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Preparation and Evaluation of Topical Gel of Valdecoxib

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ABSTRACT
Topical gels of Valdecoxib topical gel prepared using different gelling agents (Viz, carbopol, HPMC, sodium alginate, sodium CMC). Formulations were evaluated for pH, rheological behavior, drug content and in vitro drug diffusion. Selected formulations of all the gelling agents appeared to be non-Newtonian and pseudo plastic behavior. Drug content was high (>98 %) in gels. Drug release from the carbopol gels increased with the increase in the concentration of PG up to 10 %. However, drug release decreased as the concentration of the PG increased to 20 %. The drug release increased with the increase in concentration of ethanol. In case of gels containing HPMC, sodium alginate, sodium CMC as gelling agents, addition of PG up to 5 %, increased the release of drug from the gels. However, release decreased with increase in the concentration of PG up to 10 %. In case of HPMC gels, addition of ethanol decreased the release of Valdecoxib from the gels. It is concluded that PG is a good penetration enhancer and carbopol good gelling agent for Valdecoxib gels.

Keywords: Valdecoxib; topical gel; carbopol; HPMC; sodium CMC; sodium alginate; *In vitro* release study.

INTRODUCTION

Today many dosage forms are available; most of them are given by oral and parentral routes. Oral route is widely used, but it follows GI-side effects, first-pass metabolism and results decreases in the bioavailability of the drug. In such cases, parentral preparations are better than oral preparations as it avoid GI metabolism and first pass effect. Formulation of parentral preparations requires well equipped laboratory with aseptic area. These make parentral preparation costlier. [1-3] Topical preparations avoid the GI-irritation, prevent the metabolism of drug in the liver and increase the bioavailability of the drug. Topical preparations give its action directly at the site of action. Valdecoxib is chemically, 4 (5-methyl-3-phenyl-isoxazolyl) benzene sulfonamide and is a diaryl substituted isoxazole. It exhibits anti – inflammatory activity, analgesic and antipyretic properties. [4-5] The mechanism of action is believed to be due to inhibiting prostaglandin synthesis primarily through inhibition of COX-2. Valdecoxib when presented in the form of topical gel can reduce local inflammations. Hence for local inflammation or pain in the body, the topical application of Valdecoxib may be useful which also reduces the side-effects associated with oral therapy.

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In a study, the efficiency, safety and tolerability of Valdecoxib gel (1 %) in adult patients was evaluated. There was a significant decrease in the mean pain visual analogue scale. Onset of pain relief was within 15 min. The study confirmed that Valdecoxib gel (1 %) is an effective and safe option for the management of painful inflammatory joint condition. [6-9] Although the gel formulation of Valdecoxib seems to be highly useful, there is lack of literature on the formulation and evaluation of Valdecoxib gel. Therefore in the present work, it is planned to prepare and evaluate Valdecoxib gels using different gelling agents.

MATERIALS AND METHODS

Materials

Valdecoxib was gifted sample from Virdev Intermediates Pvt. Ltd., Surat, carbopol 940, sodium-alginate, sodium-CMC, propylene glycol, triethanolamine were purchased from S. D. Fine. chem. Pvt. limited, Mumbai and HPMC from N. R. chem. Pvt limited- Mumbai.

Preparation of gels

Various gel formulations were prepared using carbopol 940, HPMC, sodium alginate, 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. The drug was dissolved in suitable solvent (propylene glycol or ethanol) and added to the above solution. Other excipients (methyl paraben and propyl paraben) were also added with continuous stirring. In

carbopol gels, pH of the gel was brought to skin pH by Tea (Triethanolamine). The 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 by keeping the gels in vacuum oven for 2 h. The prepared Valdecoxib gels were inspected visually for their color. The pH was measured using a pH meter reading at room temperature.

Evaluation of gel

Rheological study [12]

The removable sample holder of the Brookfield Digital Viscometer was filled with the sample, and then inserted into a flow jacket mounted on the viscometer. A small sample adapter (RV-7 spindle), rotated at a speed of 20 rpm, was used to measure the viscosity of the preparations. The temperature of the sample was kept at 30°C by circulating water through the thermo stated water jacket. The sample was allowed to settle for 5 min prior to taking the reading. Gel viscosity measurements were evaluated using a Brookfield digital viscometer by applying increasing values of the shear rate, in order to reveal possible flow behavior of the gels.

Drug content analysis

1 g of gel was weighed accurately and transferred to 100 ml volumetric flask and dissolved in 1 % SLS. The absorbance of the above solution was measured at 239 nm using appropriate blank solution. The drug content of Valdecoxib was calculated using calibration curve.

***In vitro* Release studies** [10-11]

Valdecoxib release rates from the gels were measured through cellophane membrane using a modified Keishery chein cell[1]. Cellophane membrane allowed to equilibrating with the diffusion medium for 15 minutes by immersing in diffusion medium for 30 minutes. It was then placed on the support screen of the diffusion cell assembly. All the joints were properly sealed with adhesive tape to avoid the penetration of diffusion medium. Aqueous solution of SLS (1 % w/v) solution was used as the receptor medium and 1 g of the test gel was placed on the donor side. The receptor medium was kept at 32^{o}C. At predetermined time intervals, 5 ml samples were taken from the receptor compartment, for 6 h period and replaced by the same volume of fresh 1 % SLS to maintain a constant volume. Absorbance of these solutions was measured at 239 nm using UV/VIS double beam spectrophotometer. Cumulative percent release of valdecoxib was calculated.

Table 1: Details of formulations

Ingredient (g)	C1	C2	C3	C4	C5	C6	H1	H2	H3	H4	H5	A1	A2	A3	M1	M2	M3
Valdecoxib	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Carbopol	0.5	0.5	0.5	0.5	0.5	0.5	-	-	-	-	-	-	-	-	-	-	-
HPMC	-	-	-	-	-	-	1.50	1.50	1.50	1.50	1.50	-	-	-	-	-	-
Na Alginate		--	-	-	-	-	-	-	-	-	-	4	4	4	-	-	-
Na-CMC		-	-	-	-	-	-	-	-	--	-	-	-	-	2.5	2.5	2.5
PG	-	2.5	5	10	5	5	-	2.5	5	-	-	-	2.5	5	-	2.5	5
Alcohol	-	-	-	-	10	25	-	-	-	2.5	5	-	-	-	-	-	-
Methyl Paraben	0.32	0.32	0.32	0.32	0.32	0.32	0.32	0.32	0.32	0.32	0.32	0.32	0.32	0.32	0.32	0.32	0.32
Propyl Paraben	0.62	0.62	0.62	0.62	0.62	0.62	0.62	0.62	0.62	0.62	0.62	0.62	0.62	0.62	0.62	0.62	0.62
Tea	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	-	-	-	-	-	-	-	-	-	-	-
Water	q.s. to 50 g	q.s.to 50 g	q.s. to 50 g	q.s. to 50 g	q.s. to 50 g	q.s. to 50 g	q.s. to 50 g	q.s. to 50 g	q.s. to 50 g	q.s. to 50 g	q.s. to 50 g	q.s. to 50 g	q.s. to 50 g	q.s. to 50 g	q.s. to 50 g	q.s. to 50 g	q.s. to 50 g

Table 2: Evaluation parameters of Valdecoxib topical gel

Formulations	pH	Drug content (%w/w) (±SD), n=3	Jss Flux mcg./cm^2.h (±SD), n=3	Flux R^2 (±SD), n=3	Permeability- coefficient(P) cm/h (±SD), n=3	%Drug released in 180 min (±SD), n=3	%Drug released in 360 min (±SD), n=3
C1	6.5	96.15±0.34	0.06±0.0001	0.9985±0.0006	6×10^{-3}±1.29	3.94 ± 0.07	6.39 ± 0.10
C2	6.7	101.85±0.21	0.08±0.0001	0.9973±0.0007	8×10^{-3}±1.43	4.53 ± 0.02	7.70 ± 002
C3	6.6	96.35±1.35	0.09±0.0001	0.9987±0.0007	9×10^{-3}±1.27	4.88 ± 0.11	8.38 ± 0.09
C4	6.6	97.95±1.76	0.07±0.0001	0.9989±0.0007	7×10^{-3}±1.36	4.10 ± 0.01	6.79 ± 009
C5	6.3	99.45±0.21	0.12±0.0001	0.9926±0.0009	12×0^{-3}±1.38	6.55 ± 0.07	10.73 ± 0.15
C6	6.7	99.95±1.17	0.35±0.0001	0.9930±0.0005	35×10^{-3}±1.42	14.28 ± 0.33	27.80 ± 0.39
H1	6.5	96.66±0.89	0.065±0.0007	0.9978±0.0007	6.5×10^{-3}±1.32	4.00 ± 0.53	6.42 ± 0.27
H2	6.6	97.48±1.52	0.07±0.0007	0.9892±0.0007	7×10^{-3}±1.29	5.19 ± 0.17	7.76 ± 0.09
H3	6.4	99.27±0.10	0.065±0.0007	0.9965±0.0006	6.5×10^{-3}±1.38	4.24 ± 0.04	6.86 ± 0.02
H4	6.4	100.23±0.49	0.05±0.0001	0.9976±0.0007	5×10^{-3}±1.42	3.43 ± 0.10	5.36 ± 0.31
H5	6.5	98.33±1.37	0.06±0.0001	0.9966±0.0006	6×10^{-3}±1.37	3.84 ± 0.16	6.25 ± 0.12
A1	6.8	99.03±0.74	0.06±0.0001	0.9962±0.0003	6×10^{-3}±1.36	3.70 ± 0.07	6.09 ± 0.09
A2	6.9	97.86±0.70	0.09±0.0001	0.9979±0.0001	9×10^{-3}±1.39	5.33 ± 0.07	9.07 ± 0.07
A3	6.9	98.84±0.87	0.07±0.0001	0.9955±0.0007	7×10^{-3}±1.43	4.37 ± 0.04	7.14 ± 0.19
M1	7.0	99.46±0.99	0.06±0.0001	0.9977±0.0008	6×0^{-5}±1.36	3.83 ± 0.03	6.28 ± 0.15
M2	7.0	98.64±0.77	0.07±0.0001	0.9975±0.0007	7×10^{-5}±1.49	4.94± 0.16	7.96 ± 0.17
M3	6.9	98.88±0.98	0.06±0.0001	0.9957±0.0007	9×10^{-5}±1.46	4.14 ± 0.03	6.84 ± 0.11

Table 3: Stability study data of valdecoxib gels:

Formulations	%Drug- content Before stability (±SD),n=3	%Drug- content After stability (±SD),n=3	pH Before stability	pH After stability
C1	96.15±0.34	96.15±0.34	6.5	6.5
C 6	99.95±1.17	99.95±1.17	6.7	6.7
H1	96.66±0.89	96.66±0.89	6.5	6.5
H6	98.22±1.73	98.22±1.73	6.5	6.5
A1	99.03±0.74	99.03±0.74	6.8	6.8
A3	98.84±0.87	98.84±0.87	6.9	6.9
M1	99.46±0.99	99.46±0.99	7.0	7.0
M3	98.88±0.98	98.88±0.98	6.9	6.9

Stability studies

Selected formulations (C1, C6, H1, H6, A1, A3, M1 and M3) which showed comparatively better results were subjected to stability study. Formulations were stored at room temperature for two months. Physical evaluation of the samples stability carried out by visual inspection. Stability was evaluated by pH measurements and Spectrophotometric analysis of the drug content.

Statistical analysis

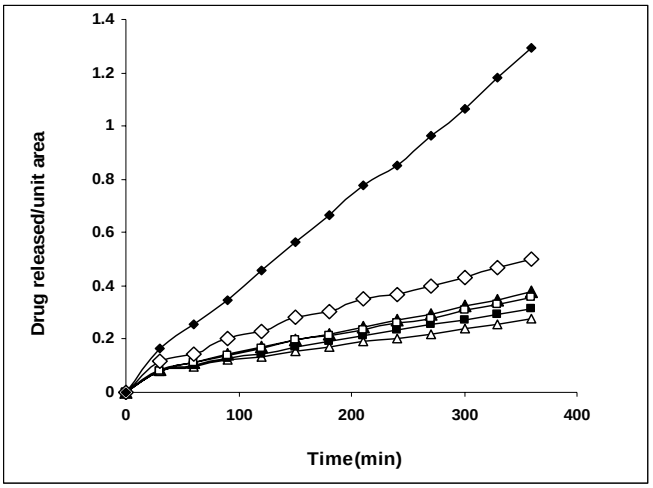
Each tablet formulation was prepared in duplicate, and each analysis was duplicated. Effect of formulation variables on disintegration time and release parameters ($t_{50\%}$ and $t_{80\%}$) were tested for significance by using analysis of variance (ANOVA: single factor) with the aid of Microsoft® Excel 2002. Difference was considered significant when $P < 0.05$.

RESULTS AND DISCUSSION

Valdecoxib (1 %) gels were prepared using various gelling agents such as carbopol, HPMC, sodium alginate and sodium CMC.

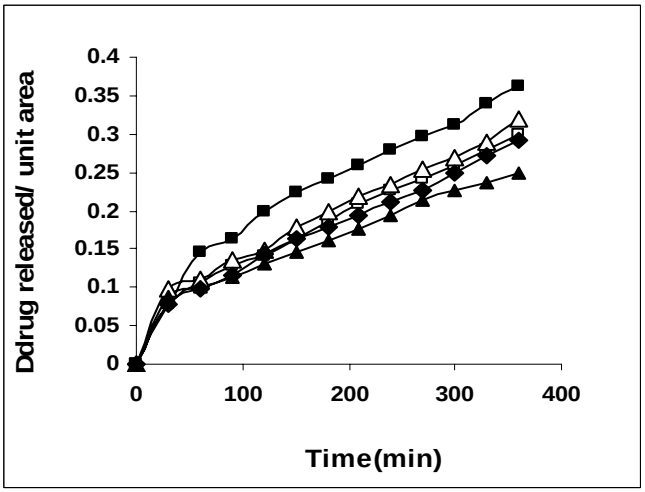
Drug content analysis

Drug content is found to be between 94.52 % and 104.83 %. All the gels show presence of high drug content and low standard deviations of results. It indicates that the drug is uniformly distributed in the gel formulation. Therefore, the method used in this study appears to be reproducible for the preparation of gels.



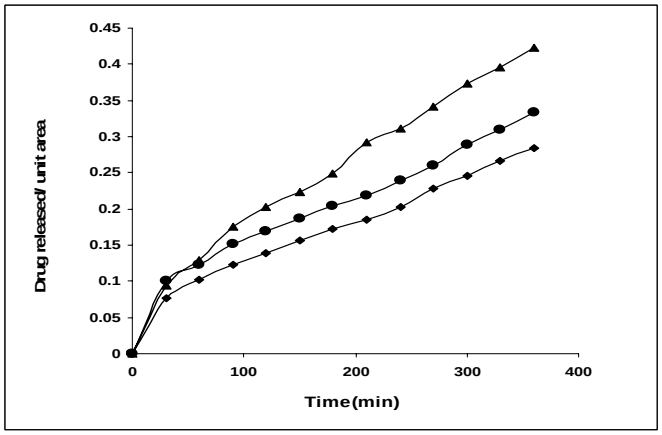
Key:△-C1; □-C2; ●-C3; ■-C4;◇-C5;◆-C6

Fig. 1: Diffusion profiles of Valdecoxib from carbopol gels



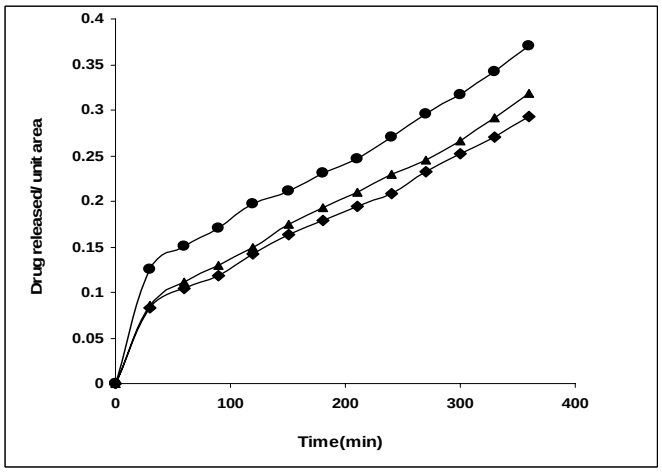
Key: □-H1;■-H2;△-H3;▲-H4;◆-H5

Fig. 2: Diffusion profiles of Valdecoxib from HPMC gels



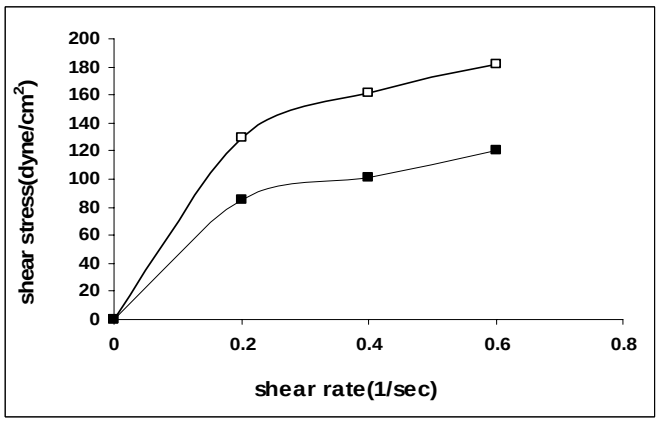
Key: ◆-A1; ▲-A2; ●-A3

Fig. 3: Diffusion profiles of Valdecoxib from sodium alginate gels



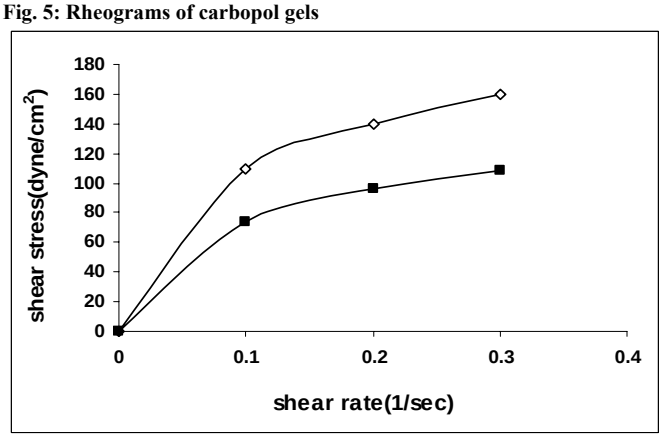
Key: ◆-M1; ▲-M2; ●-M3

Fig. 4: Diffusion profiles of valdecoxib from sodium CMC gels



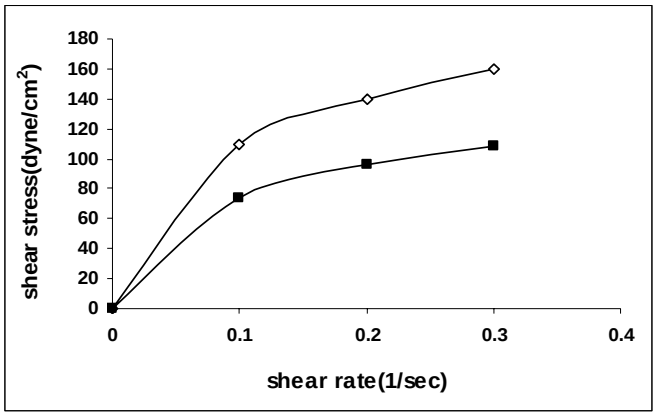
Key: (■) C1 and (□) C6

Fig. 5: Rheograms of carbopol gels



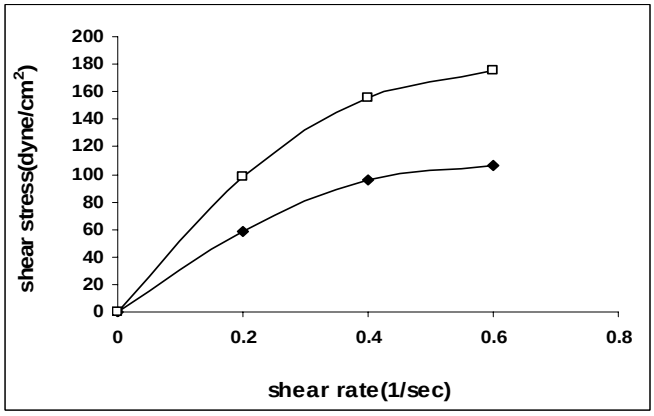
Key: (■) H1 and (□) H6

Fig. 6: Rheograms of HPMC gels



Key: (■) A1 and (□) A6

Fig. 7: Rheograms of sodium alginate gels



Key: (■) M1 and (□) M6

Fig. 8: Rheograms of sodium CMC gels

In vitro release study

Initially gels containing carbopol were prepared and evaluated for appearance, rheology, drug content and in vitro release. The gels were translucent as the drug is poorly soluble. Rheological studies indicated that gels were non-Newtonian and pseudoplastic. Drug content appears to be high (>98 %) and uniformly distributed. In vitro permeation study indicated that flux value of C1 is very less (0.06 mcg × cm^2× h^{-1}) and % released at 180 minutes and 360 minutes are also less 3.94 % and 6.39 % respectively. With an intention to enhance the release, PG was incorporated (5 % to 20 %). Drug release increased with the increase in the concentration of PG up to 10 %. However, drug release decreased when the concentration of PG increased to 20 %. To improve the release ethanol (20 % and 50 %) was incorporated as co-solvent. Drug release increased with increasing concentration of ethanol. A set of gels containing HPMC as gelling agent was prepared and evaluated for appearance, pH, rheology, drug content and in vitro release. Effect of concentration of PG and ethanol on the release of drug was studied. Drug release increased with the addition of PG up to 5 %. However, decreased with the further increase in the concentration of PG up to 10 %. In case of gels prepared with ethanol, a co-solvent, drug release did not improve with the addition of any amount of ethanol (5 % and 10 %). A set of gels containing sodium alginate as gelling agent was prepared and evaluated for appearance, pH, rheological study, drug content and in vitro release. Effect of concentration of PG on the release of drug was studied. Drug release increased with the addition of PG up to 5 %. However, decreased with the further increase in the concentration of PG up to 10 %. A set of gels containing sodium CMC as gelling agent was prepared and evaluated for appearance, pH, rheology, drug content and in vitro release. Effect of concentration of PG on the release of drug was studied. Drug release increased with the addition of PG up to 5 %. However, decreased with the further increase in the concentration of PG up to 10 %.

Stability studies

Formulation which showed promising results, were subjected to stability studies at ambient room conditions for 3 months. After 3 months, gels did not show any change in physical appearance or drug content. It indicates that the drug was stable in gels even after three months of short term storage.

Results indicated that the carbopol gels show higher release of the drug compared to other gelling agents. Therefore, it can be concluded that carbopol is a potential gelling agent for Valdecoxib gels.

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