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Formulation and evaluation of Tenoxicam Gels for Topical Use

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Tenoxicam is a non-steroidal anti-inflammatory drug that belongs to the oxicam class of derivatives. In this study, two different grades of carbopol bases 940 and 934 at a concentration of 15 % w/w were used as base. Three different polyols namely glycerin, propylene glycol and PEG-400 were added as co-solvents either alone or in combination at concentrations of 0 to 4 % w/w and using eight treatment combinations according to the 2^3 factorial design, an experiment was conducted. *In vitro* diffusion characteristics, anti-inflammatory activities and the rheological characteristics of finished formulations were studied. The *in vitro* diffusion studies showed that the drug release was faster in formulations containing the co-solvents glycerin(G_3 and F_3) and PEG-400 (G_4 and F_4) with carbopol 940 and 934 bases respectively. Drug release was faster from carbopol 934 gel forming base with all co-solvent gel formulations than from the carbopol 940 gel base formulations. The release data obtained for tenoxicam obeyed first order kinetics. The results from the study could be useful in preparing a marketable tenoxicam gel formulation with maximum drug release for efficacious use in inflammatory conditions at the site of pain.

Key Words: Tenoxicam, gels, carbopol, co-solvents.

INTRODUCTION

Gels are semisolid systems in which the liquid phase is constrained within a dimensional polymeric matrix consisting of natural or synthetic gums in which a high degree of physical or chemical cross-links has been introduced [1]. The controlled delivery of drugs to the systemic circulation with the help of gel preparation is used to minimize absorption and metabolism variability. The gels are easily biodegraded and are non-toxic [2-7].

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly prescribed drugs worldwide and are responsible for approximately one quarter of all adverse drug reaction reports. NSAIDs are widely prescribed for patients with rheumatic disease (a population at an increased risk of serious gastrointestinal complications). Topical administration of NSAIDs offers the advantage of local, enhanced drug delivery to affected tissues with a reduced incidence of systemic adverse effects, such as peptic ulcer disease and gastrointestinal hemorrhage [8].

Topical formulations of NSAIDS have been developed, especially for the treatment of minor local soft tissue injuries or local rheumatism, such as diclofenac [9], flurbiprofen [10], indomethacin [11] and piroxicam [12]. In the present study, an attempt was made to develop a better therapy for Tenoxicam, an NSAID. Tenoxicam is 4-hydroxy-2-methyl-N-(pyridin-2-yl)-2 H-thieno-[2-3 e]-1,2-thiaxine-3-carboxamide 1,1-dioxide. It is readily absorbed after oral administration and peak plasma concentration is observed at between 0.5 and 2 h [13]. The bioavailability of Tenoxicam is about 100 % after oral and 80 % after rectal administration. Tenoxicam has side effects similar to those of the other NSAIDs when administered orally. To prevent the side effects, topical application of the drug may offer the potential advantage of delivering the drug directly to the site of action. Hence, this

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reported study on formulation and evaluation of tenoxicam gels.

EXPERIMENTAL

Materials

Tenoxicam B.P. was donated by Bharat Pharmaceutical and Research Laboratories, Bangalore, Karnataka State, India. Carbopol 940 U.S.P and Carbopol 934 U.S.P were bought from B.F Goodrich Company, UK. Propylene glycol laboratory grade (L.R), polyethylene glycol - 400 L.R. and glycerin L.R were purchased from Nice Laboratories, Bombay, India. Cellulose membrane (Sigma Diagnostics, U.S.A.) having pore size of 0.45 μ, was used as a diffusion barrier during the *in vitro* release studies. Phosphate buffer solution pH 7.4 (PBS) was prepared according to the U.S.P. XIX. All other salts and chemicals used were of laboratory grade.

Equipment

A Shimadzu Spectrophotometer UV-240 (Shimadzu Corp., Kyoto, Japan); was used for spectrophotometric analysis. Brookfield Viscometer Digital L.V model DV - II + with spindle No. 4 at 30 °C (Brookfield Engineering Laboratories Inc., Middleboro, MA, USA) was used for rheological studies.

Preparation of gels

15 % w/w Carbopol gels 940 and 934 containing 0.5 % w/w of Tenoxicam were prepared with the co-solvents propylene glycol, glycerin and polyethylene glycol in combination and alone each at a concentration 0-4 % w/w using 2^3 factorial designs (Table 1). Triethanolamine was used to neutralize carbopol.

Rheological studies

The rheological behaviour of the formulated sixteen gels was studied using a Brookfield Digital Viscometer L.V model DV-II + using spindle No.4 at 30 °C.

In vitro release studies

In the present work, a pretreated cellulose membrane of 3 mm thickness was employed as the membrane for drug permeation [14]. An accurately weighed amount of gel (2 g) was uniformly spread over an area of 3.8 cm^2 of the cellulose membrane and was fastened to one side of a both open ended cylindrical tube. The tube was then immersed with the end having the cellulose membrane downward into the Dissolution Rate equipment (U.S.P. XIX) containing 400 ml of PBS, maintained at a temperature of 37 °C ± 0.1 °C. The contents in the medium were stirred with an overhead stirrer at 100 rpm. 2 ml aliquots were withdrawn at 30 min intervals and replaced by equal volumes of the diffusion medium. The samples were then assayed for drug content spectrophotometrically at a wavelength of 362 nm. The Tenoxicam content released every 30 min was calculated from the absorbance of sample using the standard calibration curve.

Anti-inflammatory activity

Based on the *in vitro* evaluation, the gel formulations that released the highest quantity of drug were selected and tested for anti-inflammatory activity using 1 % carrageenan induced paw oedema in Wister Albino rats. The animals (weighing 100 - 200 gm) were randomly divided into 4 groups of 4 animals each. The gels, equivalent to 0.5 mg, were applied to the plantar surface of the left hind paw by gently rubbing 50 times with the index finger [15-16]. Three hours after the dose of 0.1 ml, 1 % carrageenan solution in normal saline was injected subplantarly. The rats of the control group received only the base by the same mode of application. The volume of one paw was immediately measured using a mercury/water displacement plethysmograph for both the treated and the control groups. After the carrageenan injection, the volume of the paw was measured at intervals of 30 min, up to the fifth hour. The percentage inhibition was calculated as follows:

$$\% \text{ Inhibition} = (1 - V_t / V_c) \times 100$$

Where V_t is the mean volume of oedema in drug treated groups and V_c is the mean volume of oedema in the control groups. The results were analyzed using the Student's 't' test.

Table 1: 2^3 Factorial design for carbopol 940 and 934 using co-solvents

Formulation	Carbopol 934	Carbopol 940	Propylene glycol a	Glycerin b	Polyethylene glycol c
F1 control	A	-	-	-	-
F2 a	A	-	+	-	-
F3 b	A	-	-	+	-
F4 c	A	-	-	-	+
F5 ab	A	-	+	+	-
F6 bc	A	-	-	+	+
F7 ac	A	-	+	-	+
F8 abc	A	-	+	+	+
G1 control	-	B	-	-	-
G2 a	-	B	+	-	-
G3 b	-	B	-	+	-
G4 c	-	B	-	-	+
G5 ab	-	B	+	+	-
G6 bc	-	B	-	+	+
G7 ac	-	B	+	-	+
G8 abc	-	B	+	+	+

+ : High concentration of co-solvent 4 % w w : - : Low concentration of co-solvents 0 % w/w

RESULTS AND DISCUSSION

The *in vitro* release studies were done for 16 gel formulations containing co-solvents either alone or in combination, as per the 2^3 factorial designs. A plot of percent cumulative amount of drug release versus time was obtained (Figure 1).

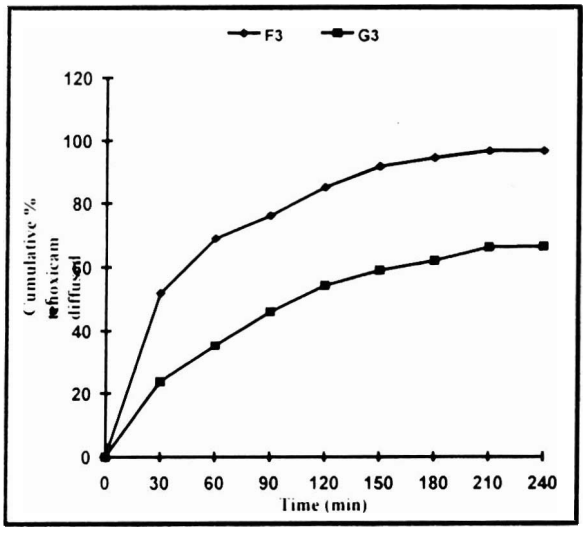

Figure 1: *In vitro* cumulative % of tenoxicam diffused through carbopol 934/940 gel formulation F3 & G3 using cellulose membrane

To ascertain whether the drug release obeys first order rate kinetics, the *in vitro* data was plotted according to equation

$$\text{Log } w = kt/2.303 + \text{Log } w_o.$$

Where w is the amount of drug left in the matrix at time 't', w_o is the initial amount of drug in the matrix, k is the first order rate constant (hr^{-1}), t is the time in hours.

Next, an attempt was made to see whether the drug release would also conform to the diffusion equation proposed by Higuchi [17], which is given by

$$Q = (De/r\,(2C_{tot} - Cs)\,C_s\,t)^{1/2}$$

where Q is the amount of drug released per unit area of the matrix exposed to the solvents, D is the diffusion co-efficient of the drug in the permeating fluid, e is the porosity of the matrix, r is the tortuosity, C_{tot} is the concentration of the drug in the matrix, C_s is the solubility of the drug in the dissolution medium and t is time. It was assumed that $C_{tot} > C_s$ by a factor of at least 3 or 4, justifying the use of this particular equation. Assuming that the diffusion co-efficient and other parameters of the above equation remain constant during release, this equation may be reduced to

$$Q = Kt^{-1/2}$$

Where $K = \sqrt{} Dt/r\,(2\,C_{tot} - C_s)\,C_s$.

The results indicated that the drug release was faster in formulations containing glycerin (F_3 and G_3) and PEG-400 ($F_4$and G_4) with carbopol 934 and 940, respectively. F_3 had 96.8 % and G_3 66.4 % cumulative release of tenoxicam for the

carbopol 934 and 940 gels respectively. On the other hand F_4 had 96.8 % and G_4 61.8 % cumulative release of tenoxicam for carbopol 934 and 940 gels respectively. Carpobol 934 gel forming base released drug faster with all co-solvent gel formulations as compared to carbopol 940 (Figure 1). Addition of propylene glycol alone had no effect in improving the release rate of drug when compared with the formulation without any co-solvents. In the other five formulations, the possibility of a synergistic effect on the release kinetics cannot be ruled out. These formulations also gave better release than the formulations containing no co-solvents. The results obtained showed that the release of tenoxicam obeyed first order kinetics by giving two linear segments up to 120 min when log cumulative percent release was plotted against time (Figure 2), thereby showing that diffusion of the drug from the gel matrix is initially fast and steady in the first 120 min and then slows down. The release data obtained for both types of polymers when plotted according to Higuchi's square root time dependent diffusion equation [17] gave linear graphs up to a period of 120 min and then showed deviation from linearity which indicated that there was slower drug release from the gel matrix. The release kinetic data according to Higuchi's square root time dependent diffusion equation for the tenoxicam gel formulations using carbopol 934 and 940 are shown in Table 2. In the anti-inflammatory activity studies all formulations exhibited a time dependent inhibition of paw oedema from the 3rd hour. Carbopol 934 and glycerin (F_3) was found to be superior to the other formulations producing a maximum of 78.26 % inhibition of paw oedema ($p<0.01$) till 5 h. F_8 with a combination of all the co-solvents of carbopol 934 gel base was also found to be 96.5 % effective in inhibiting paw oedema for up to 5 h (Table 3).

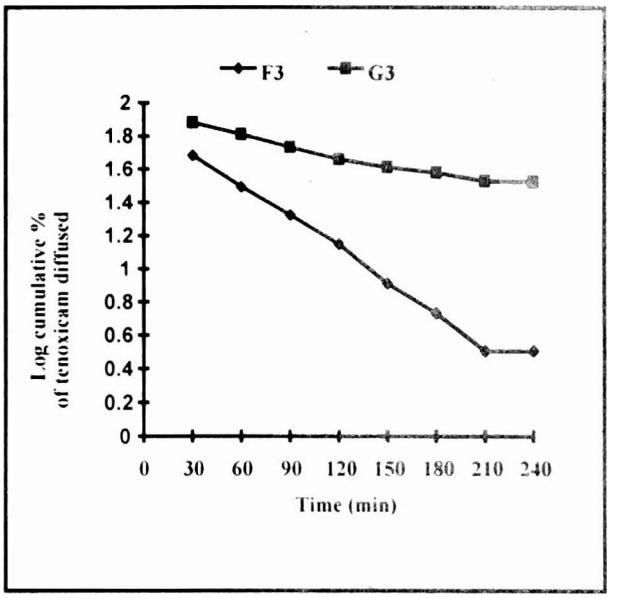

Figure 2: first order diffusion of tenoxicam from carbopol 934/940 gel formulation F3 & G3 using cellulose membrane

Table 4 shows mean viscosity values of formulations of carbopol 934 and 940. It was found from the rheological studies, that gel formulations prepared with carbopol 940 were more viscous than those prepared with carbopol 934. The total drug release rate from the carbopol 940 gels was slow, which could be due to the high viscosity, resulting in the drug molecules probably being unable to diffuse from the viscous gel matrix fast enough and ultimately resulting in lower anti-inflammatory activity.

Table 2: Kinetic values of Higuchi's equation for the in vitro diffusion of tenoxicam from carbopols 934 (F) and 940 (G) through gel formulations

Formulation	Higuchi's diffusion equation $Q = kt^{-1/2}$ slope		Diffusion coefficient K (% mg min $^{-1/2}$)		Regression coefficient (r)	
	Carbopol 934 F	Carbopol 940 G	Carbopol 934 F	Carbopol 940 G	Carbopol 934 F	Carbopol 940 G
1	0.2996	0.2834	0.2996	0.2834	0.9956	0.9982
2	0.2195	0.2526	0.2195	0.2526	0.9985	0.9992
3	0.1712	0.1862	0.1712	0.1862	0.9955	0.9980
4	0.1696	0.2142	0.1696	0.2142	0.9982	0.9989
5	0.1947	0.3263	0.1947	0.3263	0.9964	0.9938
6	0.2605	0.3783	0.2605	0.3783	0.9738	0.9922
7	0.1887	0.2778	0.1887	0.2778	0.9971	0.9986
8	0.2084	0.1611	0.2084	0.1611	0.9906	0.9974

Table 3: Comparative table showing the anti-inflammatory activity as indicated by % inhibition of paw oedema for formulations of carbopol 934 and 940 at the end of 5th hour.

Formulation	% Inhibition in paw oedema at the end of 5th hr for cabopol 934-A	Formulation	% Inhibition in paw oedema at the end of 5th hr for cabopol 940-B
F_1	2.17%	G_1	17.39%
F_2	16.74%	G_2	Not significant
F_3	78.26%	G_3	65.27%
F_4	5.8%	G_4	Not significant
F_5	76.08%	G_5	Not significant
F_6	71.74%	G_6	60.22%
F_7	43.47%	G_7	21.74%
F_8	96.5%	G_8	43.48%

Table 4: Comparative table showing the Mean viscosity values for gel formulations made with carbopol 934 and 940.

CARBOPOL 934			CARBOPOL 940		
FORMULATION	MEAN	SD	FORMULATION	MEAN	SD
F_1	46500.0	60.00	G_1	47636.67	366.92
F_2	35400.0	180.00	G_2	44743.30	240.07
F_3	48100.0	269.80	G_3	52050	645.80
F_4	20280.0	120.00	G_4	21240	225.39
F_5	48093.3	585.60	G_5	49670	363.46
F_6	45580.0	1510	G_6	44280	120.00
F_7	32520.0	60.0.	G_7	37103.30	169.21
F_8	58644.3	1126.25	G_8	58940.00	749.60

CONCLUSION

All the carbopol formulations showed encouraging results. Conclusively, carbopol 934 proved to have better drug releasing properties than carbopol 940 in topical gel formulations of tenoxicam. Among the co-solvents, glycerin proved to be the most effective, followed by PEG-400 and propylene glycol. Topical tenoxicam preparations are possible using carbopol 934 as the gel base and glycerine as a co-solvent to give better drug release and greater anti-inflammatory activity.

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