Research Article

Design and Evaluation of Diclofenac Sodium Gel

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ABSTRACT

Wide choice of vehicles ranging from solids to semisolids form has been used for skin care and topical treatment of dermatological disease. The oral use of Diclofenac sodium is not much recommended as it has many side effects, thus this gel formulation is made for better patient compliance and to reduce the dose of drug and to avoid the side effects like liver damage and kidney damage. The different preformulation studies i.e. Ultraviolet, Infrared, and Organoleptic study conforms its purity. High molecular weight water soluble polymers of Carboxy methylcellulose, Carbopol 940 LR, Xanthan gum that possesses very high viscosity, transparency, film forming properties at low concentration, are used in formulation of topical gel, along with different penetration enhancers like Oleic acid, Propylene glycol, and Tween 80. Gel formulations were characterized for pH determination, spreadability, drug content, viscosity measurement, and *in vitro* drug diffusion. From the study it was concluded that Diclofenac sodium gel containing Carbopol 940 LR with Tween 80 showed good consistency, homogeneity, and spreadability and has wider prospect for topical preparations as compared to Carboxymethyl cellulose and Xanthan gum and other penetration enhancers containing Diclofenac sodium.

Keywords: Diclofenac sodium, Carbopol, Topical gel, Tween 80.

INTRODUCTION

For topical treatment of dermatological disease as well as skin care, a wide variety of vehicles ranging from solids to semisolids and liquid preparations is available to clinicians and patients. Within the major group of semisolid preparations, the use of transparent gels has expanded both in cosmetics and in pharmaceutical preparations[1].Topical drug administration is a localized drug delivery system anywhere in the body through ophthalmic, rectal, vaginal and skin as topical routes. Topical gel preparations are intended for skin application or to other mucosal surfaces for local action or percutaneous penetration of medicament or for their emollient or protective action[2]. The physicians have a wide choice for treatment from solid dosage to semisolid dosage form and to liquid dosage formulation. Among the topical formulation clear transparent gels have widely accepted in both cosmetics and pharmaceuticals[3].

The word ‘‘gel’’ is derived from ‘‘gelatin,’’ The term ‘Gel’ was introduced in the late 1800 as chemists attempted to classify semisolid substances according to their physiological characteristics rather than molecular composition. Gels are semisolid systems in which a liquid phase is constrained within a three dimensional polymeric matrix of natural or synthetic gums in which a high degree of physical or chemical cross linking has been established[4].

The U.S.P. defines gels as a semisolid system consisting of dispersion made up of either small inorganic particle or large organic molecule enclosing and interpenetrated by liquid. The inorganic particles form a three-dimensional ‘house of cards’ structure. Gels consist of two-phase system in which inorganic particles are not dissolved but merely dispersed throughout the continuous phase and large organic particles are dissolved in the continuous phase, randomly coiled in the flexible chains. These chains are entangled with each other and shown as a single phase. The interaction between the colloidal phase, (inorganic or organic) set up the ‘structural viscosity’[5].

A gel is colloid that is typically 99% wt liquid, which is immobilized by surface tension between it and a macromolecular network of fibers built from a small amount of a gelating substance present[6]. Gels are typically formed from a liquid phase that

has been thickened with other components. The continuous liquid phase allows free diffusion of molecules through the polymers scaffold and hence release should be equivalent to that from a simple solution[7]. NSAID's are nonsteroidal drugs having excellent anti-inflammatory and analgesic activity but NSAID produces GIT ulceration, and bleeding to intestinal wall, liver and kidney trouble especially in case of oral administration, the drug undergoes substantial first pass effect and only 50% of drug is available systemically. In view, of adverse drug reaction associated with oral formulations, diclofenac sodium is increasingly administered by topical route[8].

MATERIAL AND METHOD

Diclofenac sodium was given as gift by Triveni Chemicals, Gujarat. Carbopol 940 LR, Hydroxy propyl Methyl cellulose (15 cPs LR) and Xanthan Gum were provided by SDFCL. Oleic acid and Tween 80 were also supplied by SDFCL; Propylene glycol was obtained from NICE Chemicals. All the chemicals and solvents were of analytical grade.

Method of preparation of diclofenac sodium gels, Carbopol gel

Required quantity of carbopol was agitated in water until uniformly dispersed. Agitation was continued further for about 20 minutes. Then penetration enhancer was added to the gel. Finally the gel was neutralized by adding triethanolamine in water. The drug was dispersed in small amount of water and mixed in the gel.

CMC gel

The required quantity of polymer was mixed with a part in required amount of hot water until all particles were dispersed and wetted thoroughly. The remaining part of water was added as cold water and stirred until mixed uniformly to a transparent gel matrix. Then penetration enhancer was added to the gel. The drug was dispersed in a small portion of water and incorporated in the gel. pH adjustifier is added to modify the buffering capacity of the gel, if necessary.

Xanthan gum gel

Required quantity of Xanthan gum was agitated in water and kept overnight for swelling. Finally to the gel penetration enhancer was added. The drug was dispersed in small amount of water and mixed in the gel.

Evaluation of Prepared Gels

Physical evaluation

All the formulations of diclofenac sodium were evaluated for organoleptic characteristics, occlusiveness and washability.

Measurement of pH

The pHs of the formulated gels were determined using digital pH meter. The electrode was immersed in the gel and readings were recorded from pH meter.

Viscosity study

Viscosity measurements were done on Brookfield viscometer (Model-RVT, serial no-107392) by selecting suitable spindle number and rpm. 50 gm of preparation was kept in 50 ml beaker which was set till spindle groove was dipped and rpm was set and dial reading was measured after three minutes. From the reading obtained, viscosity was calculated by using factor. The procedure was repeated three times and observations are recorded as mean.

Spreadability

A sample of 0.1 g of each formula was pressed between two slides (divided into squares of 5 mm sides) and left for about 5 minutes where no more spreading was expected Diameters of spreaded circles were measured in cm and were taken as comparative values for spreadability. The results obtained are average of three determinations[9].

Homogeneity and grittiness

All developed gels were tested for homogeneity by visual inspection after the gels have been set in the container. They were tested for their appearance and presence of any aggregates. Also, the homogeneity can be detected when a small quantity of the gel is rubbed on the skin of the back of the hand. The grittiness

of prepared gel is also observed in the same manner.

Extrudability study

The extrudability of gel formulations were determined by filling gel in the collapsible tubes. The extrudability was determined in terms of weight in grams required to extrude a 0.5 cm. ribbon of gel.

A specific quantity (100mg) of developed gel and marketed gel were taken and dissolved in 100ml of phosphate buffer of pH 6.8. The volumetric flask containing gel solution was shaken for 2hr on mechanical shaker in order to get complete solubility of drug. This solution was filtered and estimated spectrophotometrically at 276.0nm using phosphate buffer (pH 6.8) as blank[10].

Drug content

Drug content was calculated by the following formula

$$\text{Drug content} = \frac{\text{Absorbance} \times \text{Dilution factor}}{\text{Slope}} \times \frac{1}{1000}$$

In vitro release studies

The drug release from the formulations was determined by using the apparatus, which consist of a cylindrical glass tube (with 22-mm internal diameter and 76 mm height) which was opened at both the ends. 1 gm of gel equivalent to 10 mg of Diclofenac sodium was spread uniformly on the surface of cellophane membrane (previously soaked in medium for 24 hrs) and was fixed to the one end of tube. The whole assembly was fixed in such a way that the lower end of tube containing gel was just touches (1-2 mm deep) the surface of diffusion medium i.e. 100 ml of pH 6.8 phosphate buffer contained in 100 ml beaker, The assembly was placed on thermostatic hot plate with magnetic stirrer and maintained at temperature 37°±2°c the contents were stirred using magnetic bar at 100rpm for a period of 6 hrs, 5 ml of samples were withdrawn at different time intervals and replace with 5 ml of fresh buffer and after suitable dilution the sample were analyzed at 276 nm for diclofenac sodium[11-12].

Table 1: Composition of Carbopol 940 Gels with penetration enhancers

Composition of Carbopol 940 Gels with penetration enhancers

FORMULATION CODE										
INGREDIENTS	Control	Oleic Acid			Propylene glycol			Tween 80		
	F1	F4	F5	F6	F7	F8	F9	F10	F11	F12
Carbopol 934 (%w/v)(mg)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Drug(mg) (%w/v)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Oleic Acid (ml)	-	1.25	2.5	5.0	-	-	-	-	-	-
Propylene glycol(ml)	-	-	-	-	1.25	2.5	5.0	-	-	-
Tween 80 (ml)	-	-	-	-	-	-	-	1.25	2.5	5.0
Triethanolamine(gm)	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Water (ml)	50	50	50	50	50	50	50	50	50	50

Table 2: Composition of CMC Gels with penetration enhancers

Composition of CMC Gels with penetration enhancers

FORMULATION CODE										
INGREDIENTS	Control	Oleic Acid			Propylene glycol			Tween 80		
	F2	F13	F14	F15	F16	F17	F18	F19	F20	F21
CMC (%w/v)	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25
Drug (%w/v)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Oleic Acid (ml)	-	1.25	2.5	5.0	-	-	-	-	-	-
Propylene glycol (ml)	-	-	-	-	1.25	2.5	5.0	-	-	-
Tween 80 (ml)	-	-	-	-	-	-	-	1.25	2.5	5.0
Water (ml)	50	50	50	50	50	50	50	50	50	50

Table 3: Composition of Xanthan gum Gels with penetration enhancers
Composition of Xanthan gum Gels with penetration enhancers

INGREDIENTS	FORMULATION CODE						
	Control	Oleic Acid			Propylene glycol		
	F3	F22	F23	F24	F25	F26	F27
XANTHAN GUM %w/v)	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Drug (%w/v)	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Oleic Acid (ml)	-	1.25	2.5	5.0	-	-	-
Propylene glycol (ml)	-	-	-	-	1.25	2.5	5.0
Tween 80 (ml)	-	-	-	-	-	-	-
Water (ml)	50	50	50	50	50	50	50

RESULT

Table 4: Physical evaluation of formulations pH of formulations
Physical Evaluation

Following table shows results for physical evaluation of Diclofenac sodium gels.

Formulation Code	Spreadability	Washability	Occlusiveness	Color	Phase separation	Odour
F1	Easy	Washable	Yes	White	No	No
F2	Easy	Washable	No	Colourless	No	No
F3	Easy	Washable	No	White	No	No
F4	Easy	Washable	No	White	No	No
F5	Easy	Washable	Yes	White	No	No
F6	Easy	Washable	Yes	White	No	No
F7	Easy	Washable	Yes	White	No	No
F8	Easy	Washable	Yes	White	No	No
F9	Easy	Washable	Yes	Milky	No	No
F10	Easy	Washable	No	Milky	No	No
F11	Easy	Washable	Yes	Milky	No	No
F12	Easy	Washable	NA	Yellowish	No	No
F13	NA	Washable	No	Colourless	Yes	No
F14	NA	Washable	NA	Colourless	Yes	No
F15	NA	Washable	Yes	Colourless	Yes	No
F16	Easy	Washable	Yes	Whitish	No	No
F17	Easy	Washable	Yes	Colourless	No	No
F18	NA	Washable	Yes	Colourless	Yes	No
F19	Easy	Washable	NA	Yellowish	No	No
F20	Easy	Washable	NA	Yellowish	No	No
F21	Easy	Washable	No	Yellowish	No	No
F22	Easy	Washable	No	Slight yellowish	No	No
F23	Easy	Washable	No	Slight yellowish	No	No
F24	Easy	Washable	No	Slight yellowish	No	No
F25	Easy	Washable	No	Colourless	No	No
F26	Easy	Washable	No	Colourless	No	No
F27	Easy	Washable	No	Colourless	No	No

Table5: pH of various formulations

Formulation Code	pH	Formulation Code	pH
F1	5.70	F15	7.14
F2	7.80	F16	7.86
F3	7.72	F17	7.80
F4	5.74	F18	7.74
F5	5.72	F19	7.80
F6	5.77	F20	7.69
F7	6.28	F21	7.62
F8	6.02	F22	7.63
F9	6.18	F23	7.40
F10	5.71	F24	7.17
F11	5.76	F25	7.50
F12	5.25	F26	7.45
F13	7.20	F27	7.80
F14	7.16		

Table 6: Viscosity of various formulations

Viscosity

Following table shows value for viscosity of various formulations.

Formulation code	Spindle no.	rpm	Viscosity (centipoise)
F1	6	5	96000
F2	5	5	8000
F3	4	10	98000
F4	6	5	95000
F5	6	5	96000
F6	6	5	98000
F7	6	5	96000
F8	6	5	98000
F9	6	5	93000
F10	6	5	98000
F11	6	5	93000
F12	6	5	88000
F13	4	10	3200
F14	4	10	1740
F15	4	10	1200
F16	4	10	600
F17	4	10	400
F18	4	10	1000
F19	4	10	400
F20	4	10	500
F21	4	10	900
F22	4	10	9600
F23	4	10	7200
F24	4	10	8000
F25	4	10	10000
F26	4	10	8000
F27	4	10	8400

Table 7: Spreadability of various formulations

Spreadability

Following values were recorded for spreadability of formulated gels

Formulation Code	Diameter (cm)	Formulation Code	Diameter (cm)
F1	4.2	**F15**	6.2
F2	5.0	**F16**	5.3
F3	4.3	**F17**	5.5
F4	4.5	**F18**	5.8
F5	4.5	**F19**	4.6
F6	4.6	**F20**	4.7
F7	4.8	**F21**	5.3
F8	5.1	**F22**	5.0
F9	5.6	**F23**	5.2
F10	4.6	**F24**	5.4
F11	5.0	**F25**	5.2
F12	5.4	**F26**	5.3
F13	5.0	**F27**	5.5
F14	5.8		

Table 8: Homogeneity and grittiness of formulations

Homogeneity and Grittiness

Following table shows results for Homogeneity and Grittiness

Formulation Code	Homogeneity	Grittiness	Formulation Code	Homogeneity	Grittiness
F1	Yes	No	**F15**	No	No
F2	Yes	No	**F16**	Yes	No
F3	Yes	No	**F17**	Yes	No
F4	Yes	No	**F18**	No	No
F5	Yes	No	**F19**	Yes	No
F6	Yes	No	**F20**	Yes	No

F7	Yes	No	**F21**	Yes	No
F8	Yes	No	**F22**	Yes	No
F9	Yes	No	**F23**	Yes	No
F10	Yes	No	**F24**	Yes	No
F11	Yes	No	**F25**	No	No
F12	Yes	No	**F26**	Yes	No
F13	No	No	**F27**	Yes	No
F14	No	No			

Table 9: Extrudability of various formulations (-not good, +good,)
Extrudability study

The results for Extrudability are shown in the following table

Formulation Code	Extrudability	Formulation Code	Extrudability
F1	+	**F15**	+
F2	+	**F16**	+
F3	+	**F17**	+
F4	-	**F18**	+
F5	-	**F19**	+
F6	+	**F20**	+
F7	+	**F21**	+
F8	+	**F22**	+
F9	+	**F23**	+
F10	+	**F24**	+
F11	+	**F25**	+
F12	+	**F26**	+
F13	+	**F27**	+
F14	+		

Table 10: Drug content of the formulations
Drug Content

The following table shows results for drug content

Formulation Code	Drug Content	Formulation Code	Drug Content
F1	97.3	**F15**	96.8
F2	98.2	**F16**	96
F3	97.5	**F17**	95.5
F4	96.9	**F18**	95.9
F5	97.1	**F19**	95.2
F6	97.5	**F20**	96.8
F7	98.5	**F21**	97.6
F8	98.0	**F22**	98.1
F9	96.9	**F23**	97.8
F10	98.2	**F24**	98.9
F11	97.4	**F25**	98.7
F12	99.1	**F26**	98.0
F13	97.9	**F27**	97.1
F14	96.3		

Table 11: *In vitro* drug permeation data of Control samples
***In vitro* release Using Cellophane membrane**

Control Samples	Time (hrs)							
	1	2	3	4	5	6	7	8
	% Release							
Carbopol 940(F1)	4.63	8.76	13.89	21.63	28.60	33.76	37.71	41.84
CMC(F2)	6.75	8.43	13.11	20.08	26.52	30.43	33.54	37.6
Xanthan Gum(F3)	5.23	7.79	12.81	19.50	24.37	26.35	28.34	30.56

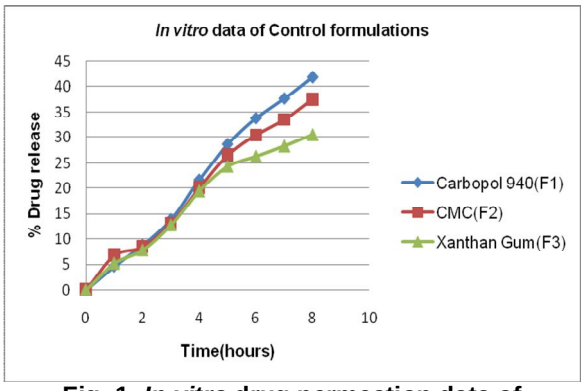

Fig. 1: *In vitro* drug permeation data of Control formulations (F1, F2 and F3)

Table 12: *In vitro* drug Permeation data of Carbopol 940 gels

***In vitro* Drug Permeation Data Carbopol 940**

Samples		Time (hrs)							
		1	2	3	4	5	6	7	8
		% Release							
Control(F1)	No additive	4.63	8.76	13.89	21.63	28.60	33.76	37.71	41.84
Additive	OLEIC ACID								
F4	2.50%	4.41	8.22	14.63	21.66	29.31	35.52	43.37	54.34
F5	5%	5.83	9.77	18.79	24.77	31.69	40.45	51.68	63.01
F6	10%	6.53	10.42	21.56	30.28	38.42	43.66	56.81	70.88
3Additive	PG								
F7	2.50%	4.68	8.85	16.54	24.27	33.49	40.89	47.53	56.41
F8	5%	5.81	9.33	20.25	27.55	36.30	44.76	53.67	65.78
F9	10%	7.66	11.22	28.46	33.79	42.44	57.73	64.54	75.02
Additive	TWEEN 80								
F10	2.50%	4.78	9.42	20.56	27.44	35.52	41.53	52.67	59.35
F11	5%	6.80	11.88	21.65	29.63	38.08	47.37	56.66	70.42
F12	10%	8.73	16.48	30.64	38.59	49.77	63.50	72.55	81.64

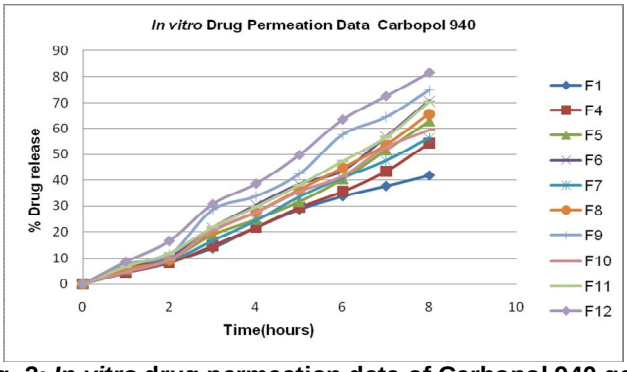

Fig. 2: *In vitro* drug permeation data of Carbopol 940 gels

Table 13: *In vitro* drug Permeation data of CMC gels
***In vitro* Drug Permeation Data CMC**

Samples		Time (hrs)							
		1	2	3	4	5	6	7	8
		% Release							
Control(F2)	No additive	6.75	8.76	13.89	20.08	26.52	30.43	33.54	37.6
Additive	OLEIC ACID								
F13	2.50%	6.45	7.69	14.87	20.67	25.35	32.35	40.90	48.52
F14	5%	6.68	9.47	17.89	23.42	28.46	35.77	44.88	53.17
F15	10%	7.34	11.67	20.79	26.76	31.33	39.68	49.60	57.60
Additive	PG								
F16	2.50%	6.43	8.55	16.56	21.02	27.88	35.64	41.57	50.74
F17	5%	7.44	10.73	19.77	24.68	30.51	38.66	47.65	58.57
F18	10%	7.43	12.21	21.47	28.47	34.76	42.48	53.54	62.26
Additive	TWEEN 80								
F19	2.50%	6.46	9.53	18.69	23.61	30.89	35.45	43.49	52.88
F20	5%	7.84	11.77	21.73	29.88	34.54	41.42	49.46	60.65
F21	10%	7.36	14.82	25.68	31.46	38.38	47.56	54.69	69.57

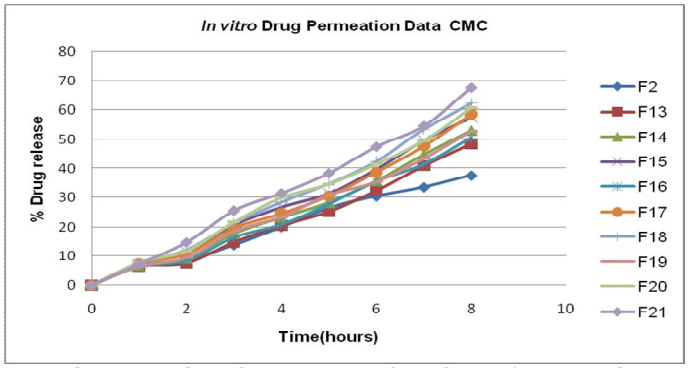

Fig. 3: *In vitro* drug permeation data of CMC gels

Table 14: *In vitro* drug Permeation data of Xanthan gum gels
***In vitro* Drug Permeation Data Xanthan Gum**

Samples		Time (hrs)							
		1	2	3	4	5	6	7	8
		% Release							
Control(F3)	No additive	5.23	7.79	12.81	19.50	24.37	26.35	28.34	30.56
Additive	OLEIC ACID								
F22	2.50%	5.65	6.53	11.55	17.77	24.68	29.74	34.43	38.77
F23	5%	5.46	7.62	12.44	19.37	26.66	31.44	38.48	44.62
F24	10%	6.35	7.80	13.85	21.29	28.73	35.65	42.89	50.62
Additive	PG								
F25	2.50%	5.57	7.62	13.48	19.56	26.85	31.62	39.62	46.03
F26	5%	6.68	7.76	14.55	21.58	29.44	35.55	42.58	50.26
F27	10%	6.36	8.45	16.55	24.55	32.43	40.66	47.87	54.55

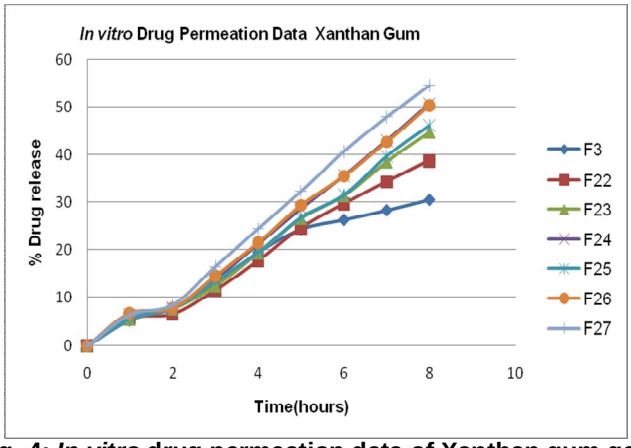

Fig. 4: *In vitro* drug permeation data of Xanthan gum gels

Extended release study for 12 hours

Extended release study for 12 hours with the best formulation i.e., using carbopol 940 gel with 10% tween 80 **F12** has been performed and its release pattern is shown in Table 12. Carbopol 940 gel with 10% tween 80 **F12** was chosen for further studies.

Table 15: Drug release pattern from selective formulation F12 for extended release study

Samples		Time (hrs)						
		1	2	4	6	8	10	12
		% Release						
Additive	Tween 80							
F12	10%	8.69	16.50	38.55	64.00	81.66	88.34	91.60

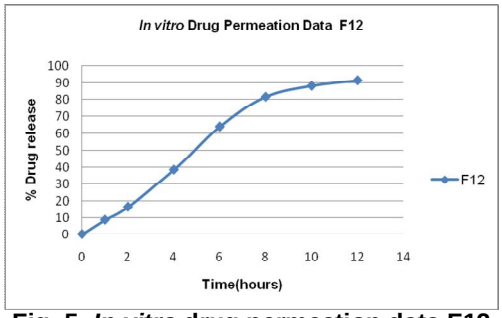

Fig. 5: *In vitro* drug permeation data F12

DISCUSSION

The melting point of drug was found to be 282^{0}C. The solubility of drug was very soluble in methanol, soluble in ethanol, slightly soluble in water, and practically soluble in ether, and chloroform. All the diclofenac sodium gels formulations were good feel and showed no clogging and lumps which indicate good texture of system.

The pH of gels was around in the range of 5.25-7.86. Viscosity is an important parameter for characterizing the gels as it affects the spreadability, extrudability and release of the drug. Viscosity of formulations was ranges between 400-98000 cps. The data obtained from viscosity studies, drug content, pH, spreadability test, extrudability studies, *in vitro* drug diffusion and skin irritation studies of various formulations was compared which gave satisfactory results. Gel is considered to be good if it takes minimum time to spread on the surface. The values of spreadability indicate that the gel is easily spreadable by small amount of shear.

Extrusion of gel from the tube is important during application and for the patient compliance. The values of extrudability of different formulations were Found good except two preparations. Drug content uniformity of all formulations was observed ranges from 95.2 to 99.1% drug content. *In vitro* Permeability study showed that permeation of formulations was comparable with each other.

CONCLUSION

It was observed that Diclofenac sodium gel containing Carbopol 940 and 10% tween show better spreadability, viscosity and consistency as compared to other formulations. The F12 (Carbopol 940 gel with 10% tween) show good pH, homogeneity and *in vitro* release, and thus release of this formulation is further studied for 12 hours. Hence the F12 formulation has wider prospects to be used as a topical drug delivery system.

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