

FORMULATION AND EVALUATION OF TOPICAL VALDECOXIB GEL

METTU SRIKANTH REDDY*, PRABHAKAR REDDY VEEREREDDY

Department of Pharmaceutics, St Peter's Institute of Pharmaceutical Sciences, Vidyanagar, Hanamkonda, Warangal – 506001, Andhrapradesh, India.
Email: srikanthreddymp@gmail.com.

Received: 19 June 2011, Revised and Accepted: 27 July 2011

ABSTRACT

Topical gels of valdecoxib were prepared using different gelling agents (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 were appeared to be non-Newtonian and showed pseudoplastic behavior. Drug content was high (>98%) in gels. Drug release from the carbopol gels increased with the increase in the concentration of propylene glycol (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 can be concluded that PG is a good penetration enhancer and carbopol as good gelling agent for valdecoxib gels).

Keywords: Valdecoxib, Topical gel, Carbopol, HPMC, Sodium CMC, Sodium alginate, Propylene glycol.

INTRODUCTION

Today many dosage forms are available of which most of them are given by oral and parenteral routes. Oral route is widely used, but it follows GI-side effects, first-pass metabolism and results in decreased bioavailability of the drug. In such cases, parenteral preparations are better than oral preparations as it avoids GI metabolism and first pass effect. Formulation of parenteral preparations requires well equipped laboratory with aseptic area. These make parenteral preparation costlier¹⁻³. Topical preparations avoid the GI-irritation, prevent the metabolism of drug in the liver and increase the bioavailability of the drug. Topical preparations act directly at the site of action².

Valdecoxib (a selective cyclooxygenase - 2- inhibitor) belongs to a family of drugs called nonsteroidal anti-inflammatory drugs (NSAIDs)⁴. NSAIDs mainly used to treat pain and arthritis. 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 properties⁵. 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 therapy⁶⁻⁷.

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 minutes. The study confirmed that valdecoxib gel (1%) is an effective and safe option for the management of painful inflammatory joint condition⁸⁻⁹. 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

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 agents¹⁰⁻¹¹. Required

quantity of gelling agent was weighed 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 was added to the above solution. Other excipients (methyl paraben and propyl paraben) were also added with continuous stirring. In carbopol gels, pH of the vehicle was brought to neutral pH (5-7) by TEA (Triethanolamine). The final weight of the gel was adjusted to 50 gm 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 hr. The prepared valdecoxib gels were inspected visually for their color. The pH was measured using a pH meter reading at room temperature.

Estimation of valdecoxib in the topical gels

1 gram of gel was weighed accurately and transferred to 100 ml volumetric flask and dissolved in 1% sodium lauryl sulfate. 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. The mean percent drug content is given in Table 3.

Rheological study

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. All viscosities measurements were performed at 30°C.

In Vitro Evaluation of Gel

Valdecoxib release rates from the gels were measured through cellophane membrane using a modified Keishery chain cell. Cellophane membrane was allowed for equilibrating with the diffusion medium for 15 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) 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°C. At predetermined time intervals, 5 ml samples were taken from the receptor compartment for 6-hr 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.

Stability study

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.

RESULTS AND DISCUSSION

Table 1 shows the formulae used to prepare the carbopol, HPMC, sodium alginate and sodium CMC gels. When all the formulations were subjected to physical examination, the gels appeared to be translucent. It suggests that the drug did not completely dissolve but dispersed/suspended in the gel matrix. Initially, carbopol (0.5 and 1% w/w) based gels were prepared using 1% valdecoxib in the gels. In order to neutralize the gels and adjust the pH of the gel to be compatible with the normal pH of the skin (pH 5-7), triethanolamine is used. Gels containing 0.5 % carbopol were thin and leaked out of the tubes at room temperature. Therefore, further studies were not performed with these gels. Methyl paraben and propyl paraben have been used as preservatives for gels. The transport behavior of valdecoxib is investigated systemically by varying the concentration of carbopol (1% w/w), PG (5 to 10% w/w) and alcohol (20 to 50 % w/w).

Rheological study

Since, viscosity is a measurement at only one shear rate, different types of materials (Newtonian and non-Newtonian) can have the same viscosity. Therefore, a wider range of shear rate values was studied to establish the gel nature. Plots of shear rate versus shear stress are shown in Figures 1, 2, 3 and 4 respectively for carbopol, HPMC, sodium alginate and sodium CMC gels. All the systems showed non-Newtonian flow and exhibited pseudoplastic behavior, suggesting that gels do not flow at low shear stress and room temperature.

In vitro release study

Figure 5 shows the permeation profiles of carbopol formulations (C1-C6). The steady state flux values of these formulations are shown in Table 3. The steady state flux of C1 is $0.06 \text{ mcg} \times \text{cm}^{-2} \times \text{h}^{-1}$. Addition or increase in the concentration of propylene glycol increased the steady state flux values (in the order of $C3 > C2 > C4 > C1$). It suggests that the permeation of valdecoxib increased with the addition of propylene glycol. The solubility of the drug in the vehicle will influence the partition coefficient of the drug. Addition of propylene glycol might have increased the solubility of the drug and hence partition coefficient of the drug between the gel and barrier, in turn increased the penetration rate of drug. The release rates of valdecoxib from these formulations are listed in Table 2. The formulations containing propylene glycol (C2 and C3) showed increase ($p < 0.05$) in release with increase in the concentration of propylene glycol in the gels. It indicates that propylene glycol provided more solubilised drug in the vehicle. However, the flux and permeability coefficient values decreased from as the propylene glycol increased from 10 to 20 % (C4) in accordance with Trotter et al 2004¹² investigations.

The results of our study may be attributed to the higher dilution of valdecoxib in higher concentration of propylene glycol (20%) and simultaneously, competitive higher flux of propylene glycol due to the large differences in size of PG and valdecoxib (molecular weight-76 and 314 respectively). Of all the formulations containing propylene glycol (C2 - C4), formulation containing 10% propylene glycol (C3) showed higher flux values. Therefore, to study the effect of co-solvent, ethanol, was incorporated in the formulations (C5 and C6). The steady state flux values found to increase (from $0.12 \text{ mcg} \text{ cm}^{-2} \text{ h}^{-1}$ to $0.35 \text{ mcg} \text{ cm}^{-2} \text{ h}^{-1}$) with the addition of ethanol (20% and 50% respectively). Table 2 shows that amount of drug permeated increased ($p < 0.05$) with the addition of propylene glycol up to 10%. However, permeation values release decreased ($p < 0.05$) with further increase in the concentration of propylene glycol (20%). The addition of ethanol (50%) also significantly increased ($p < 0.05$) the permeation of the drug from the gels.

Gels containing HPMC as a gelling agent

A set of gels (H1- H5) was prepared using HPMC (3%) as a gelling agent. The effect of concentration of propylene glycol and ethanol on the permeation of valdecoxib from the gels was studied (Figure 6).

Table 3 shows that addition of 5% propylene glycol increased the steady-state flux values. However, there was no influence of further increase in the concentration of propylene glycol (10%) on the steady-state flux. The decrease in the flux and permeability values with increase in the propylene glycol up to 10% may be related to the interpretations of the Trotter et al 2004¹², as discussed with the carbopol formulations.

In other set of formulations (H4 and H5) propylene glycol was replaced with ethanol (5 and 10% respectively) to study the influence of ethanol on the permeation of drug. Table 2 shows that the flux values increased ($p < 0.05$) with the addition of ethanol. It indicates that ethanol had a positive impact on the permeation of drug. Figure 6 shows the release profiles of HPMC gels. The release of the drug from the gel increased ($p < 0.05$) with the addition of propylene glycol up to 5%. However, release decreased ($p < 0.05$) with further increase in the concentration of propylene glycol (10%). In case of gels containing ethanol, release decreased ($p < 0.05$) as compared with that of other formulations (Table 2).

Gels containing sodium alginate and sodium CMC as a gelling agents

Figure 7 and 8 show the permeation profiles of sodium alginate and sodium CMC formulations respectively. Table 2 shows that the addition of propylene glycol (5 and 10%) increased the steady-state flux values. Although increased, the steady-state flux values of A3 and M3 formulations are less than A2 and M2 formulations. The decrease in the flux (permeability and drug release) values with increase in the propylene glycol up to 10% may be related to the interpretations of the Trotter et al 2004¹². These results indicate that addition of 5% propylene glycol to sodium alginate and sodium CMC gels are sufficient to increase the release of drug.

Analysis of Release Data

A Higuchi equation¹³ was used to analyze the released data of valdecoxib from different formulations, which is valid if the release process from a solution-type semi-solid slab meets the following assumption:

$$Q = 2C_0 (Dt / \pi)^{1/2} \quad \text{----- (1)}$$

Where, Q is the amount of drug released per unit area (mg/cm^2); C_0 the initial drug concentration in the vehicle (mg/cm^3); D is the diffusion coefficient (cm^2/sec); and t is time. This equation was derived based on the following assumptions: (1) a single drug species is present in the vehicle, (2) only the drug molecules diffuse into the receptor phase, (3) the diffusion coefficient is invariant with respect to time or position within the vehicle, (4) the total drug release is less than 30%, (5) the drug reaching the receptor site is diluted instantaneously.

When the cumulative amount of valdecoxib released were plotted as a function of the square root of the time (eq.-1), linear correlations ($r^2 > 0.979$) were observed. Table 3 summarizes the slopes (representing diffusion rates) and correlation coefficients of gels prepared using carbopol, HPMC, sodium alginate and sodium CMC respectively as gelling agents. The slope values of the most of the formulations appeared to be ≤ 0.5 and $R^2 > 0.979$ indicating that the release of valdecoxib from the vehicles was in compliance with the Higuchi diffusion model (i.e., the release kinetic confirms to matrix control diffusion). This relationship is observed in systems in which the drug is either fully dissolved or suspended in gel and thus membrane used has no effect on the release of the drug.

CONCLUSION

Valdecoxib (1%) gels were prepared using various gelling agents such as carbopol, HPMC, sodium alginate and sodium CMC. 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 ($0.06 \text{ mcg} \times \text{cm}^{-2} \times \text{h}^{-1}$) 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, drug release 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, 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, drug release 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, drug release decreased with the further increase in the concentration of PG up to 10%.

Above 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.

Table 1: Formulations of valdecoxib gels

Ingredients(gm)	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	-	-	-	-	-	-
Sodium alginate	-	-	-	-	-	-	-	-	-	-	-	4	4	4	-	-	-
Sodium 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 (50 gm)	q.s																

Table 2: Evaluation of valdecoxib topical gels

Formulations	pH	Drug content (%w/w) (\pm SD), n=3	Jss Flux mcg./cm ² .h (\pm SD), n=3	Flux R ² (\pm SD), n=3	Permeability-coefficient(P) cm/h (\pm SD), n=3	%Drug released in 180 min (\pm SD), n=3	%Drug released in 360 min (\pm SD), n=3
C1	6.5	96.15 \pm 0.34	0.06 \pm 0.0001	0.9985 \pm 0.0006	6 \times 10 ⁻³ \pm 1.29	3.94 \pm 0.07	6.39 \pm 0.10
C2	6.7	101.85 \pm 0.21	0.08 \pm 0.0001	0.9973 \pm 0.0007	8 \times 10 ⁻³ \pm 1.43	4.53 \pm 0.02	7.70 \pm 0.02
C3	6.6	96.35 \pm 1.35	0.09 \pm 0.0001	0.9987 \pm 0.0007	9 \times 10 ⁻³ \pm 1.27	4.88 \pm 0.11	8.38 \pm 0.09
C4	6.6	97.95 \pm 1.76	0.07 \pm 0.0001	0.9989 \pm 0.0007	7 \times 10 ⁻³ \pm 1.36	4.10 \pm 0.01	6.79 \pm 0.09
C5	6.3	99.45 \pm 0.21	0.12 \pm 0.0001	0.9926 \pm 0.0009	12 \times 10 ⁻³ \pm 1.38	6.55 \pm 0.07	10.73 \pm 0.15
C6	6.7	99.95 \pm 1.17	0.35 \pm 0.0001	0.9930 \pm 0.0005	35 \times 10 ⁻³ \pm 1.42	14.28 \pm 0.33	27.80 \pm 0.39
H1	6.5	96.66 \pm 0.89	0.065 \pm 0.007	0.9978 \pm 0.0007	6.5 \times 10 ⁻³ \pm 1.32	4.00 \pm 0.53	6.42 \pm 0.27
H2	6.6	97.48 \pm 1.52	0.07 \pm 0.0007	0.9892 \pm 0.0007	7 \times 10 ⁻³ \pm 1.29	5.19 \pm 0.17	7.76 \pm 0.09
H3	6.4	99.27 \pm 0.10	0.065 \pm 0.007	0.9965 \pm 0.0006	6.5 \times 10 ⁻³ \pm 1.38	4.24 \pm 0.04	6.86 \pm 0.02
H4	6.4	100.23 \pm 0.49	0.05 \pm 0.0001	0.9976 \pm 0.0007	5 \times 10 ⁻³ \pm 1.42	3.43 \pm 0.10	5.36 \pm 0.31
H5	6.5	98.33 \pm 1.37	0.06 \pm 0.0001	0.9966 \pm 0.0006	6 \times 10 ⁻³ \pm 1.37	3.84 \pm 0.16	6.25 \pm 0.12
A1	6.8	99.03 \pm 0.74	0.06 \pm 0.0001	0.9962 \pm 0.0003	6 \times 10 ⁻³ \pm 1.36	3.70 \pm 0.07	6.09 \pm 0.09
A2	6.9	97.86 \pm 0.70	0.09 \pm 0.0001	0.9979 \pm 0.0001	9 \times 10 ⁻³ \pm 1.39	5.33 \pm 0.07	9.07 \pm 0.07
A3	6.9	98.84 \pm 0.87	0.07 \pm 0.0001	0.9955 \pm 0.0007	7 \times 10 ⁻³ \pm 1.43	4.37 \pm 0.04	7.14 \pm 0.19
M1	7.0	99.46 \pm 0.99	0.06 \pm 0.0001	0.9977 \pm 0.0008	6 \times 10 ⁻⁵ \pm 1.36	3.83 \pm 0.03	6.28 \pm 0.15
M2	7.0	98.64 \pm 0.77	0.07 \pm 0.0001	0.9975 \pm 0.0007	7 \times 10 ⁻⁵ \pm 1.49	4.94 \pm 0.16	7.96 \pm 0.17
M3	6.9	98.88 \pm 0.98	0.06 \pm 0.0001	0.9957 \pm 0.0007	9 \times 10 ⁻⁵ \pm 1.46	4.14 \pm 0.03	6.84 \pm 0.11

Table 3: Slope and R² values of Higuchi model of valdecoxib gels

Formulations	Slope (\pm SD), n=3	R ²
C1	0.324 \pm 0.0007	0.9805
C2	0.355 \pm 0.0006	0.9839
C3	0.436 \pm 0.0006	0.9816
C4	0.334 \pm 0.0007	0.9707
C5	0.473 \pm 0.0009	0.9824
C6	0.576 \pm 0.0005	0.9712
H1	0.338 \pm 0.0007	0.9859
H2	0.394 \pm 0.0006	0.9957
H3	0.343 \pm 0.0007	0.9818
H4	0.272 \pm 0.0007	0.9840
H5	0.321 \pm 0.0009	0.9827
H6	0.425 \pm 0.0005	0.9812
A1	0.311 \pm 0.0003	0.9810
A2	0.484 \pm 0.0001	0.9811
A3	0.355 \pm 0.0007	0.9813
M1	0.318 \pm 0.0008	0.9812
M2	0.344 \pm 0.0007	0.9811
M3	0.3861 \pm 0.0007	0.9811

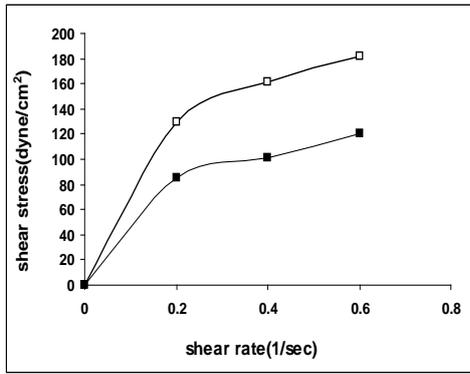


Fig. 1: Rheograms of carbopol gels
Key: (■) H1 and (□) H6

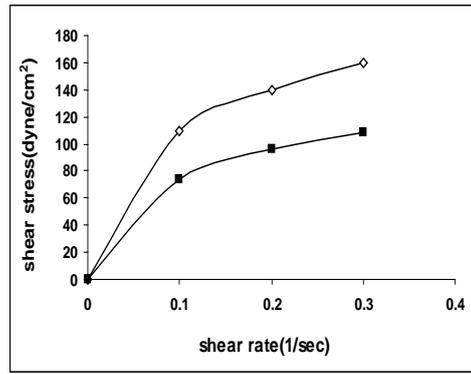


Fig. 2: Rheograms of HPMC gels
Key: (■) C1 and (□) C6

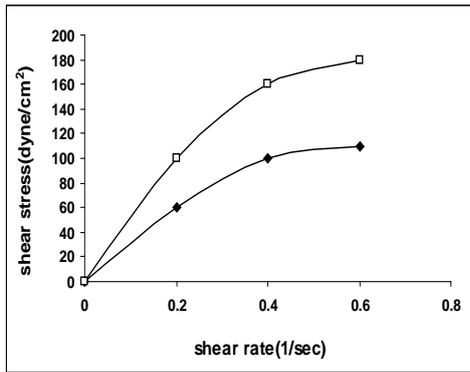


Fig. 3: Rheograms of sodium alginate gels
Key: (■) M1 and (□) M6

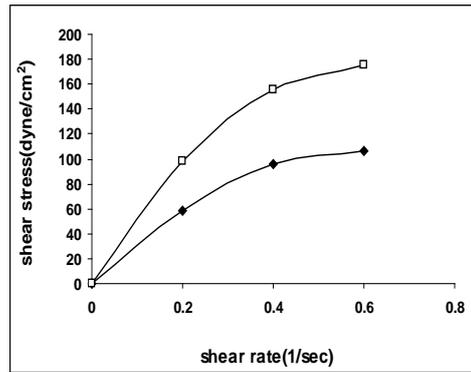


Fig. 4: Rheogram of sodium CMC gels
Key: (■) A1 and (□) A6

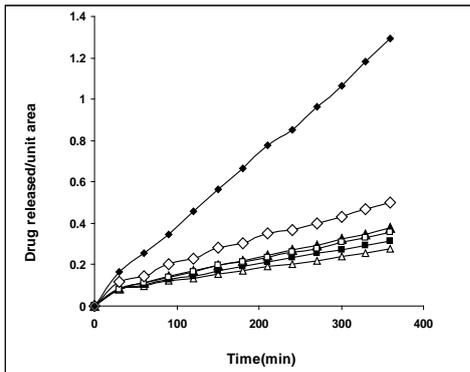


Fig. 5: Diffusion profiles of valdecoxib from carbopol gels
Key: △-C1; □C2; ●C3; ■C4; ◇-C5; ◆-C6

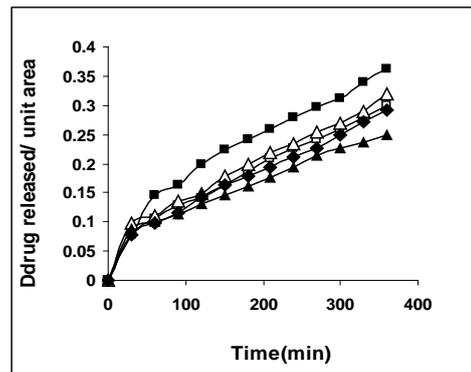


Fig. 6: Diffusion profiles of valdecoxib from HPMC gel
Key: □H1; ■H2; △-H3; ▲H4; ◆-H5

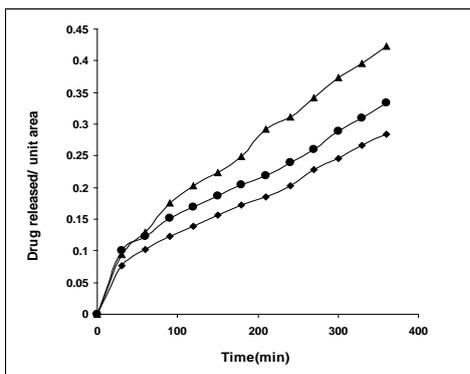


Fig. 7: Diffusion profiles of valdecoxib from sodium alginate gels
Key: ◆-A1; ▲A2; ●A3

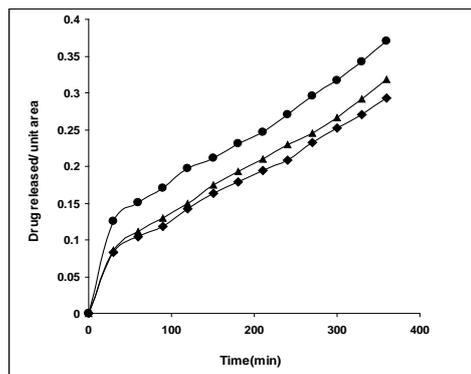


Fig. 8: Diffusion profiles of valdecoxib from sodium CMC gels
Key: ◆-M1; ▲-M2; ●-M3

REFERENCES

1. Kikwai L, Renta P, Jon C, Kolot A, Ansel, Mandip S, et al. In vitro and in vivo evaluation of spantide II. AAPS PharmSciTech 2005; 6:561-8.
2. Kulkarni PK, Pradeep K. Emulsion-gels as topical drug delivery vehicles-a review. Int J Pharm Edu 2002; 36:119-3.
3. Uma DS, Ganesan M, Mohanta GP, Manavalan R. Designing and evaluation of tetracyclic hydrochloride gels. Indian Drugs 2002; 39:552-4.
4. Chen LC, Elliott RA, Ashcroft DM. Systematic review of the analgesic efficacy and tolerability of COX-2 inhibitors in post-operative pain control. J Clin Pharm Ther 2004; 3:215-9.
5. Capone ML, Tacconelli S, Sciulli MG, Patrignani P. Clinical pharmacology of selective COX-2 inhibitors. Int J Immunopathol Pharmacol 2003; 2:49-58.
6. Chavez ML, Carrie J, Dekorte CJ. Valdecoxib: A Review. Clin Ther 2003; 25:817-51.
7. Goldstein JL, Eisen GM, Agarwal N, Stenson WF, Kent JD, Verburg KM. Reduced incidence of upper gastrointestinal ulcer complications with the COX-2 selective inhibitor, valdecoxib. Aliment Pharmacol Ther 2001; 5:527-38.
8. Jagtap SA, Chincholi S, Taneja PK, Ismail ND, Dongree N, Desai A. Evaluation of the efficacy, safety and tolerability of valdecoxib gel (1%) in adult patients with painful inflammatory joint disease. Ind J Med Assoc 2003; 101:764-6.
9. Ambike AA, Mahadik KR, Paradkar A. Stability study of amorphous valdecoxib. Int J Pharm 2004; 282:151-62.
10. Loveleen PK, Rajeev G, Gupta GD. Development and evaluation of topical gel of minoxidil from different polymer bases in application of Alopecia. Int J Pharmacy and Pharm Sci 2010; 2:43-7.
11. Abhijeet P, Jui VJ, Polshettiwar SA. Formulation and evaluation of *in-vitro* antimicrobial activity of gel containing essential oils and effect of polymer on their antimicrobial activity. Int J Pharmacy and Pharm Sci 2011; 3:234-7.
12. Trottet L, Merly C, Mirza M, Davis AF. Effect of finite doses of propylene glycol on enhancement of in vitro percutaneous permeation of loperamide hydrochloride. Int J Pharm 2004; 274:213-9.
13. Higuchi WI. Analysis of data on the medicament release from ointments. J Pharm Sci 1962; 51:802-4.