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RESEARCH ARTICLE

FORMULATION AND EVALUATION OF CELECOXIB GEL

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ABSTRACT:
The present research has been undertaken with the aim to develop a topical gel formulation of celecoxib, which would attenuate the gastrointestinal relater toxicities associated with oral administration and to investigate the effect of DMSO on permeation of celecoxib. Celecoxib is a highly selective cyclooxygenase-2 (COX-2) inhibitor. In the present study gel with different concentrations of carbapol, sodium alginate and sodium carboxy methylcellulose were prepared. Gels were subjected for various evaluation tests such as pH measurement, spreadibility and extrudability. In-vitro dissolution studies were performed in phosphate buffer of pH 5.6 and polyethylene glycol 400 (7.4 pH) for 12 hrs by using Keshary-Chien diffusion cell apparatus. The gel formulation consisting of 7.5% w/w sodium alginate with DMSO found to be suitable for topical application based on in vitro evaluation. Sodium alginate based gels with DMSO revealed of 90% cumulative drug release after 12 hours. From the above observations, Sodium alginate seems to be a promising pharmaceutical adjuvant in the formulation of celecoxib gels.
Keywords: Celecoxib, In-*vitro* release, DMSO, gel, Transdermal delivery.

INTRODUCTION

Drug delivery through the skin has been a promising concept for a long time because skin is easy to access, has a large surface area with vast exposure to the circulatory and lymphatic networks and the route is noninvasive. Transdermal gel preparations are intended for superficial skin application or to some mucosal surfaces for local action or skin penetration of medicament or for their soothing or protective action. The nonsteroidal anti-inflammatory drugs (NSAID's) are having excellent anti-inflammatory and analgesic activity but NSAID's produces GIT ulceration, liver and kidney trouble in case of oral administration. To avoid the adverse effect, alternate routes of administration have been tried by investigators.[1] The aim of this study was to develop suitable transdermal gel formulations of celecoxib using various gelling agent with permeation enhancers in order to reduce adverse drug reaction associated with oral formulations.

Celecoxib was the first synthesized non-steroidal anti-inflammatory drug (NSAID) able to selectively inhibit COX-2 activity[2] and exhibits anti-inflammatory, analgesic and antipyretic activities. It is chemically designated as 4-[5-(4-methylphenyl)-3- (trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide and is a diaryl substituted pyrazole. It has been used in the treatment of rheumatoid arthritis, osteoarthritis, acute pain familial adenomatous polyposis, and primary dismenorrhea. Long term oral administration of celecoxib causes serious side effects, such as gastrointestinal toxicity, gastric mucosal ulceration, hemorrhage and recently, cardiotoxic effects, that restrict its oral use and make it a good candidate for transdermal administration.[3] These potential side effects may be overcome by the topical administration of the drug .This route of drug delivery has gained popularity because it avoids first pass effects, gastrointestinal irritation, and metabolic degradation associated with oral administration. Skin permeation enhancers could be used to improve drug skin penetration.[4] Also, celecoxib having molecular weight of 381.38 and melting point in the range of 157-158^{o}C can be considered ideal to permeate through the skin. An attempt has been made to use three different polymers of different class viz. natural, semi-synthetic and synthetic and evaluate the effect of these on release kinetics of the drug.

The reasons for incorporating the drug Celecoxib into transdermal (Gel) drug delivery system include, it is non-irritating to the skin, it is extensively bound to plasma proteins (97%), has short biological half-life & low molecular wt., could provide localized action at particular site. Also topical gels are non occlusive, easy to wash/clean, non staining hence have advantages over other topical routes.

MATERIALS:

Celecoxib was a kind gift sample from Alembic chemical works, Baroda. Carbapol 934 P was procured from Research Labs. Sodium carboxy methyl cellulose and Sodium alginate were procured from Loba chemie Mumbai. All other ingredients used were of analytical grade.

METHODS:

Various gel formulations were prepared using carbopol P 940, sodium alginate and sodium CMC as gelling agents. Required quantity of gelling agent was weighted and dispersed in a small quantity of distilled water to form a homogeneous dispersion. 1% of Celecoxib was dissolved in suitable solvent (propylene glycol or ethanol) and added

to the above solution. Other excipients were also added with continuous stirring. In carbopol gels, pH of the gel was brought to skin pH by Triethanolamine. During pH adjustment, the mixture was stirred gently with a spatula until homogeneous gel was formed. All the samples were allowed to equilibrate for at least 24 hours at room temperature prior to performing rheological measurements.[5-10] Final weight of the gel was adjusted to 50 g with distilled water. The gels were stored in wide mouthed bottles. Entrapped air bubbles were removed. The prepared celecoxib gels were inspected visually for their color. The pH was measured using a pH meter reading at room temperature. Similarly gel formulations of celecoxib were prepared using carbopol P 940 sodium CMC and sodium alginate with DMSO.

Table 1: Composition of Optimized formulae of celecoxib gels

Formulations	Celecoxib	Carbapol	Sodium alginate	Sodium CMC	Chloroform	Tri-ethan olamine	PEG 400	DMSO	Alcohol 66 %v/v q.s.	Glycerin	Methyl paraben	Purified water (q.s.)
F_1	1.00	2	--	--	10.00	1.65	04.00	---	100.00			
F_2	1.00		6.25		10.00			---		10.00	0.2	100
F_3	1.00			3.00	10.00				10	15.00	0.2	100
F_4	1.00	2			10.00	1.65	04.00	2.00	100.00			
F_5	1.00		6.25		10.00			2.00		10.00	0.2	100
F_6	1.00			3.00	10.00			2.00	10	15.00	0.2	100

All the values mentioned in the table are in %W/W

EVALUATION OF CELECOXIB GEL

The prepared gels were evaluated for physical appearance, spreadability, pH, Extrudability drug content, and *in vitro* release study. The physical appearance and homogeneity of the prepared gels were tested by visual observations.

pH:

The pH of the gel formulations was determined using a pH meter (Elico LI 120). The measurement was performed at 1st, 15th and 30th day after preparation to detect any pH fluctuations with time.

Extrudability:

In the present study, the method adopted for evaluating gel formulation for extrudability was based upon the quantity in percentage of gel extruded from aluminum collapsible tube on application of weight in grams required to extrude at least 0.5 cm ribbon of gel in 10 seconds. More quantity extruded better was extrudability. The measurement of extrudability of each formulation was in triplicate and the average values are presented.[11] The extrudability was then calculated by using the following formula:

Extrudability = Applied weight to extrude gel from tube (in gm) / Area (in cm2)

Spreadability:

Spreadability was measured using the spreadability apparatus. The apparatus consists of two slides in which one slide is firmly fixed in a wooden frame while the other slide can easily slide over the surface of the fixed one. An excess of gel was placed between the two slides of the apparatus. A weight of 1Kg was allowed to rest on the slide for 5 minutes so that a uniform film of gel was formed and the air between the slides was expelled. The excess gel was removed carefully from the edges of the slides. The bottom slide was properly anchored and the top slide was subjected to a pull of 80 gms weight. The time (in seconds) required by the top slide to cover a distance of 7.5 cm be noted. A shorter interval indicates better Spreadability.[12-16]

Spreadability was then calculated using the following formula:

$$S = M \times L / T$$

Where, S = is the spreadability, M = is the weight in the pan (tied to the upper slide), L = is the length moved by the glass slide and T = represents the time taken to separate the slide completely

In vitro drug release:

The in vitro drug release from gel formulations was studied across cellophane membranes using modified Keshery Chien diffusion cell[17]. The receptor compartment was filled with the mixture of phosphate buffer of pH 5.6 and polyethylene glycol 400 adjusted to pH 7.4 and maintained at 37 ± 0.5°C C with constant magnetic stirring. Accurately weighed quantity of gel was placed on the donor compartment. The samples (1ml) was collected from the receptor compartment at predetermined time interval and replaced by equal volume of fresh receptor solution to maintain constant volume allowing sink condition throughout the experiment. The amounts of celecoxib in the sample were assayed spectrometrically (Systronics 119 UV-Vis spectrophotometer) at 252 nm against appropriate blank.

RESULTS AND DISCUSSION

Physical examination

The prepared Celecoxib gel formulations were transparent in carbopol 934, white viscous in Na-CMC and brownish gummy in sodium alginate with a smooth and homogeneous appearance. This might be due to the nature of gelling agent, carbapol being synthetic might be of most pure quality giving a clear appearance, while sodium CMC

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being of semisynthetic category is resembling white viscous behavior. Sodium alginate was used as a natural gelling agent but due to the nature of alginic acid the formulation appeared brownish and gummy. They were also less viscous as compared to the other two. All the formulations were easily spreadable (Table 2). The pH values of all the prepared formulations ranged from 6.5 to 7.0, which were considered acceptable to avoid the risk of irritation upon application to the skin.[18, 19]

Table 2: Physicochemical properties of celecoxib gels

Formulation	pH	Spreadability Gm-cm/sec	Extrudability	Mean % drug release after 12 hrs ± SD
F_1	6.70 ± 0.03	11.69	15.17	71.66±0.4674
F_2	7.09 ± 0.04	14.39	17.19	81.61±0.5609
F_3	6.56 ± 0.03	13.14	14.13	72.33±0.4795
F_4	6.35 ± 0.04	11.71	15.19	79.58±0.7158
F_5	6.39 ± 0.01	14.41	17.28	89.55±0.3308
F_6	6.54 ± 0.02	13.15	14.33	75.43±0.5774

In-vitro Diffusion Studies

Diffusion studies were performed using Keshary-Chien diffusion cell apparatus. Accurately weighed quantity of sample was placed over the cellophane membrane which was placed over the donor compartment. Aliquots of sample were withdrawn at specific intervals & drug release was determined. At the end of 12 hours the mean % drug release from 2% carbapol gel was found to be 73 %, from 7.5 % Sodium alginate gel was found to be 82% & from 3 % Na-CMC gel was found to be 72.3 %.

The release studies clearly reveal that the drug celecoxib is released to a lesser extent from both synthetic and semisynthetic polymers. These polymers might be retarding the release of the drug while the drug is released to a greater extent in sodium alginate as it is natural in nature.

Table 3: In-Vitro Comparative Drug Release Profile of Formulation **F_1, F_2, F_3, F_4, F_5 and F_6 in %**

Time in hours	F_1	F_2	F_3	F_4	F_5	F_6
0	0	0	0	0	0	0
1	08.81	08.86	08.00	08.26	08.21	08.18
2	16.50	17.71	16.55	21.18	19.70	14.61
3	19.94	20.72	21.53	27.40	27.34	23.91
4	40.87	41.96	40.49	40.79	44.37	41.41
5	45.85	52.93	43.37	52.41	65.38	51.17
6	54.92	79.95	55.01	71.49	83.89	57.72
12	71.66	81.61	72.33	79.58	89.56	75.43

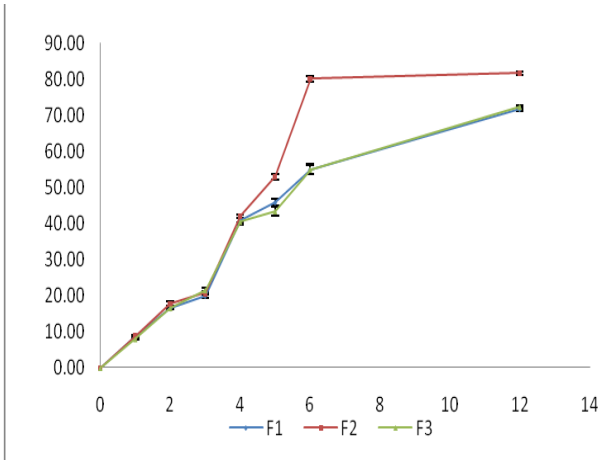

Figure 1: Comparative In-Vitro Release profile from Formulation F_1, F_2, F_3 (without DMSO)

Effect of penetration enhancer

One of the approaches for improving the topical drug delivery is use of penetration enhancer. In this study use of Dimethyl sulphoxide as penetration enhancer on the permeation of celecoxib has been studied. Diffusion characteristics as 2% carbapol gel was found to be 80 %, from 7.5 % Sodium alginate gel was found to be 90% & from 3 % Na-CMC gel was found to be 75.43 %. A net raise in penetration was observed to an extent of about 9%.

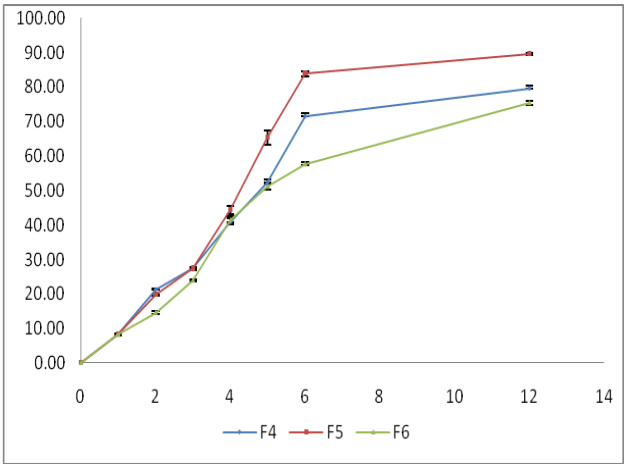

Figure 2: Comparative In-Vitro Release profile from Formulation F_4, F_5, F_6 (with DMSO)

CONCLUSION:

From above results, it can be concluded that celecoxib gel formulations were prepared with different gelling agents: carbopol, Na CMC and sodium alginate showed acceptable physical properties and drug release study. All prepared gel showed acceptable physical properties concerning color, homogeneity, consistency, spreadability and pH value. Among all gel formulations, sodium alginate gel shows superior drug release followed by Na CMC, and Carbapol 940P showed decreasing order of drug release. In carbopol gel formulations, the drug release was decreased with increase in carbopol concentration because polymer concentration increases, viscosity increases. All gel formulations containing penetration enhancer (DMSO) were used. From the above results it can be concluded that the celecoxib gel formulation F5 containing 6.25% sodium alginate with 2% DMSO was suitable for topical application.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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