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DESIGN AND EVALUATION OF TOPICAL HYDROGEL FORMULATION OF DICLOFENAC SODIUM FOR IMPROVED THERAPY

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ABSTRACT: Topical gel preparations are intended for skin application or to certain mucosal surfaces for local action or transdermal penetration of medicament or for their emollient or protective action. Topical delivery of drugs can be achieved by incorporating drug into the gel matrix for effective delivery of drugs, thus avoiding first pass metabolism and for increased local action in pain management and skin diseases. NSAID's are non-steroidal drugs having excellent anti-inflammatory and analgesic activity but NSAID's produces GIT ulceration, liver and kidney trouble especially in case of oral administration. In view of adverse drug reaction associated with oral formulations, many NSAID's are increasingly administered by topical route. Hydrophilic polymers like Guar gum and Carbopol 940 of varying concentrations were used in an attempt to develop topical hydrogel formulations of diclofenac sodium. Evaluation tests for visual appearance, pH, viscosity, spreadability, assay, *in vitro* drug release, *ex vivo* drug release were carried out. In vitro drug release studies were carried out by using USP V dissolution apparatus. The effects of polymer composition on the rate of *ex vivo* drug release from the gel formulations were examined through rat abdominal skin mounting on franz diffusion cell at 32 ± 0.5^{o}C. No prominent changes in physicochemical properties of formulation were observed after exposure to accelerated conditions of temperature (40 ± 2^{o}C) and humidity conditions (75 ± 5%RH). The gel formulation consisting of 1% w/v Guar gum 1% w/v Carbopol940 at 1:1 ratio was found to be suitable for topical application based on *in vitro* evaluation and *ex vivo* permeation studies. These results suggest the feasibility of the topical gel formulation of diclofenac sodium.

INTRODUCTION: Topical drug administration is a localized drug delivery system anywhere in the body through ophthalmic, rectal, vaginal and skin as topical routes. Skin is one of the most readily accessible organs on human body for topical administration and is main route of topical drug delivery system[1-2].

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In recent years scientific and technological advancement have been made in the research and development of hydrogel drug delivery systems by overcoming physiological adversities such as first pass metabolism and for improved local action. Several approaches are currently utilized to treat pain, inflammation, skin diseases, for disinfection of skin and as controlled release devices in the field of wound dressing. Research studies were carried out on the formulation of transdermal gels of anti-inflammatory agents by using various polymers. The present study includes the formulation of transdermal gels of diclofenac sodium by using polymers of natural and semi-synthetic origin and

Gels consist of a solid three-dimensional network that spans the volume of a liquid medium[3]. This internal network structure may result from physical bonds (physical gels) or chemical bonds (chemical gels), as well as crystallites or other junctions that remain intact within the extending fluid. Virtually any fluid can be used as an extender including water (hydrogels), oil, and air (aerogel). Both by weight and volume, gels are mostly fluid in composition and thus exhibit densities similar to those of their constituent liquids.

Hydrogel is a network of polymer chains that are water-insoluble, sometimes found as a colloidal gel in which water is the dispersion medium[4]. Hydrogels are superabsorbent (they can contain over 99% water) natural or synthetic polymers. Hydrogels also possess a degree of flexibility very similar to natural tissue, due to their significant water content. Hydrogels are crosslinked polymer networks that absorb substantial amounts of aqueous solutions. Hydrogels have played a key role in is drug delivery technology.

NSAID's are non-steroidal drugs having excellent anti-inflammatory and analgesic activity but NSAID's produces GIT ulceration, liver and kidney trouble especially in case of oral administration [5]. In view of adverse drug reaction associated with oral formulations, many NSAID's are increasingly administered by topical route. Topical delivery of drugs can be achieved by incorporating drug into the gel matrix for effective delivery of drugs, thus avoiding first pass metabolism and for local action in skin diseases and pain management.

The chief disadvantage of oral NSAID's administration is not the insufficient bioavailability but rather the serious side effects of the drug. These adverse effects are mainly due to poor agent specificity, resulting from the drug binding to certain (e.g., prostaglandins) receptors. The primary site of such adverse action is the gastrointestinal tract. Orally administered NSAID'S are therefore poorly tolerated and causes stomach ulcerations. It would be desirable to reach the therapeutic drug concentration in the target tissue while simultaneously keeping the systemic and gastrointestinal agent concentrations as low as possible. Obviously, such a goal can only be achieved by delivering NSAID'S into the body via the route other than the mouth.

In present work, attempt was made to formulate and evaluate topical hydrogel drug delivery systems. Attempts were made to enhance drug absorption and exposure to improve therapy by controlling the rate of drug release from dosage forms. Rate of drug release was modified using cross-linking agents, gelling or thickening agents. The ultimate aim was to improve bioavailability of the drug and to improve the market formulation by the use of combination of hydrophilic polymers.

MATERIALS AND METHODS:

Materials: Diclofenac sodium was procured from local vendor, Carbopol 940 (Loba Chemie Pvt. Ltd., Mumbai, India), Guargum (Qualigens Fine Chemicals, Mumbai, India), Benzalkonium chloride (Prime laboratories, Hyderabad), Isopropyl myristate (Alpha Chemika, Maharashtra, India), sodium hydroxide (Prime laboratories, Hyderabad), potassium dihydrogen phosphate (Alpha Chemika, Maharashtra, India) were procured and used in this investigation.

Formulation of Diclofenac sodium topical hydrogel: Hydrogel (also called aquagel) is a network of polymer chains that are hydrophilic, sometimes found as a colloidal gel in which water is the dispersion medium [6]. Hydrogels are highly absorbent (they can contain over 99% water) natural or synthetic polymers. Hydrogels also possess a degree of flexibility very similar to natural tissue, due to their significant water content.

Hydrophilic polymers like guar gum and carbopol 940 were selected and 0.1N NaOH solution used as cross linking agent[7-8]. Carbopol940 is soluble in water while guar gum produces colloidal dispersion in water. 0.1-5% w/v concentrations of polymeric dispersions were made separately and were found to be having good mechanical properties when guar gum and carbopol 940 colloidal dispersions mixed in certain proportions.

The topical hydrogels using different proportions were prepared as follows:

1. Hydrogels were fabricated using different concentrations of polymeric dispersions.
2. 0.1, 0.5, 0.75, 1% concentrations of carbopol940 colloidal dispersions were prepared using distilled water.
3. 0.1, 0.5, 0.75, 1% concentrations of guar gum colloidal dispersions were prepared using distilled water.
4. After complete dispersion, both the polymer solutions were kept in dark for 24 h for complete swelling.
5. Dispersions of polymers were made using magnetic stirrer (500rpm). After dispersing carbopol940 in distilled water, colloidal dispersion of guar gum was added to it under magnetic stirring. 1% v/v isopropyl myristate and 0.0025% w/v benzalkonium chloride were added[9-10]. Aqueous drug solution was added to the polymeric dispersion after addition of sodium hydroxide solution.

Finally, the remaining distilled water was added to obtain a homogeneous dispersion of gel under magnetic stirring.

Evaluation of topical diclofenac sodium hydrogel [11]:

Physical appearance: The physical appearance and homogeneity of the prepared gels were tested by visual observations. The marketed formulation was considered as reference.

Spread ability test: Spread ability can be determined by applying the gel over an even surface and observed for the gritty nature of the hydrogel if present.

P^H determination: The pH of the gel formulations was determined by using a pH meter. For pH determination, 1% of hydrogel formulation in deionized water was prepared and pH was determined.

Drug content: For assay of the drug in gels, diclofenac sodium was extracted from 1 g of each gel formulations with 20 mL of phosphate buffer pH7.4 for 30 min. The resultant mixture was filtered through membrane filter (pore size 0.45 µm). The absorbance of the sample was determined spectrophotometrically at 276 nm (Elico SL150 UV-VIS spectrophotometer) after appropriate dilution with phosphate buffer pH 7.4. The concentration of diclofenac sodium was estimated from the calibration curve.

Determination of viscosity: The viscosity of the gel formulations was determined using Brookfield viscometer with spindle no. 7 at 100 rpm at the temperature of 25^0C.

***Ex vivo* drug permeation studies:** The abdominal hair of Wistar male albino rats, weighing 150- 200 g, was shaved using a razor after sacrificing by spinal dislocation. The abdominal skin was surgically removed and adhering subcutaneous fat was carefully cleaned. The epidermis was then separated from dermis by soaking the full thickness skin in 2 M sodium bromide solution in water for 6-8 h. The epidermis was thoroughly washed with water and stored in freezer for further use. For *ex vivo* permeation studies, skins were allowed to hydrate for 1 h before being mounted on the Franz diffusion cell with the stratum corneum (SC) facing the donor compartment.

The receptor compartment was filled phosphate buffer pH7.4 and receptor phase was maintained at 32 ± 0.5^oC. 1 g of the gel was placed on the SC side in the donor compartment. The amount of drug permeated was determined spectrophotometrically at 276 nm by removing 1 mL aliquot through a hypodermic syringe fitted with a 0.22 mm membrane filter, at designated time intervals for 30 min. The volume was replenished with the same volume of pre-warmed receiver solution to maintain sink conditions[12].

Accelerated stability studies: Stability studies were carried out on optimized formulation according to International Conference on Harmonization (ICH) guidelines. The formulation packed in aluminium tube was subjected to accelerated stability testing for 3 months as per ICH norms at a temperature (40 ± 2^oC) and relative humidity 75 ± 5%. Samples were taken at regular time intervals of 1month for over a period of 3months and analyzed for the change in pH,

spreadability, drug content and *in-vitro* drug release by procedure stated earlier. Any changes in evaluation parameters, if observed were noted. Tests were carried out in triplicate and mean value of the observed values was noted along with standard deviation.

RESULTS AND DISCUSSION: In present work, attempt was made to formulate and evaluate topical hydrogel drug delivery systems. Attempts were made to modify drug absorption and exposure to improve pharmacokinetics and pharmacodynamics by controlling the rate of drug release from dosage forms. Rate of drug release will be controlled by using cross-linking agents, gelling or thickening agents.

The ultimate aim is to reduce number of doses in order to receive acute and elegant dosage forms convenient to patient meeting requirement of steady state blood concentration of drug, leading to better compliance to therapy. Topical hydrogels were formulated by varying proportions of polymers and they were evaluated.

The topical hydrogels of diclofenac sodium using different proportions of polymers were developed. From the developed gels, gels of better physicochemical properties were selected. Different proportion of polymers used in development of gels is tabulated in **Table 1** and optimization of the formula based on the physical properties of the gel was carried out and the data is tabulated in **Table 7**.

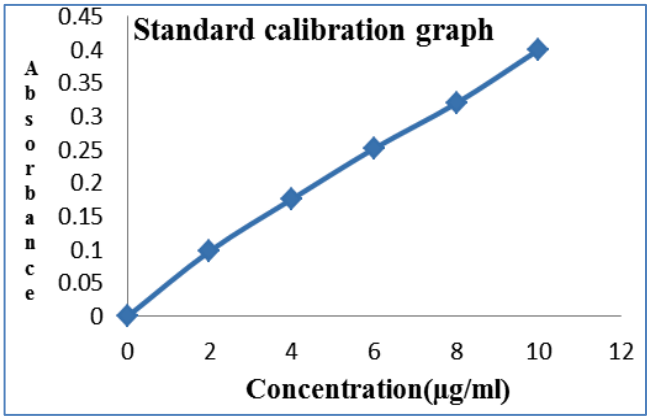

FIGURE 1: STANDARD CALIBRATION GRAPH OF DICLOFENAC SODIUM. y=0.039x+0.011; R^2=0.9997

TABLE 1: COMPOSITION OF GELS

Ingredients (in mg)	FORMULATION CODE							
	F1	F2	F3	F4	F5	F6	F7	F8
Diclofenac sodium	1000	1000	1000	1000	1000	1000	1000	1000
Carbopol-940	0.375	0.5	0.25	0.375	0.5	0.25	0.375	0.5
Guar gum	0.05	0.05	0.375	0.375	0.375	0.5	0.5	0.5
Isopropyl myristate (mL)	1	1	1	1	1	1	1	1
Benzalkonium chloride	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Purified water (q.s.)	100mL	100mL	100mL	100mL	100mL	100mL	100mL	100mL

TABLE 2: EVALUATION OF DICLOFENAC SODIUM TOPICAL HYDROGELS

Formulation code	Visual appearance	Drug content	Viscosity (cps)	Spread ability
F1	Thick, translucent	98.5 ± 0.2	8819 ± 2	++
F2	Thick, translucent	98.7 ± 0.2	8850 ± 1.5	++
F3	Thick, translucent	99.2 ± 0.1	8980 ± 1.5	++
F4	Thick, translucent	99.7 ± 0.1	9142 ± 2.5	++
F5	Thick, translucent	99 ± 0.4	9236 ± 1.5	++
Formulation code	**Visual appearance**	**Drug content**	**Viscosity (cps)**	**Spread ability**
F6	Thick, translucent	99.4 ± 0.2	9344 ± 2	++
F7	Thick, translucent	99.7 ± 0.1	9589 ±2	++
F8	Thick, translucent	99.6 ± 0.3	9636 ± 1.5	++
Marketed	Thick, opaque	99.7 ± 0.1	9643 ± 1.7	++

+ Good Spreadability; ++ Better Spreadability

TABLE 3: *IN VITRO* DRUG DISSOLUTION STUDIES OF DICLOFENAC SODIUM TOPICAL HYDROGEL FORMULATIONS F-1 TO F-5

Time (min)	Cumulative % of drug release				
	F1	F2	F3	F4	F5
5	73.1 ± 0.3	73.6 ± 0.5	51 ± 1	41 ± 0.1	44.9 ± 0.7
10	74.1 ± 0.2	79.7 ± 0.2	57.4 ±0.4	55 ± 0.2	56.2± 0.05
15	76 ± 0.1	80.4 ± 0.4	70.3 ± 0.1	60.4 ± 0.4	64.1 ± 0.2
20	77.7 ± 0.1	80.6 ± 0.2	72.4 ± 0.5	63.7 ± 0.2	68.4 ± 0.5
30	79.8 ± 0.3	81.4 ± 0.6	79.5 ± 0.4	68.1 ±0.2	74.1 ± 0.3

n = 3 ± SD

TABLE 4: *IN-VITRO* DRUG DISSOLUTION DATA OF GEL FORMULATIONS F-6 TO F-8, PURE DRUG AND MARKETED FORMULATION

Time (min)	Cumulative % of drug release				
	F6	F7	F8	pure drug	Marketed formulation
5	49.7 ± 0.2	25.6 ± 0.1	28.4 ± 0.4	93.6 ± 0.3	13.6 ± 0.025
10	54.2 ± 0.3	33.1 ± 0.3	36.1 ± 0.3	99 ± 0.05	25.8 ± 0.3
15	58.5 ± 0.3	39.6 ± 0.4	39.7 ± 0.3	99.8 ± 0.1	34.7 ± 0.3
20	62.8 ± 0.2	49.1 ± 0.5	45.9 ± 0.7	99.8 ± 0.1	40.5 ± 0.6
30	67.5 ± 0.4	51.5 ± 0.6	82.5 ± 0.5	99.9 ± 0.1	45.2 ± 0.2

n=3± SD

TABLE 5: *EX-VIVO* DRUG PERMEATION STUDIES OF DICLOFENAC SODIUM TOPICAL HYDROGEL FORMULATION (F1-F5)

Time (min)	Cumulative % of drug release				
	F1	F2	F3	F4	F5
5	52.1 ± 0.2	52.9 ± 0.1	39.1 ± 0.3	21.3 ± 0.2	21.9 ± 0.4
10	52.9 ± 0.2	58.6 ± 0.4	41.2 ± 0.4	34 ± 0.4	33.9 ± 0.3
15	55 ± 0.1	60 ± 0.8	58.7 ± 0.4	39.5 ± 0.3	42.3 ± 0.5
20	56.9 ± 0.2	60.3 ± 0.5	59.7 ± 0.5	42.5 ± 0.5	50 ± 0.6
30	59.3 ± 0.4	60.4 ± 0.5	61.9 ± 0.4	49.5 ± 0.9	52.3 ± 0.5

n = 3 ± SD

TABLE 6: *EX-VIVO* DRUG DIFFUSION DATA OF GELS (F6-F8 AND MARKETED FORMULATION)

Time (min)	Cumulative % of drug release			
	F6	F7	F8	Marketed formulation
5	28.6 ± 0.5	12.7 ± 0.3	15.7 ± 0.4	12.8 ± 0.4
10	32.4 ± 0.6	19.7 ± 0.5	25.3 ± 0.8	23.4 ± 0.5
15	39.2 ± 0.5	24.5 ± 1.1	32.1 ± 0.9	30.7 ±0.9
20	44.4 ± 0.5	36 ± 0.9	41.2 ± 1	39.1 ± 0.3
30	49.3 ± 0.4	40.7 ± 0.5	64.6 ± 0.2	43.2 ± 0.3

n = 3 ± SD

TABLE 7: OPTIMIZATION OF DICLOFENAC TOPICAL HYDROGEL

Carbopol 940 (%w/v)	Guargum (%w/v)				NaOH (xN)
	0.1	0.5	0.75	1	
0.1	+	++	++	+	0.1
0.5	++	+	+++F3	+++F6	0.1
0.75	+++F1	++	+++F4	+++F7	0.1
1.0	+++F2	++	+++F5	+++F8	0.1

+ Gelatinous solution, ++ thin, transparent gel, +++ thick, translucent gel.

***In vitro* evaluation:** The physicochemical properties of the gel formulations were shown in **Table 3.** From the results it is evident that all gel formulations showed uniform homogeneity and spread ability. The physical appearance of the gel formulations was white translucent in nature.

The drug content of the gel formulations was in the range of 98.7 ± 0.2 to 99.7 ± 0.1, showing content uniformity. The pH of the gel formulations was in the range of 6.9 ± 0.07 to 7 ± 0.1, which lies in the normal pH range of the skin and would not produce any skin irritation. There was no significant change in pH values as a function of time for all formulations. The physicochemical properties of prepared gel formulations were in good agreement with those of a marketed product.

The viscosity of the gel formulations generally reflects its consistency. It is seen that viscosity changes as concentration of polymers changes and among the gel formulations it ts seen F8 formulation (Carbopol 940 1%w/v: Guar gum 1%w/v) to be having higher viscosity (9636 ± 1.5cps) when compared to other developed gels and is comparable with the marketed formulation (9643 ± 1.7cps).

In vitro drug release studies were carried out to select appropriate polymer composition for gel formulation having suitable consistency for topical application. *In vitro* drug release was determined by performing in vitro drug dissolution studies using USP V apparatus (Paddle over Disc). The cumulative in vitro drug release data is given in the **Table 5** and found F8 to release 82.5 ± 0.5 % as marketed product releases 45.2 ± 0.2 %. From the results (**Fig. 2, 3, 4**) it is seen that F8 formulation shows better *in vitro* drug release when compared with marketed formulation. Based on the physicochemical properties and *in vitro* drug release, the formulation F8 was found to be suitable for topical application.

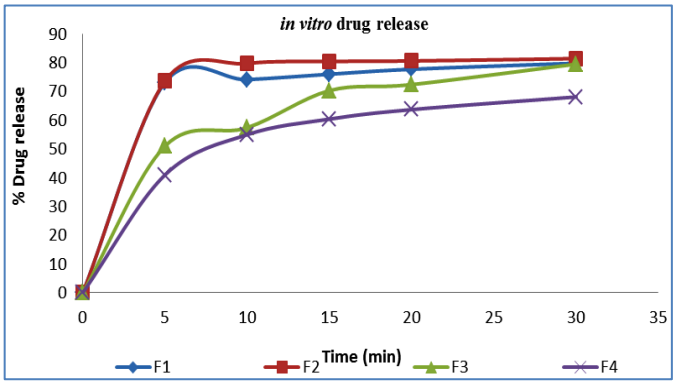

FIGURE 2: *IN VITRO* DRUG RELEASE OF DEVELOPED GEL FORMULATIONS (F1- F4)

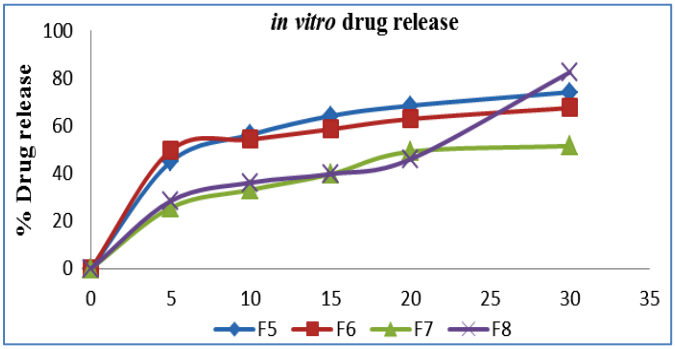

FIGURE 3: *IN- VITRO* DRUG RELEASE OF DEVELOPED GEL FORMULATIONS (F5 – F8)

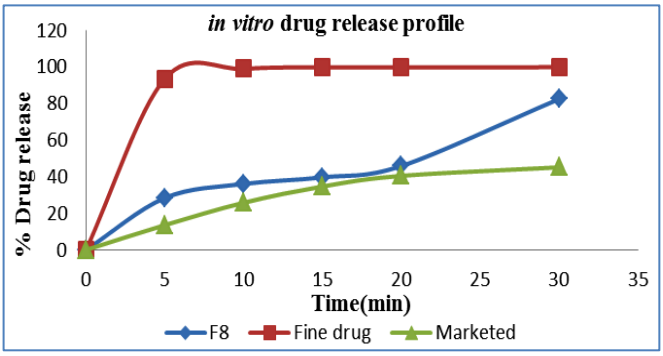

FIGURE 4: *IN-VITRO* DRUG RELEASE OF F8, FINE DRUG, MARKETED PRODUCT

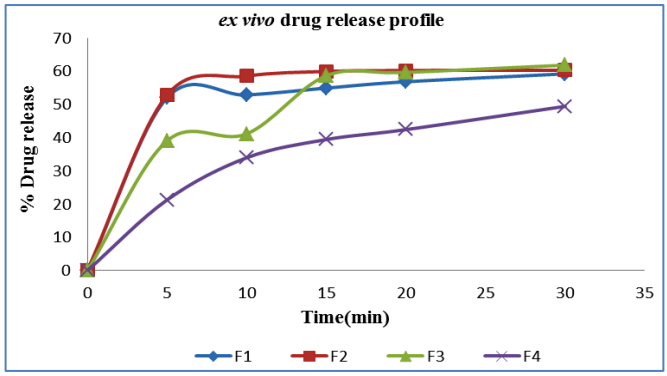

FIGURE 5: *EX VIVO* DRUG RELEASE PROFILE OF DEVELOPED GELS (F1 - F4)

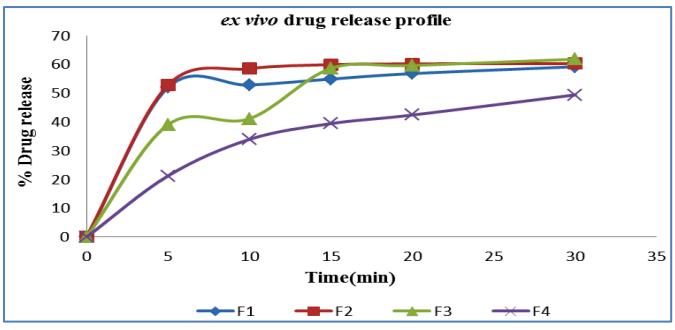

FIGURE 6: *EX VIVO* DRUG RELEASE PROFILE OF DEVELOPED GELS (F5 – F8)

***Ex vivo* evaluation: Figure 5, 6, 7** depicts the *ex vivo* skin permeation profile of diclofenac sodium from gels across rat abdominal skin. The skin permeation profile showed the same pattern as that of the *in vitro* drug release profile. The % ex vivo cumulative drug release from formulation F8 at the end of 30 min was found to be 80.9 ± 0.2 % and found to be better when compared with that of marketed formulation whose % *ex vivo* cumulative drug release was found to be 43.2 ± 0.3 %.

Accelerated stability studies: Significant changes were not noticed. The formulation F8 was found to be stable after exposure to accelerated temperature and humidity conditions for a period of 3 months. No significant changes were seen in physical evaluation parameters and given in the **Table 8.** The *in-vitro* drug release data was given in the **Table 9.**

TABLE 8: PHYSICAL PARAMETERS AFTER ACCELERATED STABILITY STUDY OF FORMULATION F8

Physical Parameter	Temperature: 40° ±2°C ;Relative humidity (RH): 75 ± 5%RH			
	Initial	After 1 month	After 2 months	After 3 months
pH	7 ±0.07	6.9 ± 0.07	6.9 ± 0.07	6.9 ± 0.07
Assay	99.6 ± 0.1	99.5 ± 0.1	99.4 ± 0.1	99.3 ± 0.1
Viscosity (cps)	9636 ± 1.5	9639 ± 1.2	9645 ± 1.5	9649 ± 2

n = 3 ± S

TABLE 9: *IN-VITRO* DRUG RELEASE DATA AFTER ACCELERATED STABILITY STUDY OF FORMULATION F8

Time (min)	Cumulative % of drug release (mean)			
	Initial	After 1 month	After 2 months	After 3 months
5	28.4	28.2	27.9	27.8
10	36.1	35.9	35.8	35.6
15	39.7	39.5	39.2	38.9
20	45.9	45.6	45.4	45.2
30	82.5	82.1	81.9	81.8

Table 8 and 9 shows no significant changes in physicochemical properties and *in-vitro* drug release profile of optimized formulation even after its exposure to accelerated conditions of temperature (40°C) and humidity conditions (75 ± 5%RH). Hence, the developed formulation was found to be stable after subjecting to accelerated stability conditions.

CONCLUSION: The diclofenac sodium hydrogel for topical application was formulated using guar gum and Carbopol 940 and evaluation tests were performed. The topical delivery of diclofenac sodium from the prepared gel formulations across rat abdominal skin was found to be improved when compared to marketed formulation based on ex vivo permeation studies. Proper selection of polymers and their proportions is a prerequisite for designing and developing a transdermal drug delivery system. The formulated gels showed good homogeneity, good stability and better drug release rates when compared to marketed formulation. The formulation F8 (optimized formulation) consisting of 1%w/v guargum-1%w/v carbopol 940 was found to be suitable for topical application based upon its evaluation parameters.

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