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Formulation and optimization of Aceclofenac gel

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The present research work is to formulate and optimize Aceclofenac gel. Fourier Transfer Infrared Spectroscopy (FT-IR) study revealed no chemical interaction between drug and polymers. The formulations were prepared by using various polymers like Carbopol 934 and HPMC K15M. The formulated gels were evaluated for several physico-chemical parameters like drug-polymer interaction, pH, Viscosity, Spredability, Drug content uniformity, *In vitro* drug release. The formulation F9 Showed maximum drug diffusion rate. The optimization study was carried out to find out effect of two independent variable on diffusion rate at 3 hour and diffusion rate at 6 hour. Optimization was performed by the help of software DESIGN EXPERT 8.0.6 trial. From this study, it was find out that as the concentration of polymer increases, the drug release will decreases.

Keywords: Aceclofenac, Carbopol 934, HPMC K15M, Optimization

Topical drug delivery systems are gaining increase in popularity and several drugs have been successfully delivered by this route for both local and systemic action. In recent years, most of non-steroidal anti inflammatory drugs (NSAID's) have been designed to deliver the drug in the form of topical gels, to avoid gastrointestinal irritation, to overcome "first pass" effect and to maximize the drug concentration at the site of action. Gels have better potential as a vehicle to administered drug topically in comparison to ointment, because they are non-sticky requires low energy during the formulation (Chein, 1992). The purpose of this research work was to formulate and evaluate Aceclofenac gel and find out effect of Carbopol 934 and HPMC K15M on formulation. Formulation chart was prepared by applying 3^2 full factorial design using two independent variables, i.e. concentration of Carbopol 934 and HPMC K15M (Aukunuru et al., 2007)

The formulations were prepared by using various polymers like Carbopol 934and HPMC. The formulated gels were evaluated for several physico-chemical parameters like drug-polymer interaction, pH, Viscosity, Spreadability, Drug content uniformity, *In vitro* drug release. The best formulation was selected. The formulation F9 Showed maximum drug diffusion rate. The optimization study was carried out to find out effect of two independent variable on diffusion rate at 3 hour and diffusion rate at 6 hour. Optimization was performed by the help of software DESIGN EXPERT 8.0.6 trial (Vishnumoorthy, 2011).

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Materials and methods

Materials: Aceclofenac was obtained as a gift sample from Yarrow chemical Ltd, Bombay .Carbopol 934 and HPMC K15M were obtained from Yarrow chemical Ltd, Bombay. All the other chemicals used in the formulations were of analytical grade.

Methods:

Preparation of Standard Curve: 100 mg of Aceclofenac was accurately weighed and dissolved using pH 7.0 phosphate buffer solution in 100 ml standard flask and 5, 10, 15, 20 and 25 µg/ml were prepared by suitably diluting the stock solutions with pH 7.0 PBS, each sample was then analyzed spectrophotometrically at 275 nm using UV Visible spectrophotometer.

Drug - Excipients compatibility study: Compatibility of the drug with excipients was determined by FT-IR spectral analysis, this study was carried out to detect any changes on chemical constitution of the drug after combined it with the excipients.

Designing of formulations: Formulation of gel of Aceclofenac was designed using design expert software trial version 8.0.1 by applying 3^2factorial design. Amount of polymer used was taken as an independent variables i.e, amount of Carbopol 934(X_1) and HPMC K15M (X_2) as independent variables and percentage drug release at 3hrs(Y_1) and at 6hrs(Y_2) was considered as dependent variables. By using this data total nine preliminary were prepared (i.e, F1 to F9) as shown in the table Table 1(A) and 1 (B).

Table 1A: 3^2 full factorial design layout for Aceclofenac gel

BATCH NO.	X1	X2
F1	0	+1
F2	+1	+1
F3	+1	-1
F4	-1	0
F5	0	0
F6	-1	+1
F7	+1	0
F8	0	-1
F9	-1	-1

Table 1B: **amount of independent variables**

INDEPENDENT VARIABLES	LOW(-1)	MEDIUM(0)	HIGH(+1)
Conc. of Carbopol 934(gm) (X1)	1	1.75	2.5
Conc. of HPMC K15M(gm) (X2)	1.5	2	3

Formulation of gel:

Accurately weighed amount of Carbopol 934&HPMC K15M was placed in known amount of distilled water. After complete dispersion, the polymer solution was kept in dark for 8 hours for complete swelling. Accurately weighed amount of Aceclofenac was dissolved in a specified quantity of propylene glycol. The drug solution was added slowly to the aqueous dispersion of polymer with continuous stirring. Menthol was dissolved in Iso Propyl Alcohol. Finally, the remaining ingredients were added to obtain a homogeneous dispersion

of gel. The formed gel was then neutralized by sufficient quantity of triethanolamine. Final volume was adjusted by water.

Evaluation of gels

1. Appearance

The appeared gels were inspected visually for Clarity, Colour, and presence of any particle. The test is important regarding patient compliance

2. pH

Ph of the gel was determined sing digital pH meter. About 1 gm of gel was stirred in distilled water till a uniform suspension effected. The volume was made up to 40 ml and pH of the solution was measured.

3. Skin irritation

Test for irritation was performed on human volunteers. About 1.0 gm of gel was applied on an area of 2 square inch to the back of hand and observed for lesions or irritations.

4. Drug content

A specific quantity of developed gel was taken and dissolved in 100 ml of phosphate buffer of pH 6.8. From that 1 ml was taken and made up to 10 ml. This solution was filtered and estimated spectrophotometrically at 275nm using phosphate buffer pH 6.8 as blank.

5. Viscosity

Viscosity of the gel was determined by using Brookfield viscometer, using spindle No.4.

6. Spreadability

Spreadability of formulations was determined by woodwn block and glass slide apparatus, consist of slide fixed on wooden block and upper slide with one end tide to a weight pan. An excess of gel (2-5gm) was placed in between the glass slide. A fixed weight was added to pan. The time in seconds required to separate the two slides was taken as a measure of spreadability. It is calculated by

$$S=M.L/T$$

Where S=spreadability; M=weight tied to upper slide; L =length of glass slide T=time taken

7. In vitro drug diffusion study

The membrane permeability studies of various formulations of Aceclofenac gel can be carried out using Kesharychien diffusion cell. The receptor compartment is filled with saline phosphate buffer of pH 7.4 and methanol (90:10) and keeps at 32±0.5^{o}c stirred with the help of magnetic stirrer. Methanol 10% is added to maintained sink condition. About 200-300mg of gel is placed on cellulose chamber. One ml of sample is withdrawn from receptor compartment at 1, 2, 3, 4, 5, 6 hour and replaced with same volume of medium. All samples are diluted up to 10ml with medium and analysed at 275nm.

Optimization: Results obtained from the preliminary formulations are applied in design expert software and analyzed for two responses i.e release rate at 3Hrs (Y1) and Release rate at6 Hrs (Y2).

Results and discussion

In the present study the UV absorption maxima was observed at 275 nm. The obtained results revealed that the maximum absorbance appeared at 275nm. (Figure 1)The comparison of the IR spectrum of pure drug and polymers revealed that there is no appreciable change in the positions of characteristic absorption bands of groups and bonds. Even though slightly differ in appearance but no change is observed in the positions of the

bands in spectra, this clearly suggests that there is no interaction between the drug and the polymer used for this study (Figure 2 a, b, c).

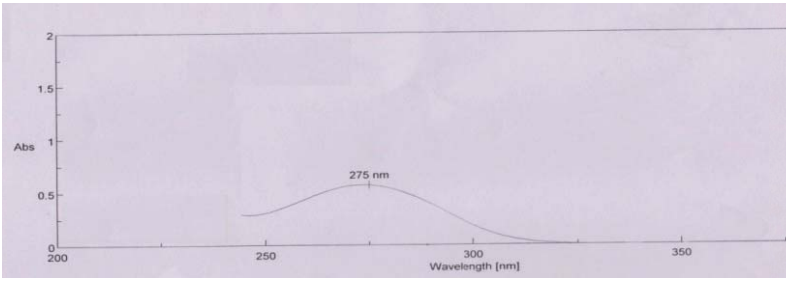


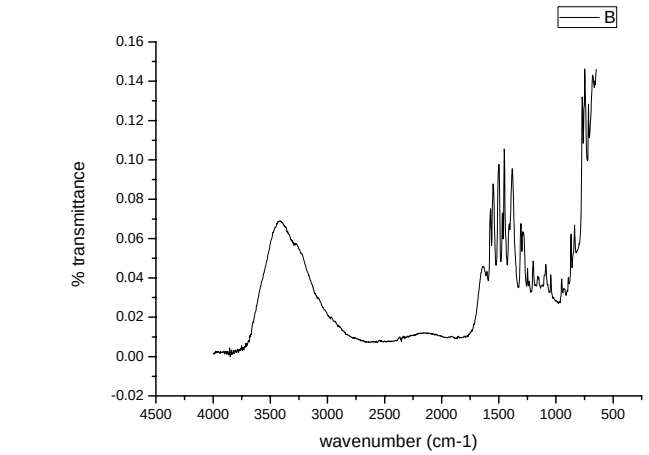
Figure 1: UV absorption maxima

Table 2: Formulation chart of Aceclofenac gel

Batch no.	Aceclofenac (gm)	Carbopol 934 (gm)	HPMC (gm)	Methyl salicylate (ml)	Menthol (gm)	Tri ethanolamine (ml)	Methyl paraben (gm)	IPA (ml)	Propylene glycol (ml)	water
F1	1	1.75	3	10	1	1	0.1	6	10	Up to 100
F2	1	2.5	3	10	1	1	0.1	6	10	
F3	1	2.5	1.5	10	1	1	0.1	6	10	
F4	1	1	2	10	1	1	0.1	6	10	
F5	1	1.75	2	10	1	1	0.1	6	10	
F6	1	1	3	10	1	1	0.1	6	10	
F7	1	2.5	2	10	1	1	0.1	6	10	
F8	1	1.75	1.5	10	1	1	0.1	6	10	
F9	1	1	1.5	10	1	1	0.1	6	10	

Table 3: Various physico chemical parameters

Batch no.	Appearance	Homogenesity	Skin irritation	Spreadability	pH	Drug content	Viscosity(cp)
F1	Clear	Good	Nil	40.35	7.1	95.2 %	31400
F2	Clear	Good	Nil	39.75	7.3	95.8 %	34200
F3	Clear	Good	Nil	42.05	6.9	95.1 %	31100
F4	Clear	Good	Nil	43.65	7.1	95.4%	29900
F5	Clear	Good	Nil	42.60	7.0	96.4 %	30400
F6	Clear	Good	Nil	41.40	7.2	95.3 %	31500
F7	Clear	Good	Nil	42.00	7.2	95.9 %	33600
F8	Clear	Good	Nil	42.65	7.3	95.6 %	30800
F9	clear	Good	Nil	43.70	7.3	97.00%	29600



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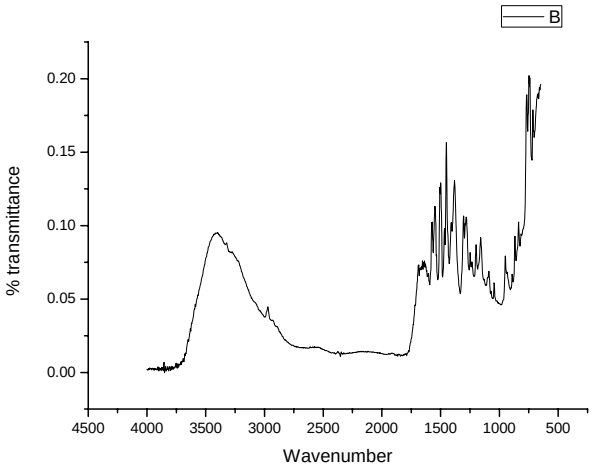

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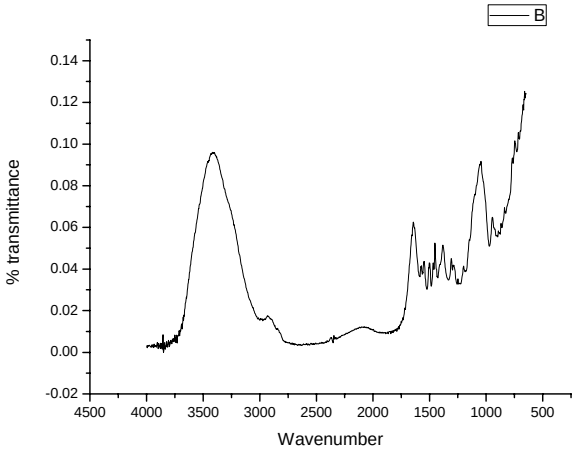


c

Figure 2. FTIR Spectra of (a)-pure drug, (b)-drug+Carbopol 934, (c)-drug+HPMC

The prepared gels were inspected visually for the clarity, colour and presence of any particle. The test important regarding patient compliance. All gels were clear and transparent. All developed (F1-F9) gels showed good homogeneity with absence of lumps.

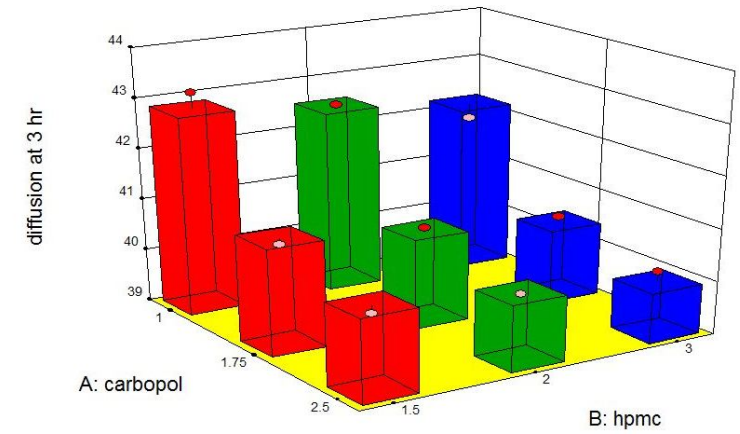
The pH value of all developed formulations of gels (F1-F9) were in the range of 6.9 to 7.3. All the formulations showed no significant skin irritation on intact skin. Thus observations indicate acceptability of these gels for topical use. The value of spreadability indicates that the gel is easily spreadable by small amount of shear. Spreadability of gels were in the range of 39.75-43.65 gm/sec. Formulation F2 shows least Spreadability and F9 shows highest. The percentage drug content of all prepared gel formulations were found to be 93.2 % to 97 %. The percentage drug content of formulations were found satisfactory. Hence methods adopted for gels formulations were found suitable. The viscosity of various formulated Aceclofenac gels was measured using a Brookfield viscometer. The rheological behavior of all formulated gels systems was studied. In gel system, consistency depends on the ratio of solid fraction, which produces the structure to liquid fraction. Viscosity of various formulated Aceclofenac gels was found in range of 29600 to 34200 centipoises.(Table 3).Diffusion profile of preliminary formulations compared at two check points i.e. percentage cumulative drug release at 3 hours and percentage cumulative drug release at 6 hours. Formulations F2 and showed least percentage cumulative drug release value 40.19 % at 3 hours and formulation F9 showed highest percentage of drug release value 43.19% in 3 hours. Percentage cumulative drug release value of all formulations ranges from 40.19 % to 43.19% at 3 hours. Formulation F2 showed least percentage cumulative drug release value 75.14 % at 6 hours and formulation F9 showed highest percentage of drug release value 79.93 % in 6 hours. Percentage cumulative drug release value of all formulations ranges from 75.14 % to 79.93 % at 12 hours (Table 4).

Table 4: Cumulative drug release of formulations

Time (hr)	% Cumulative Drug Release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	9.585	10.462	11.36	10.415	10.722	9.992	9.397	10.785	10.673
2	32.055	30.925	31.112	29.385	31.738	29.075	30.605	32.255	29.89
3	40.56	40.19	40.441	42.592	40.797	41.966	40.269	40.956	43.19
4	51.35	51.12	51.573	54.345	52.415	53.28	52.169	51.823	54.751
5	68.02	66.02	65.88	68.129	66.504	68.650	66.060	66.252	67.577
6	76.19	75.14	75.921	78.35	77.181	77.913	75.35	78.865	79.931

It was clear from the above table that the drug release decreased with increase in concentration of gelling agents. In addition viscosity increased as polymer concentration increased. Viscosity is negatively related to the release of active substances from the formulations and its penetration through the diffusion barriers. Formulation F9 and F4 showed fast drug release because of lower concentration of polymers.

For the factorial study based on 3^2 full factorial design nine experimental runs are conducted and responses for the nine formulations are given in the Table No 5.4. Range of responses Y_1, the cumulative% drug release after 3 hrs was 40.19 %(minimum) in formulation No.2 (F1) and 43.19%(maximum) in formulation No.9 (F9). Similarly response Y_2 was maximum in formulation No9 (F9) and minimum in formulation No.2 (F2).ANOVA was performed to estimate the significance of the model. The ANOVA analysis for both the responses shown that the both the models are significant. The software analyse the datas and generated 3D plots showing the effect of independent variables on dependent variables.(Figure No. 3(a), 3(b)



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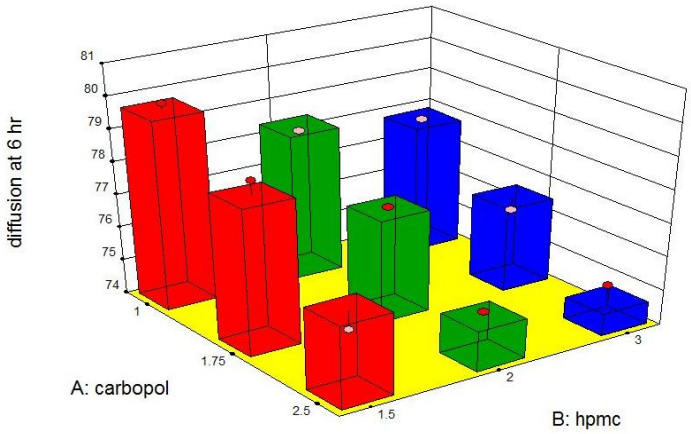


b

Figure 3 (a): effect of Carbopol 934 and HPMC K15M on drug release rate at 3 hour
Figure 3 (b): effect of Carbopol 934 and HPMC K15M on drug release rate at 6 hour

After generating the model equations to relate the dependent and independent variables, the process was optimized for two responses (Y_1 and Y_2). Optimum formulation was selected based on the constraints set on independent variables: Y_1 (40.19 – 43.19%), Y_2 (75% – 79.93%). The final optimal experimental parameters were calculated using the extensive grid search and feasibility search provided in the Design Expert software. The 8 solutions provided by the software from which 4 formulations are randomly selected which was tabulated in the Table 5. Four check point formulations were selected, for which the results of all the dependent variables were found to be within the limits. Table No 6 lists the obtained and predicted values of the check point formulations along with the % prediction error. Linearity correlation plots between the observed experimental values and the predicted values are shown in Fig. 4 and Fig. 5. The accelerated stabilities studies were carried for developed formulations (OF1 TO OF4). Formulations were analyzed for homogeneity, pH, spreadability and drug content. After six weeks studies, it is revealed that there were no changes observed in homogeneity. Formulations showed slight changes in pH, but it were in acceptable limits (± 0.5). Study of drug content remaining in all

formulations reveals that there was no definite change observed for drug degradation as shown in Table 7.

Table 5: Solutions provided by Design Expert software

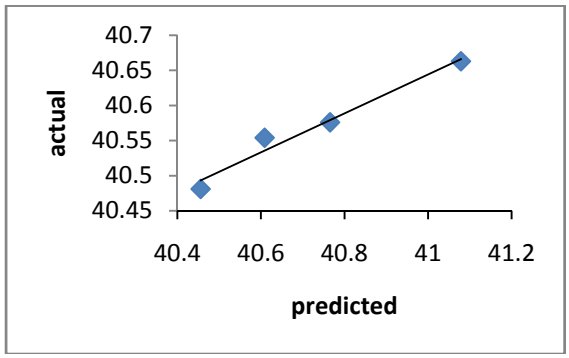
Time (Hours)	% CUMULATIVE DRUG RELEASE OF OPTIMIZED FORMULATIONS			
	OF1	OF2	OF3	OF4
1	11.321	10.001	9.761	11.291
2	30.349	29.45	31.934	33.177
3	40.923	40.160	40.451	41.101
4	52.810	51.416	50.12	52.350
5	68.541	66.254	65.671	65.913
6	79.119	77.213	76.11	76.943

Table 6: The obtained and predicted values

Optimized formulation	Release at 3 hours			Release at 6 hours		
	Predicted	Actual	%Error	Predicted	Actual	%Error
OF1	41.0789	40.663	-1.01%	78.4433	79.01	0.722
OF2	40.7656	40.576	-0.463%	77.1667	77.213	0.0691
OF3	40.4556	40.481	0.064%	76.62	76.251	-0.481%
OF4	40.6089	40.554	-0.132%	76.5033	76.943	0.575%

Table 7: Stability studies of the optimized formulations (OF1 – OF4)

Sr. no	Formulations	Weak	pH	Spreadability	Drug content
1	**OF1**	0	7.3	42.65	95.6%
		2	7.2	42.05	95.2%
		4	7.1	40.74	95.1%
		6	7.1	39.79	94.2%
2	**OF2**	0	7.0	42.6	96.4%
		2	7.1	41.63	96.3%
		4	7.0	41.22	95.7%
		6	7.0	40.51	95.0%
3	**OF3**	0	6.9	42.05	95.1%
		2	7.0	41.54	94.8%
		4	6.9	41.19	94.2%
		6	6.9	40.35	93.2%
4	**OF4**	0	7.1	40.35	95.2%
		2	7.1	40.12	95.1%
		4	7.0	38.63	93.4%
		6	7.0	37.29	91.7%



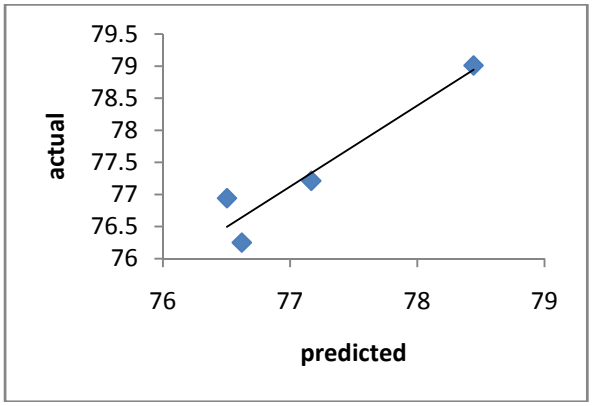


Figure 4 & 5: the predicted vs Actual plots

Conclusion

From this study, it was concluded that the polymers used in the formulation have great effect on various parameters, as the concentration of polymer increases, the drug release will decreases.

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