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Original research paper

Topical dosage form of valdecoxib: Preparation and pharmacological evaluation

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Valdecoxib, a selective COX-2 inhibitor, produces serious side effects when given orally. This has led to its withdrawal. Topical application of valdecoxib was formulated and evaluated for its efficacy and safety. Standard procedures were followed and male Wistar albino rats were used to test the anti-inflammatory effect and effect in hyperalgesic conditions. Ointments, creams, and gels containing valdecoxib 1% (*m*/*m*) were prepared. These were tested for physical appearance, pH, spreadability, drug content uniformity, *in vitro* diffusion. Gel prepared using Carbopol 940 (F-X) was selected after the analysis of the results. Formulation F-X was evaluated for acute skin irritancy, anti-inflammatory effect, optimum effective concentration of valdecoxib, effect on hyperalgesia, inhibition of the granulation tissue formation and anti-arthritic effect. Determination of valdecoxib in test animals plasma and determining the blood clotting time and bleeding time were conducted to study the safety of topical valdecoxib. Valdecoxib gel containing 1% (*m*/*m*) of the drug was significantly ($p < 0.05$) more effective in inhibiting hyperalgesia associated with inflammation, compared to placebo gel, but exhibited significantly ($p < 0.05$) lower suppression of inflammation than commercial rofecoxib gel. Concentration of valdecoxib used in the preparation minimizes the risk of systemic effects, as shown by the analysis of rat plasma for the presence of valdecoxib; hence, this may be the alternative to oral preparations. The bleeding and clotting time showed no significant difference before and after application of F-X.

Keywords: valdecoxib, topical gel, *in vitro*, *in vivo* evaluation

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Non steroidal anti inflammatory drugs (NSAIDs) have been increasingly introduced as topical preparations for local treatment of musculoskeletal soft tissue rheumatic conditions (1). This concept may be extended to the selective COX-2 inhibitors, so as to

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minimize their side effects. The side effects cited for valdecoxib pose increased risk of cardiovascular events and well-described serious potentially life threatening gastrointestinal bleeding (2). The selection of vehicle bases decides the consistency, physical properties and also affects the drug release from the preparations (3). Therefore in this work, different bases were selected for pharmaceutical evaluation. Topical administration requires lower doses when compared with that of oral dosage forms, hence it is hypothesized that systemic absorption may be negligible. An add internal advantage of localized peripheral administration is optimization of drug concentration at the site of the origin of pain, leading to lower systemic levels with fewer adverse effects (4). In this work, the efficacy of using valdecoxib as a topical preparation is evaluated by pharmaceutical tests and pharmacological evaluation and was compared with the commercial topical rofecoxib preparation.

EXPERIMENTAL

Valdecoxib was a gift sample from Safe Line Formulation (India). Carbopol 940 was purchased from B-Pura Labs (India). Commercial sample of rofecoxib 1% (*m*/*m*) was purchased from a retail pharmacy shop. Heat-killed *Mycobacterium tuberculosis* H37RA was procured from the Indian Council for Medical Research (ICMR) (India). Carrageenean was purchased from Sigma Chemicals (USA). Other chemicals used were of analytical reagent grade.

UV spectrophotometer (Shimadzu model 1601, Shimadzu, Japan), pH meter (Systronics, India), penetrometer (Systronics), Franz diffusion cell were the apparatus used.

Formulations

Fourteen different formulations were prepared using an ointment base, a cream base and a gel base according to the formulae given in Table I.

Appropriate standard method of fusion (where the solid fats were melted and mixed) and trituration were followed for preparation of the ointment, cream and gel (5). Valdecoxib was incorporated in the bases to get 1% (*m*/*m*). All preparations were packed in wide-mouthed transparent plastic jars with screw-capped lids. The following tests were carried out on all the preparations.

Drug content

Each formulation (500 mg) was weighed and 0.5 mol L^{-1} sodium hydroxide was added and triturated. Valdecoxib was extracted in the medium and was made up to 100 mL with the same. After filtration of this stock, suitable dilutions were made, if necessary, and absorbance was measured at 244 nm. Drug content was calculated from the linear regression equation obtained from the calibration data. Results given in Table I are the average of triplicate values.

Table I. Formulae and drug contents of ointment, cream and gel

Formulation	Ingredients	Concentration (%, *m*/*m*)	Drug content
		mean ± SD (%)	
F-I	Emulsifying wax	3	0.75 ± 0.51
	Soft paraffin	50	
	Liquid paraffin	20	
F-II	Emulsifying wax	20	0.76 ± 0.52
	Soft paraffin	60	
	Liquid paraffin	20	
F-III	Emulsifying wax	25	1.10 ± 1.14
	Soft paraffin	55	
	Liquid paraffin	20	
F-IV	Wool fat	10	1.20 ± 0.64
	Oleic acid	7	
	Calcium hydroxide	3	
	Arachis oil	30	
	Water q.s.	50	
F-V	Wool fat	5	0.76 ± 0.40
	Hard paraffin	5	
	Cetostearyl alcohol	5	
	Soft paraffin	85	
F-VI	Wool fat	10	1.30 ± 0.41
	Hard paraffin	5	
	Cetostearyl alcohol	5	
	Soft paraffin	80	
F-VII	Emulsifying ointment	40	1.20 ± 0.38
	Chlorocresol	1	
	Purified water	59	
F-VIII	Emulsifying ointment	30	1.58 ± 1.23
	Chlorocresol	1	
	Purified water	69	
F-IX	Carbopol	1	1.04 ± 0.16
	Propylene glycol	10	
	Triethanolamine	1.5	
	Ethanol	30	
	Purified water q.s	100	
F-X	Carbopol 940	1	0.98 ± 0.25
	Propylene glycol	10	
	Triethanolamine	1.5	
	Ethanol	30	
	Purified water q.s.	100	

Table I. continued

Formulation	Ingredients	Concentration (%, *m*/*m*)	Drug content
		mean ± SD (%)	
F-Xa	Carbopol 940	1	0.50 ± 0.21
	Propylene glycol	10	
	Triethanolamine	1.5	
	Ethanol	30	
	Purified water q.s.	100	
F-Xb	Carbopol 940	1	1.46 ± 0.01
	Propylene glycol	10	
	Triethanolamine	1.5	
	Ethanol	30	
	Purified water q.s.	100	
F-Xc	Carbopol 940	1	2.01 ± 0.10
	Propylene glycol	10	
	Triethanolamine	1.5	
	Ethanol	30	
	Purified water q.s.	100	
F-0	Carbopol 940	1	–
	Propylene glycol	10	
	Triethanolamine	1.5	
	Ethanol	30	
	Purified water q.s.	100	

Drug release

In vitro diffusion study was performed using the Franz diffusion cell (6, 7). Phosphate buffer pH 7.4 was used as receptor fluid and dehaired abdominal skin of Wistar albino rats was used as a semi permeable membrane. On the dorsal side of the skin, which is exposed to the donor compartment, 100 mg of formulation was placed and samples of 5 mL were withdrawn at intervals of 90 minutes. Fresh phosphate buffer pH 7.4 (5 mL) was replaced to maintain a volume of receptor fluid. The samples were analyzed at 244 nm against fresh receptor fluid as blank. Diffusion was carried out in the same manner as for the test formulations for the bases used in the formulations without incorporating valdecoxib. Diffusion profile of valdecoxib from all formulations was calculated, as described above. Results are given in Fig. I.

Physical evaluation

Physical appearance was observed visually. pH was measured using a pH meter. Spreadability was observed by spreading 1 g of formulation on a clean even glass surface. Consistency was measured by measuring the yield value using a penetrometer (8, 9). Stability of the gel was determined by observing syneresis following the freeze-thaw cycle (8, 9).

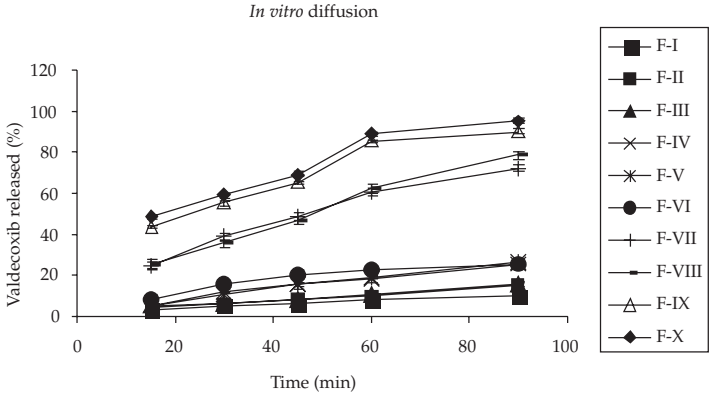

Fig. 1. *In vitro* diffusion profile of F-I to F-X (mean ± SD, n = 3).

Pharmacological evaluation

Male Wistar albino rats, 4–6 weeks old, weighing 120–180 g, were used for the studies. Each group consisted of six animals. The animals were fed a balanced rodent pellet diet and tap water *ad libitum*. All animals were obtained from inbred strains from the C. L. Baid Metha College of Pharmacy's animal house (Chennai, India). The study protocol was approved by the institutional animal ethics committee. The animals were housed at room temperature of 28 ± 1 °C with 12 h light/dark cycle. All animals were randomly assigned to different groups and a period of one month was allowed for adaptation before commencement of each experiment. In all evaluations group I (control) was the placebo group (F-O); group II was reference standard (rofecoxib gel, 1%, *m*/*m*) group and groups III, IV, V and VI were test groups (F-X, F-Xa, F-Xb, F-Xc) with 1, 0.5, 1.5 and 2% (*m*/*m*) valdecoxil in the gel, respectively (see Table I).

Acute skin irritation study

Dorsal hairs at the back of the rats were clipped off one day prior to the commencement of the study. Animals showing normal skin texture were housed individually in cages with copography meshes to avoid contact with the bedding. One side of each animal was used for intact study and the other for testing on abraded skin. Abrasion was non-bleeding incision of stratum corneum. About 50 mg of test sample was applied over one square centimeter area of intact and abraded skin. Animals were immobilized in a restrainer for 24 h. Skin responses were evaluated according to the visual analog scale used in the Draize technique (10, 11).

Inhibition of carrageenean induced paw edema (acute model)

Test samples containing 0.5% (group IV), 1% (group III), 1.5% (group V), 2% (group VI) (*m*/*m*) of valdecoxib in the gel base were prepared and examined for topical anti-inflammatory action as described above. Results are given in Table II.

Table II. Inhibition of carrageenean induced paw edema[a]

Group	Edema volume (mean ± SEM, mL)[b,c] after				
	1 h	2 h	3 h	4 h	5 h
I	0.15 ± 0.04	0.19 ± 0.04	0.26 ± 0.06	0.30 ± 0.06	0.34 ± 0.06
II	0.12 ± 0.01[c] (20.0)	0.15 ± 0.04[c] (21.0)	0.12 ± 0.07[c] (53.8)	0.10 ± 0.01[c] (66.7)	0.10 ± 0.01[c] (70.6)
III	0.12 ± 0.04[c] (20.1)	0.16 ± 0.06[c] (21.3)	0.18 ± 0.09[c] (30.8)	0.16 ± 0.02[c] (46.7)	0.13 ± 0.07[c] (61.8)
IV	0.12 ± 0.00[c] (20.0)	0.15 ± 0.04[c] (21.0)	0.18 ± 0.06[c] (30.8)	0.19 ± 0.06[c] (36.7)	0.20 ± 0.07[c] (41.2)
V	0.13 ± 0.04[c] (13.3)	0.15 ± 0.06[c] (21.0)	0.17 ± 0.06[c] (34.6)	0.15 ± 0.04[c] (50.1)	0.13 ± 0.04[c] (61.8)
VI	0.13 ± 0.04[c] (13.3)	0.15 ± 0.04[c] (21.0)	0.16 ± 0.05[c] (38.5)	0.14 ± 0.03[c] (53.3)	0.13 ± 0.04[c] (61.8)

[a] Dose per paw applied – 200 mg valdecoxib except for the control in which placebo gel was used.
[b] Each group has 6 animals.
[c] Inhibition (%) is given in parentheses.
[d] Significant difference compared to group I (control) ($p < 0.05$).

Volume of unilateral hind paws of test animals was measured. On each paw, 100 mg of test preparation was carefully rubbed twice 1 and 2 h before carrageenean administration. The test animals were placed in cages with meshes to avoid coprophagy. 0.1 mL of carregeenean 1% (m/V) was injected subcutaneously into the paw and the volume of hind paw was measured at hourly intervals for 5 h using a mercury plethysmometer (10, 11). Percentage inhibition was calculated. Results are given in Table II.

Inhibition of carrageenean induced hyperalgesia

An exaggerated response to moderate stimuli in a paw injected with carrageenean was evaluated by the standard method (12), where the thermally evoked paw withdrawal latency was determined. Results are given in Table III.

Table III. Inhibition of hyperalgesia

Group	Paw withdrawal latency (mean ± SEM, s) after			
	1 h	2 h	3 h	4 h
I	4.3 ± 0.4	3.1 ± 0.4	2.7 ± 0.3	2.7 ± 0.3
II	11.2 ± 0.3[a]	9.3 ± 0.2[a,b]	9.2 ± 0.4[a,b]	8.2 ± 0.3[a,b]
III	11.6 ± 0.3[a]	11.2 ± 0.3[a,b]	10.3 ± 0.3[a,b]	9.5 ± 0.2[a,b]

[a] Significant difference compared to group I (control) ($p < 0.05$).
[b] Significant difference between groups II and III ($p < 0.05$).

Inhibition of proliferation of the granulation tissue (sub-acute model)

Sterile cotton (20 ± 1 mg) soaked in 0.2 mL of distilled water containing penicillin (0.1 mg) and streptomycin (0.13 mg) was implanted subcutaneously bilaterally in the lumbar region under ether anesthesia and animals were divided into three groups (control, standard, test). Topical application (twice a day for seven days) of the preparation was done on normal skin over the cotton-implanted site. On the 8th day after sacrifice, granular tissue, proliferated around the cotton was removed, dried (60 °C for 24 h) and weighed. Mass of the tissue was determined and used as the basis for evaluation (13, 14).

Inhibition of adjuvant arthritis (chronic model)

Heat-killed *Mycobacterium tuberculosis* H37RA was used to prepare complete Freund's adjuvant (15). The prepared complete Freund's adjuvant (0.1 mL equivalent to 0.6 mg), was injected subcutaneously into the plantar site of the right hind paw of male Wistar albino rats under ether anaesthesia. After 14 day, animals with secondary inflammation (left hind foot, bilateral front foot and/or tail) were selected. On the 15th day, the test and standard preparations were applied once a day for 7 days. After 5 h, the paw was rinsed with warm water and edema was measured daily on the right hind paw for 7 days. Results are given in Table IV.

Table IV. Inhibition of adjuvant arthritis

Day	Group I	Group II	Group III
	Paw volume (mean ± SEM, n = 6, mL)[a,b]		
1	0.11 ± 0.0	0.12 ± 0.0	0.11 ± 0.01
15	0.21 ± 0.01	0.13 ± 0.01 (36.9)	0.16 ± 0.01 (22.3)
16	0.22 ± 0.01	0.12 ± 0.01 (45.45)	0.14 ± 0.01 (42)
17	0.26 ± 0.01	0.14 ± 0.01 (46.2)	0.13 ± 0.01 (50)
18	0.26 ± 0.01	0.14 ± 0.01 (46.2)	0.13 ± 0.01 (50)
19	0.28 ± 0.01	0.11 ± 0.01 (64.3)	0.13 ± 0.01 (53.6)
20	0.28 ± 0.01	0.10 ± 0.01 (64.3)	0.12 ± 0.01 (57.1)
21	0.28 ± 0.01	0.10 ± 0.01 (64.3)	0.11 ± 0.01 (60.7)

[a] Values in parentheses indicate the percentage of reduction in paw volume compared to the control.
[b] Significant difference compared group I (control) ($p < 0.05$).

Valdecoxib concentration in plasma and bleeding and clotting time

Gel formulation F-X (100 mg) was applied on the hind paw of six healthy male Wistar rats, twice a day for one week, blood was collected by retro-orbital puncture. Plasma samples were analyzed for valdecoxib by the reported RP-HPLC method (16).

Blood clotting time and bleeding time of the rats were measured by the reported method (17). Following this, F-X (100 mg) was applied on the hind paw of the test animals twice a day for one week. Blood clotting and bleeding time were measured after this treatment.

Statistical analysis

All results are expressed as mean ± SD or mean ± SEM. Differences were compared using one-way ANOVA followed by Dunnet's *t*-test.

RESULTS AND DISCUSSION

Valdecoxib content in all prepared formulations F-I to F-X was theoretically 1% (*m*/*m*). In evaluation, it varied between 0.75 ± 0.51 and 1.58 ± 1.23 (mean ± SD, %). Among the preparations, F-IX and F-X, which are gels prepared using Carbopol and Carbopol 940, respectively, exhibited drug contents of 1.04 ± 0.16 and 0.98 ± 0.25 (mean ± SD, %).

Drug release results show that F-IX and F-X release more than 40% of the drug within the first 15 minutes and F-X releases a maximum of 95.6% after 90 minutes (Fig. 1). Other preparations did not release valdecoxib to the extent observed for F-IX and F-X. Based on the above results, F-X was selected for further study.

Physical appearance was observed visually. F-X was translucent, smooth in texture. pH was 6.7 ± 0.1. This is approximately neutral and may be suited for topical application without any discomfort. F-X gel spreads smoothly on a clean even glass plate with minimum pressure without any solid or gritty particles. Yield value measured for F-X was $(121.6 \pm 0.1) \times 10^{-5}$ kPa. There was no syneresis for F-X when subjected to the freeze--thaw cycle formulations. Absence of syneresis is an indicator of gel stability. The results show that the gel base with Carbopol 940 (F-X) is pharmaceutically acceptable for formulating valdecoxib.

Preliminary test for irritation resulted in selecting the gel for further tests because it proved to be non-irritant. As valdecoxib is 28,000 times more selective in binding with COX-2 receptor than with COX-1 and rofecoxib is 800 times more selective (18), hence, effectiveness of valdecoxib was evaluated against rofecoxib. Also, in clinical trials rofecoxib was used for comparison with valdecoxib (19).

In the pharmacological test, valdecoxib gel showed a significant anti-inflammatory activity when tested on various models of inflammation. Commercial gel containing rofecoxib was used as reference standard in all evaluations. In the acute model, test formulation F-X showed 61.8% inhibition. The reference standard, rofecoxib gel showed 70.6% inhibition (Table II). In the subacute model of inflammation, reference rofecoxib showed significantly ($p < 0.05$) better anti-proliferative effect (61.8%), than formulated valdeco-

xib in F-X (41.2%). Valdecoxib at 0.5% (*m*/*m*) was ineffective in reducing edema and at 1.5 and 2.0% no significant added effect was seen compared to 1% valdecoxib added. In the chronic model (Table IV), rofecoxib exhibited significant ($p < 0.05$) inhibition to the extent of 64.3% on the 19th day after adjuvant induction and formulated valdecoxib showed 60.7% 21 days after adjuvant induction. In this study, rofecoxib was significantly ($p < 0.05$) better than both placebo gel and F-X. Valdecoxib gel F-X possessed significant anti-nociceptive effect topically, as observed in the carrageenean induced hyperalgesia model (Table III). The paw withdrawal latency was evaluated at hourly intervals for a period of 4 h from the time of the application of the placebo gel, reference standard and F-X. The paw withdrawal latency was enhanced to 9.5 seconds with F-X valdecoxib gel, 8 seconds with commercial rofecoxib gel against the 2.6 seconds for the control at the end of the 4th hour. There is a significant ($p < 0.05$) difference between the control and group III that received treatment with F-X formulation. Group III also exhibits significant ($p < 0.05$) difference in pain perception as exhibited by prolongation in the paw withdrawal latency after the 2nd, 3rd and 4th hours when compared to group II. This shows that the anti-nociceptive effect is better for valdecoxib (F-X) than rofecoxib (commercial gel-reference standard). This observation is in concurrence with the results of a study done by Christensen *et al.* (20), who reported that valdecoxib was superior to rofecoxib in relieving acute post-surgical pain when administered orally. The optimum drug concentration required to elicit anti-inflammatory effect was found to be 1% *m*/*m* To conclude, rofecoxib gel is significantly better for anti-inflammatory action whereas valdecoxib gel is more effective for the anti-nociceptive action in the carrageenean induced hyperalgesia model.

Serious side effects of valdecoxib may be due to the expression of COX-2 receptors in vascular endothelium (16). Literature reports show that daily administration of 10 mg kg^{-1} body mass of valdecoxib to male Wistar rats, along with aspirin at a dose of 100 mg kg^{-1} body mass, continuously for 4 weeks significantly alters certain hemostatic parameters. The blood plasma level of valdecoxib above 101.1 ng mL^{-1} is associated with risks like alteration in cardiovascular events (16). A preliminary attempt to quantitatively estimate valdecoxib in rat plasma was executed by the RP-HPLC method. Valdecoxib was not detected by the reported method. This tentatively proves that valdecoxib is not absorbed to a measurable extent in the systemic circulation after local application. Therefore, it may be hypothesized that F-X gel is safe without any serious side effects. Blood clotting time and bleeding time were 124 ± 4 (mean ± SEM, $n = 6$) (in seconds), 87 ± 2 before treatment, and 123 ± 3 and 88 ± 3, respectively, after treatment. There is no significant difference in blood bleeding and clotting time before and after treatment.

CONCLUSIONS

Topical route of application has a great potential as an effective and safe way to administer valdecoxib for local analgesic effect. Preliminary blood tests in rats may indicate negligible systemic absorption and side-effects. Not detectable levels of valdecoxib in the animals plasma may point to negligible systemic absorption, thereby leading to negligible side-effects. Blood bleeding and clotting times were not affected. Further experiments are to be conducted in other animal models for analgesic and anti-inflammatory effect. Based on the results of these tests, trials may be performed on humans.

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S A Ž E T A K

Dozirani pripravak valdekoksiba za topičku primjenu: Priprava i farmakološka evaluacija

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Valdekoksib, selektivni COX-2 inhibitor, primijenjen peroralno urokuje ozbiljne nuspojave, zbog čega je povučen iz uporabe. U ovom radu izrađen je i evaluiran pripravak valdekoksiba za topičku primjenu. Uporabljeni su standardni postupci za procjenjivanje protuupalnog i analgetskog djelovanja na muškim Wistar albino štakorima. Priređene su masti, kreme i gelovi s udjelom valdekoksiba od 1% (*m/m*) kojima je procijenjen fizički izgled, pH, mazivost, ujednačenost sadržaja ljekovite tvari, *in vitro* difuzija. Nakon analize rezultata, za farmakološka ispitivanja je izabran gel s Carbopol 940 (F-X). Procijenjena je akutna iritacija kože tog pripravka, njegov protuupalni učinak, optimalna koncentracija valdekoksiba, učinak na stanje hiperalgezije, inhibicija stvaranja granulocita i antiartritični učinak. Za procjenu sigurnosti topičke primjene valdekoksiba, određena je njegova koncentracija u krvnoj plazmi, te vrijeme zgrušavanja krvi. Gel s udjelom valdekoksiba 1% (*m/m*) imao je značajno veći učinak u inhibiciji hiperalgezije povezane s upalom ($p < 0,05$) nego placebo pripravak, ali je imao značajno manji učinak ($p < 0,05$) od gela s rofekoksibom. Analiza plazme na prisutnost valdekoksiba ukazuje na niski rizik sistemskog učinka. Vrijeme krvarenja i zgrušavanja nije se bitno promijenilo prije i poslije uporabe F-X. Zbog toga bi ovaj pripravak mogao biti alternativa peroralnim pripravcima.

Ključne riječi: valdekoksib, gel za topičku primjenu, *in vitro*, *in vivo* evaluacija

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