2.8
10	Ibuprofen with modified hydrophilic ointment base USP and DMSO (10%) as enhancer	40 ± 2.3'

Each value is a mean ± S.E.M. of 4 determinations (n =6 animals in each group). Significantly different from formulation devoid of an enhancer. 'P < 0.01

**Gel base: Carbopol 940 = 1.0, Methyl paraben = 0.15, Sodium metabisulfite = 0.5. Purified water as 100.

"Canadian formulary cream base: Stearyl alcohol = 20.8, Sodium lauryl sulfate = 0.6, Polyethylene glycol 4000 = 11.2, Glycerin = 17.0, Methyl paraben = 0.15, Propyl paraben = 0.06, Purified water qs 100.

"Modified hydrophilic ointment base USP: White petrolatum = 25.0, Stearyl alcohol = 15.0, Propylene glycol = 12.0, Sodium lauryl sulfate = 1.0, Methyl paraben = 0.15, Propyl paraben = 0.06 Purified water qs 100

Table 2. Inhibition of carrageenin induced rat paw edema by plain bases (unmedicated formulation)

Formulation	% edema inhibition after 6 hours	
	Study group	Control group
Gel base	15.5 ± 1.9	15.0 ± 2.7
Cream base	15.8 ± 2.3	17.0 ± 0.9
Ointment base	15.4 ± 1.6	14.2 ± 0.5

Values are mean of 4 determination

hydrophilic milieu compared to the stratum corneum. Thus, in order to achieve a prompt and desired antiinflammatory effect, it is essential to enhance the flux of these drugs through the skin. Although methods such as iontophoresis[3] and ultrasound[4] have been employed to enhance thetransdermal flux of the drugs, they are rarely used due to their high cost. Use of penetration enhancers offers a cheaper, simpler and convenient method of improving transdermal bioavailability and diffusivities thereof.

From the results it can be inferred that these enhancers potentiated the antiinflammatory effectiveness of these formulations. This could be attributed to increase in the transdermal flux of these drugs[5,6] and thereby improving the bioavailability. Probable mechanism of these enhancers include extraction of stratum corneum lipids, lipoproteins and nucleoproteins, displacement of bound water and loosening of the polymeric structure in the corneocyte and osmotically inducing delamination of stratum corneum, causing it to swell and thus induce channels to form in the matrix which promote the passage of these drugs.

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REFERENCES

1. Sanghavi NM, Puri RD, Kamath PR. Study on topical formulations Indian Drugs 1988;26: 165-8.

2. Winter CA, Risley EA, Nuss GW. Carrageenin · induced edema in hind paw of the rat as an assay for antiinflammatory drugs. Proc Soc Exptl Bio 1962;544-7.

3. Tyle P. Iontophoretic devices for drug delivery. Pharm Res 1986;3:318-26.

4. Kost J, Levy D, Langer R. Ultrasound effect on transdermal drug delivery. Proc 13th Int Symp on Contr Release of Bioactive Materials 1986;177-8.

5. Sanghavi NM, Puri RD. Effect of sorption promotors on the transdermal delivery of ibuprofen. Indian Drugs 1991;28:460-1.

6. Puri RD, Sanghavi NM, Matharu RS. Effect of sorption promotors on the transdermal delivery of piroxicam. 1 lth Pharmaceutical Technology Conference, Manchester, U.K 1992;393-413.

7. Jonathan Hadgraft. Transdermal drug delivery system. New York: Marcel & Dekker Inc.. 1989;204-229.