Research paper

FORMULATION AND OPTIMIZATION OF TOPICAL GEL CONTAINING SOLID DISPERSION OF ACECLOFENAC USING QUALITY BY DESIGN APPROACH

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ABSTRACT:

The objective of this research was to develop and optimize topical gel containing Aceclofenac using quality by design QbD based on a 2^3 factorial design. Aceclofenac is a non-steroidal anti-inflammatory drug used for the treatment of pain and inflammation. Aceclofenac is insoluble in water and may cause gastrointestinal side effects being a BCS class II drug. In order to decrease gastric ulcerogenic effects, gels have been developed. The optimized gel showed improved saturation solubility of $(0.091+0.009)$ to the corresponding physical mixture of pure Aceclofenac. Aceclofenac solubility was increased by using sodium starch glycolate as a solid dispersion carrier, which also improved the drug's skin penetration profile. Ex vivo permeation drug permeation through skin was found to be increase with increasing amount of SSG and Ethyl alcohol, Permeation flux were in the range 0.014 ± 0.002 and 0.059 ± 0.011 μg/ cm2/h. Improved permeation profile, prepared solid dispersion showed improved aq. solubility of Aceclofenac (0.248) than that of corresponding physical mixture (0.126) and pure Aceclofenac (0.091).

KEYWORDS: Topical gel; Carbopol 940; Aceclofenac; Optimization; Factorial design.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) like aceclofenac, which is chemically [2-(2,6-dichlorophenyl)amino] phenylacetoxyacetic acid, are used to treat pain and inflammation (Chakraborty et al., 2010). Aceclofenac, like other nonsteroidal anti-inflammatory drugs (NSAIDs), can cause stomach ulcers, gastrointestinal bleeding, and problems with the liver and kidney (Insel, 1992).

Additionally, the topical route reduces the risk of side effects, improves patient compliance, prevents first-pass metabolism, and extends the duration of the plasma drug level's maintenance. Aceclofenac has a low solubility in water, that might make it hard to get through the hydrophilic base (Nagariya et al., 2010) . Using the "Quality by Design (QbD)" approach, the current study

attempted to develop Carbopol 940 gel for topical application that contains solid dispersion of aceclofenac and uses sodium starch glycolate as a carrier to improve the skin permeation profile of aceclofenac. The QbD strategy includes formulation design and development, with manufacturing processes ensuring predetermined product specifications (Nayak et al., 2011). Understanding how process and formulation parameters affect product quality and subsequent optimization parameters in relation to final specifications is crucial to this strategy (Maltesen et al., 2008). The amounts of SSG (mg), tri-ethanolamine (ml), and ethanol (ml) were taken into consideration. The chose QbD system permitted an effective determination of the best detailing organization and of the most appropriate exploratory circumstances in the briefest time and with the base number of examinations. For the ex-vivo permeation study, the best formulation was investigated.

MATERIALS AND METHODS

Aceclofenac was obtained from Suyash Lab, India. Carbopol 940 and Sodium starch glycolate were obtained from C.I. Laboratories, India, Tri-ethanolamine and ethanol were commercially purchased. All other reagents were of analytical grade and commercially available.

Preparation of semisolid dosage forms

Various semisolid formulations of aceclofenac were prepared according to the compositions given in Table 6.1 using different dermatological bases. In each of the formulations, AF was incorporated into the base at a concentration of 1% (m/m). Trituration using the geometric dilution procedure was used to obtain a homogeneous mass.

Preparation of aceclofenac-sodium starch glycolate solid dispersion (Dua et al.,2010)

Aceclofenac-sodium starch glycolate (1:4) solid dispersion was prepared by solvent evaporation technique. Aceclofenac was dissolved in ethanol to get clear solution. Then, sodium starch glycolate was dispersed as fine particles and the solvent was removed by evaporation on a water bath at 60^0 C. The dried mass was stored in desiccators until constant mass was obtained, pulverized and passed through sieve no. 22.

Preparation of Carbopol 940 gel containing aceclofenac-sodium starch glycolate solid dispersion

Aceclofenac-sodium starch glycolate solid dispersion equivalent to 150mg aceclofenac was

dissolved in ethanol and deionised water, respectively. Both the solutions are mixed thoroughly. Then 100mg of Carbopol 940, previously soaked in 6.50 ml of deionised water overnight, was added to the above mixture with stirring at 500rpm by magnetic stirrer.

Table 1 Composition of topical formulations of Aceclofenac

S.No.	Ingredient (%) w/w	F1	F2	F3	F4	F5	F6	F7	F8
1	Aceclofenac	1	1	1	1	1	1	1	1
2	Emulsifying wax	0	0	0	0	0	0	0	30
3	Carbopol 940	2	2	2	2	0	0	0	0
4	Sodium starch glycolate	0	0	0	0	0.5	0.5	0.5	0.5
5	Triethanolamine	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
6	Ethanol	30	30	30	30	30	30	30	30
7	Methyl paraben	0.15	0.15	0.15	0	0.2	0	0	0
8	Propyl paraben	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
9	Hard paraffin	0	0	0	0	3	0	0	0
10	Water	*q.s*	*q.s*	*q.s*	*q.s*	*q.s*	*q.s*	*q.s*	*q.s*

Experimental design

Optimization by 2^3 factorial design

A 2^3 factorial design was used for the optimization of Carbopol 940 gels containing aceclofenac-sodium starch glycolate. Amount of sodium starch glycolate ($X1$, mg), amount of tri-ethanolamine ($X2$, ml) and amount of ethanol ($X3$, ml) were selected as independent variables (factors), which were varied at two levels (low and high). The cumulative drug permeation through the excised mouse skin after 10 h (CDP10, %) and permeation flux (PF, µg/cm2/h) were used as dependent variables (responses). Design-Expert was used for generation and evaluation of the statistical experimental design. The values of responses for each trial formulations were fitted in the design to get model equations for each response. For optimization, effects of various independent variables upon measured responses were modeled using following mathematical model equation involving independent variables and their interactions for various measured responses generated by 2^3 factorial design is as follows:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_4X_1X_2 + b_5X_1X_3 + b_6X_2X_3$$

where Y is the dependent variable, while b_0 is the intercept, b_1, b_2, b_3, b_4, b_5, and b_6 are regression coefficients; X_1, X_2 and X_3 are undependable variables; X_1X_2, X_2X_3, and X_1X_3 are interactions between variables.

Eight trial formulations were formulated and evaluated for their responses investigated. The matrix of the design including investigated factors and responses are shown in following table 2:

Table 2 – 2^3 full factorial design (coded values in bracket) with observed response values for different Carbopol 940 gels containing aceclofenac-sodium starch glycolate (1:4) solid dispersion.					
	Normalized levels of independent variables (factors) employed				
Code	**Sodium starch glycolate (mg), X_1**	**Tri-ethnolamine (ml) X_2**	**Ethyl alcohol (ml), X_3**	**CDP 10(%) (Cumulative drugpermeation after 10h)**	**PF (µg/cm2/h) (Permeation flux)**
F-1	150.00 (+1)	0.10 (+1)	4.00 (+1)	17.808 ± 0.710	0.040 ± 0.002
F-2	150.00 (+1)	0.10 (+1)	1.00 (−1)	12.546± 1.500	0.026 ±.0.004
F-3	150.00 (+1)	0.02 (−1)	4.00 (+1)	18.845± 1.137	0.041 ±0.003
F-4	150.00 (+1)	0.02 (−1)	1.00 (−1)	11.697± 0.527	0.025 ±0.003
F-5	25.00 (−1)	0.10 (+1)	4.00 (+1)	9.286± 0.466	0.022 ±0.005
F-6	25.00 (−1)	0.10 (+1)	1.00 (−1)	5.687± 1.026	0.014 ±0,002
F-7	25.00 (−1)	0.02 (−1)	4.00 (+1)	12.016± 0.404	0.025 ±0.004
F-8	25.00 (−1)	0.02 (−1)	1.00 (−1)	6.813±0.215	0.016 ± 0.002

EVALUATION PARAMETERS

(a) pH Determination

 pH of the prepared gel was measured using a digital pH meter by placing the glass electrode completely into the gel system and compared with marketed formulation.

(b) Viscosity Measurement

The viscosities of these formulated gels were determined by using a Brookfield DV-III ultra V6.0 RV at 25 ± 0.3 ◦C. (Chawla and Saraf, 2012).

(c) Measurement of gel strength

The gel strength of prepared gel was considered after 48h of preparation by measuring the amount required to move upper plate by 3 cm, when 1g of gel was placed between two 20cm plates. The gel strength was calculated by using the formula:

$$S = M \times L /T$$

Where S is the gel strength, M is the weight tied to the upper slide, L is the length glass slide travelled and T is time taken. Homogeneity of various gel formulations were tested by visual

observations (Covert, 1986).

(d) Determination of drug content

For each batch, 500 mg of gel was dissolved in 500 ml of phosphate buffer saline, pH 7.4 with stirring at 500 rpm by magnetic stirrer for 1 h. After suitable dilution, the absorbance of the above solution was analyzed by UV–vis spectrophotometer at 274 nm wavelength using appropriate blank solution.

(e) Swelling Property

The extent of swelling was measured in terms of percent (%) weight gained by the formulation. The swelling behavior of formulations F-1, F-2, F-3, F-4, F-5, F-6, F-7, F-8. In 20 mg semi solid beads from each formulation were kept in petridishes containing pH 6.8 phosphate buffers. At the end of 1 hour, the beads were withdrawn, soaked with tissue paper and weighed. Then for every 1 hour, weights of the beads were noted, and the process was continued till the end of 8 hours.

S.I = {(Mt-Mo) / Mo} X 100Where, S.I =

swelling index,

Mt = weight of beads at time't' andMo = weight of

beads at time, t = 0.

(f) Drug release study

In vitro release studies of F1 to F8 formulation of aceclofenac-loaded Carbopol 940 topical gel containing aceclofenac-sodium starch glycolate solid dispersion was optimized in terms of cumulative drug permeation through the excised mouse skin after 10 h (%) and permeation flux ($\mu g/cm^2/h$) by three-factor and two-level (2^3) factorial design.

(g) *Ex Vivo* permeation study

These gels were studied for ex vivo permeation through excised mouse skin. The formulations containing aceclofenac-sodium starch glycolate (1:4) solid dispersion were sustained over 10 h. In the optimization of these gels, it was found that drug permeation through mouse skin was found to be increased withincreasing amount of sodium starch glycolate and ethyl alcohol. This phenomenon can be attributed by the aceclofenac solubility improvement with the increasing amount of sodium starch glycolate in the gels containing aceclofenac-sodium starch glycolate (1:4) solid dispersion and increased skin permeation enhancement capacity of increasing amount

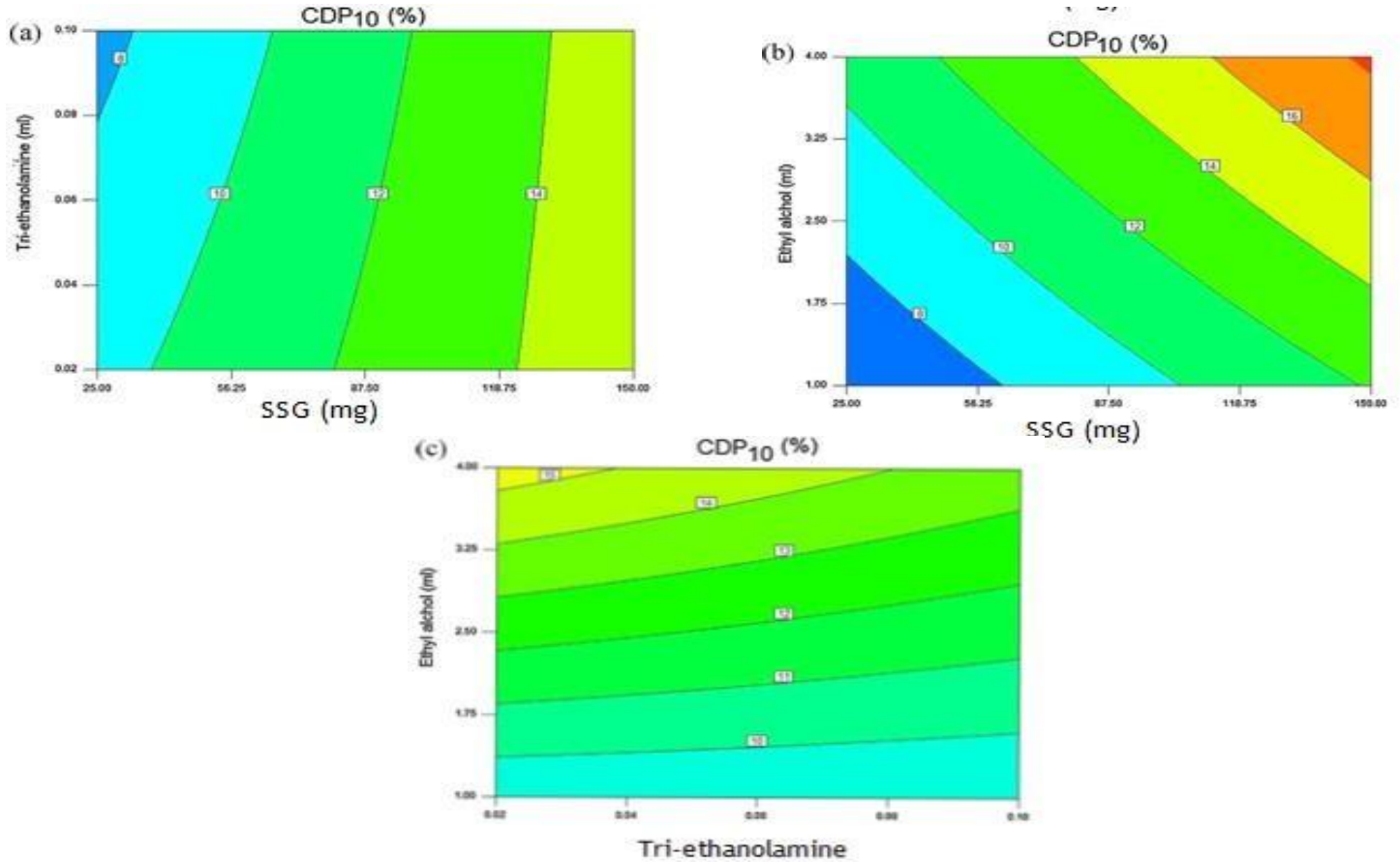of ethanol, present in the gel formulations (Pillai and Panchagnula, 2004).

RESULTS

Fig 1: Contour plot of effect of a) SSG (mg), b) tri ethanolamine (ml) and c) ethyl alcohol on CDP $_{10}$ (%)

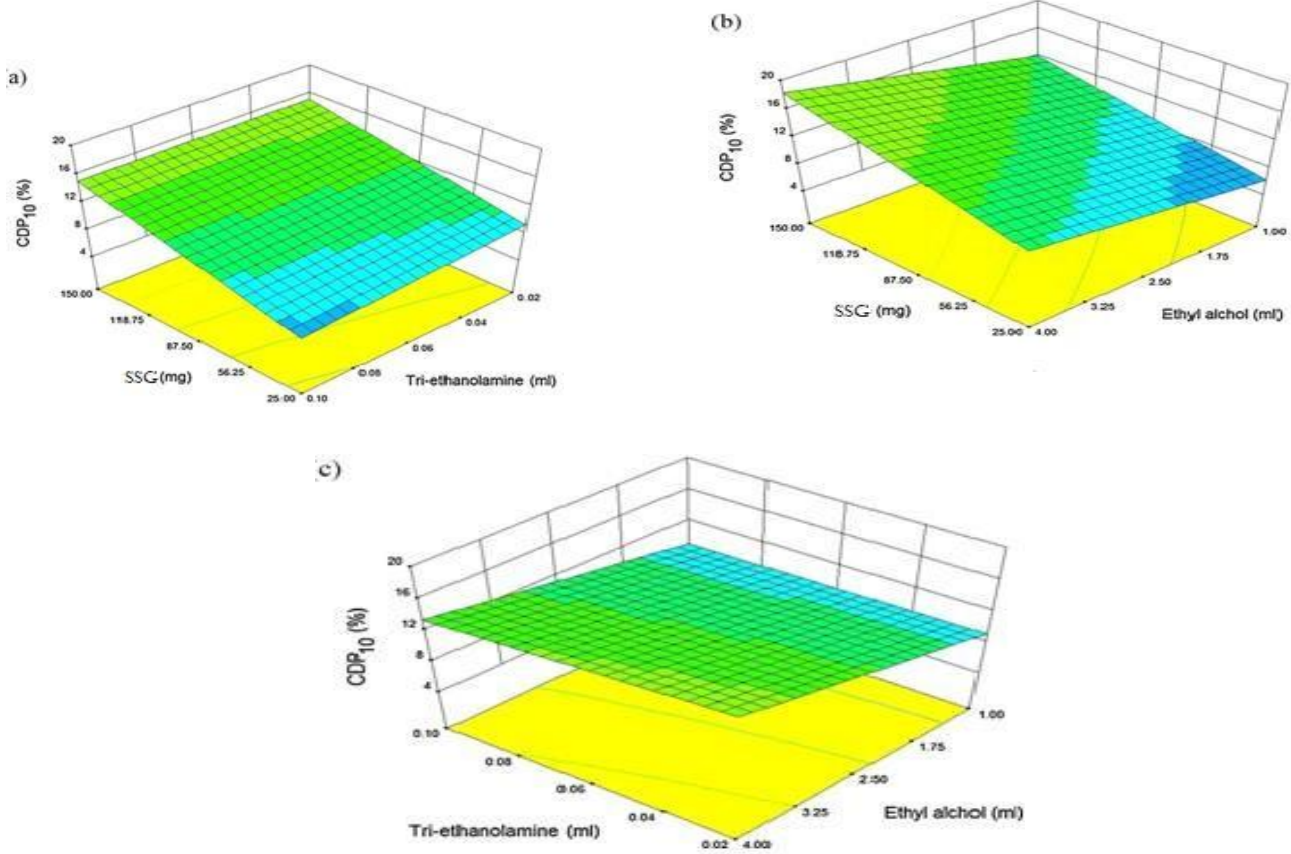| Table 3: ANOVA for the response parameters					
Source	**Sum of Squares**	**Df**	**Mean Square**	**F-value**	**p-value**
a) For CDP 10 (%) Model:	154.88	6	25.81	2596.8	0.0150(S)
X_1	91.78	1	91.76	9231	0.0066 (S)
X_2	2.04	1	2.04	205.65	0.0443(S)
X_3	56.24	1	56.24	5658	0.0083(S)
X_1X_2	1.68	1	1.68	169.18	0.0488(S)
X_1X_3	1.63	1	1.63	163.69	0.497(S)
X_2X_3	1.52	1	1.52	153.16	0.0153 (NS)

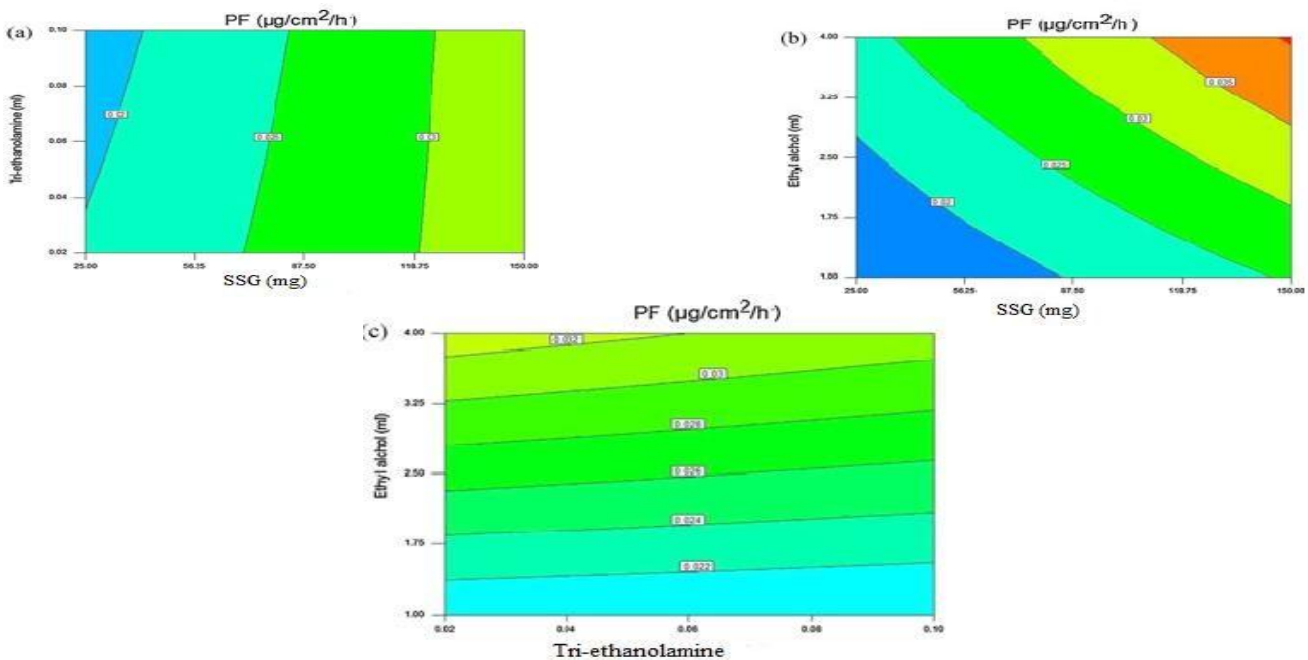**Fig 2: Response surface plot of Effect of a) SSG (mg), b) tri-ethanolamine (ml)and c) ethyl alcohol (ml) on CDP$_{10}$ (%).**

Fig 3: Contour plot of effect of a) SSG (mg), b) Tri-ethanolamine (ml), c) ethyl alcohol

Table 4: ANOVA for the response parameters					
Source	Sum of Squares	df	Mean Square	F-value	p-value
a) For PH (%) Model:	6.828×10^{-4}	6	1.138×10^{-4}	910.33	0.0254 (S)
X1	3.781×10^{-4}	1	3.781×10^{-4}	3025	0.0116 (S)
X2	3.127×10^{-6}	1	3.127×10^{-6}	25	0.1257 (NS)
X3	2.761×10^{-4}	1	2.761×10^{-4}	2209	0.0135 (S)
X1X2	3.125×10^{-6}	1	3.125×10^{-6}	25	0.1257 (NS)
X1X3	2.112×10^{-5}	1	2.112×10^{-5}	169	0.0489 (S)
X2X3	1.125×10^{-6}	1	1.125×10^{-6}	9	0.2048 (NS)

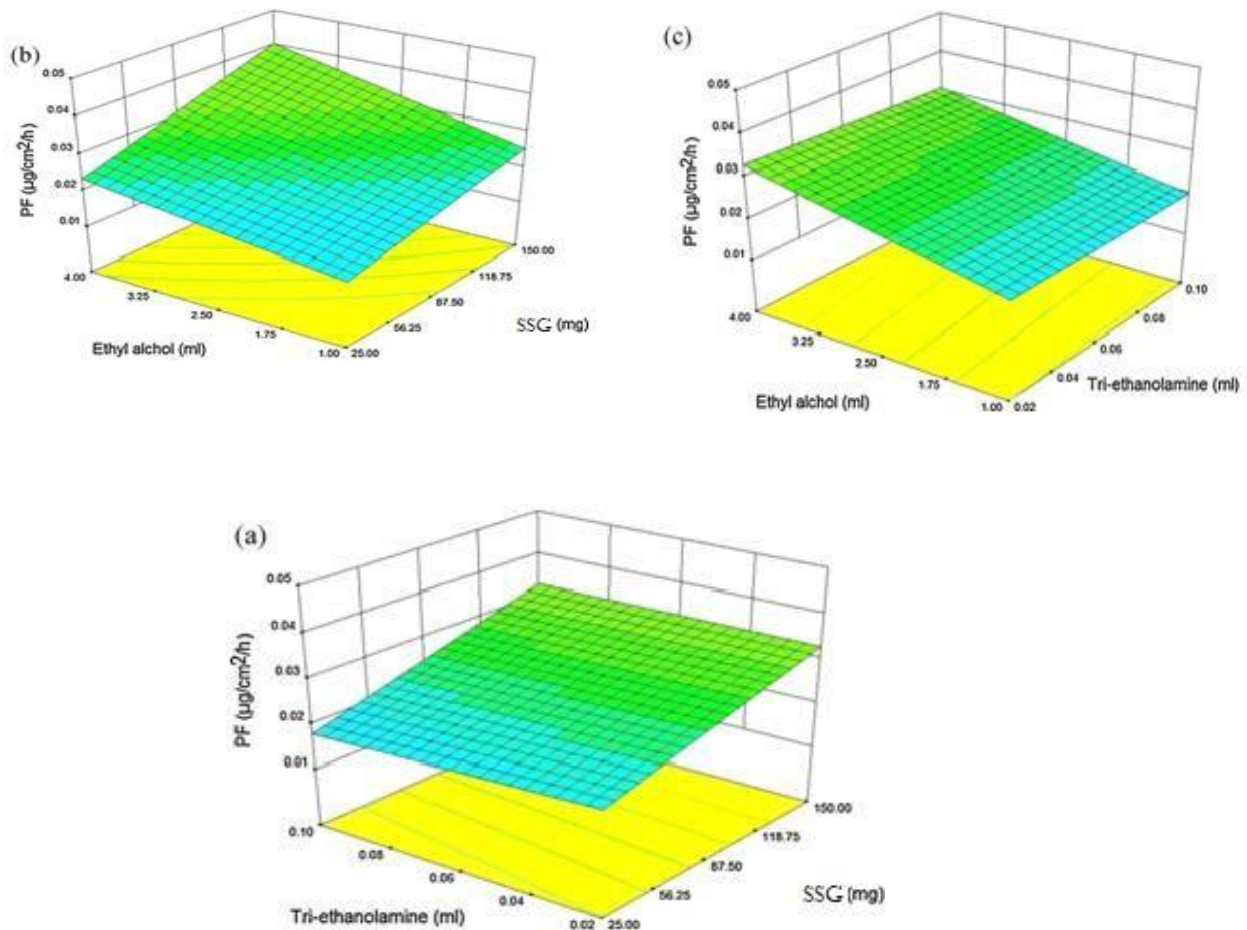Fig 4: Response surface plot of Effect of a) SSG (mg), b) tri-ethanolamine (ml)and c) ethyl alcohol (ml) on on PF (µg/cm2/h).

Table 5: pH, Viscosity, Gel strength and drug content uniformity, CDP_{10} % and permeation flux of formulation

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Formulation	pH	Viscosity (Pa-s)	Gel strength	Drug Content Uniformity %	CDP$_{10}$ % (Cumulative drug permeation after 10h)	PF (µg/cm2/h) (Permeation flux
F-1	7.1	0.407±0.036	0.248±0.065	97.50 ± 1.09	17.808 ± 0.710	0.040 ± 0.002
F-2	7.2	0.311±0.027	0.177±0.051	97.70 ±1.52	12.546± 1.500	0.026 ±.0.004
F-3	7.2	0.345±0.014	0.172±0.091	99.50 ±1.35	18.845± 1.137	0.041 ±0.003
F-4	7	0.247±0.012	0.158±0.078	99.10 ±1.23	11.697± 0.527	0.025 ±0.003
F-5	6.7	0.173±0.017	0.144±0.022	100.23 ±1.13	9.286± 0.466	0.022 ±0.005
F-6	7.2	0.179±0.010	0.144±0.058	97.50 ±1.04	5.687± 1.026	0.014 ±0,002
F-7	6.7	0.174±0.010	0.124±0.078	98.70 ±1.31	12.016± 0.404	0.025 ±0.004
F-8	6.9	0.218±0.021	0.116±0.0078	99.70±1.12	6.813±0.215	0.016 ± 0.002

Table 6 Swelling Index of formulation

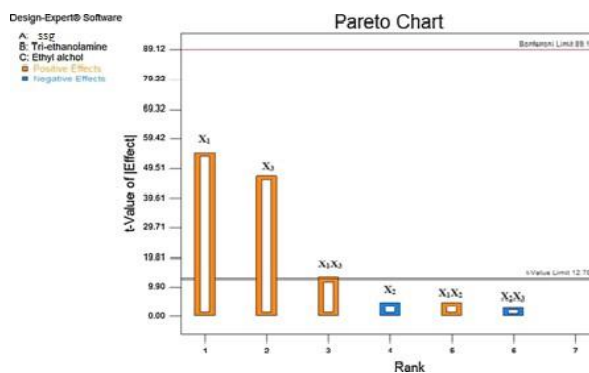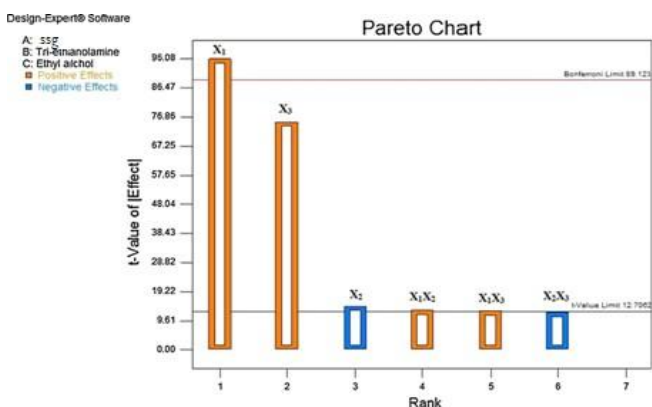| Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8
1	9.57±0.16	12.2±0.36	18.22±0.19	9.45±0.27	10.2±0.21	8.44±0.16	13.45±0.26	14.99±0.21
2	15.23±0.04	18.14±0.25	25.02±0.05	13.02±0.12	15.36±0.01	18.23±0.23	22.12±0.12	30.05±0.32
3	23.22±0.05	26.01±0.12	31.18±0.12	25.02±0.15	24.01±0.12	26.13 ±0.	28.05±0.25	32.04±0.12
4	34.26±0.23	40.13±0.19	43.09±0.16	31.14±0.40	33.50±0.12	38.12±0.	40.08±0.30	44.26±0.16
5	45.12±0.12	48.12±0.18	52.34±0.12	36.23±0.05	42.14±0.16	46.05±0.	52.13±0.21	55.03±0.15
6	48.10±0.14	49.17±0.16	55.65±0.25	63.20±0.18	65.23±0.30	69.12±0.	72.25±0.26	77.23±0.18
7	50.32±0.18	53.02±0.23	60.21±0.23	63.20±0.12	70.32±0.31	74.16±0.	78.14±0.12	82.13±0.26
8	52.12±0.20	60.10±0.32	63.12±0.04	70.15±0.01	74.12±0.20	80.12±0.	82.12±0.25	85.41±0.25

Fig 5: Pareto chart relating CDP$_{10}$ (%)   **Fig. 6: – Pareto chart relating PF (µg/cm2/h).**

Table: 7 *Ex Vivo* Permeation data of formulation

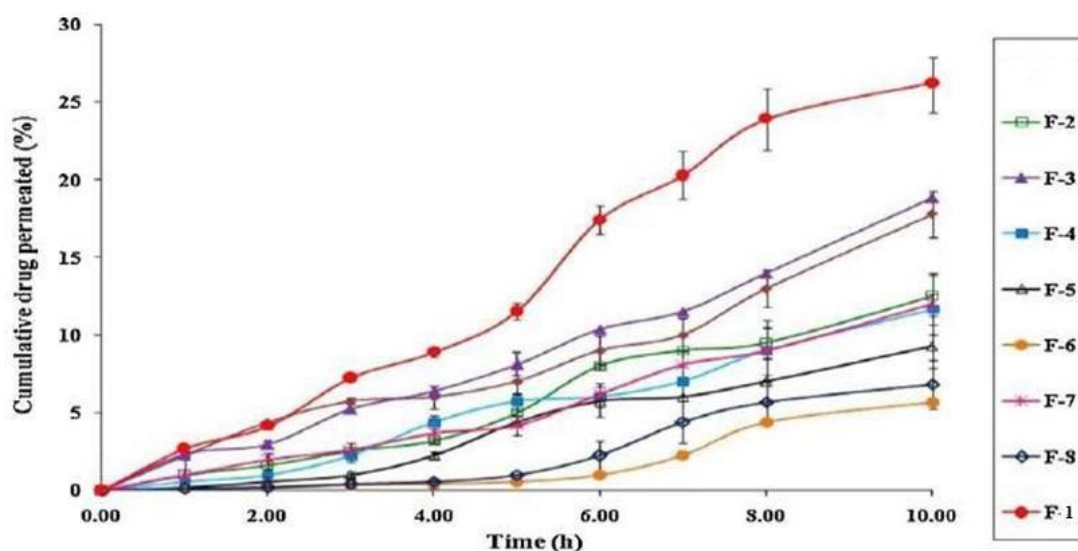| Code	F1	F2	F3	F4	F5	F6	F7	F8
Sodium starch glycolate (mg) X1	260 (+1)	150 (+1)	150 (+1)	150 (+1)	25 (−1)	25 (−1)	25 (−1)	25 (−1)
Tri- ethanola mine (ml), X2	0.01(+)1	0.10 (+1)	0.02 (−1)	0.02 (−1)	0.10 (+1)	0.1 (+1)	0.02 (−1)	0.02 (−1)
Ethyl alcohol (ml), X3	4.20(+)1	1.00 (−1)	4.00 (+1)	1.00 (−1)	4.00 (+1)	1 (−1)	4 (+1)	1.00 (−1)

Fig 7: *Ex vivo* permeation of aceclofenac from various Carbopol 940 topical gels containing aceclofenac-sodium starch glycolate (1:4) solid dispersion through excised mouse skin.

DISCUSSION

The objective of the present investigation is development optimization and evaluation of topical gel containing aceclofenac-sodium starch glycolate (1:4) solid dispersion using "Quality by Design QbD" approach based on 2^3 factorial design.

The concentration of saturated aqueous solution of prepared aceclofenac-sodium starch glycolate (1:4) solid dispersion was measured and compared with the corresponding physical mixture, and pure aceclofenac. The prepared solid dispersion showed improved aqueous solubility of aceclofenac (0.248 ± 0.020 mg/ml) than that of corresponding physical mixture (0.126 ± 0.012 mg/ml) and pure aceclofenac (0.091 ± 0.009 mg/ml). This might be attributed to an improved wetting of drug particles and localized solubilization by the hydrophilic polymeric carrier, sodium starch glycolate.

The formulaion was evaluated for pH, determination of drug content, Measurement of gel strength, Viscosity, FTIR, Ex Vivo permeation The pH was found within the range of 6.52-7.24. The gel strengths of these formulated gels were within the range between 0.116 ± 0.078 and 0.248 ± 0.065 g/cm/s. The gel strengths were found to be increased with increased viscosity value measured. The viscosity of these gels was within the range of 0.173 ± 0.017 to 0.407 ± 0.036 Pa-s. Among all formulations, the optimized gel exhibited maximum viscosity of 0.407 ± 0.036 Pa-s.

These gels were studied for ex vivo permeation through excised mouse skin. The formulations containing aceclofenac-sodium starch glycolate (1:4) solid dispersion were sustained over 10 h. In the optimization of these gels, it was found that drug permeation through mouse skin was found to be increased with increasing amount of sodium starch glycolate and ethyl alcohol. The permeation fluxes for all these gels through the excised mouse skin were within the range between 0.014 ± 0.002 and 0.059 ± 0.011 µg/cm^2/h.

CONCLUSION

Carbopol 940 topical gel containing aceclofenac-sodium starch glycolate solid dispersion was successfully developed by QbD approach based on 2^3 factorial design. These formulated gels showed sustained permeation of aceclofenac over 10 h in ex vivo skin permeation study using excised mouse skin. These gels were characterized by pH, viscosity, and gel strength. FTIR study clearly indicated absence of any significant interaction between the drug, aceclofenac and other excipients present in the formulation. Overall, these results indicated the promise of Carbopol 940 topical gel containing aceclofenac-sodium starch glycolate (1:4) solid dispersion for transdermal delivery of aceclofenac with improved permeation profile and thus, improved patient compliance.

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Conflicts of interest: There are no conflicts of interest.

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