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Research Article

FORMULATION, OPTIMIZATION AND EVALUATION OF CLOBETASOL PROPIONATE GEL

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ABSTRACT

Objective: The present study was aimed to develop topical gel of Clobetasol propionate with the help of carbopol-934 and Hydroxypropyl methylcellulose K4m as gelling agents. Polymers play major role in various characterization parameters of topical gel such as in vitro release and rheological properties.

Methods: Gels were prepared with carbopol-934 and Hydroxypropyl methylcellulose K4m as gelling agents. In all the gels formulated, the drug concentration was kept constant at 0.05%. The concentration of propylene glycol and ethanol was kept constant at 15% and 40 % respectively. Propylene glycol served as a co-solvent for drug. The concentration of carbopol-934 and Hydroxypropyl methylcellulose K4m was selected as independent variables and optimised using a 3^2 full factorial design. The percentage drug release after 8 hours (Q8) and Viscosity were selected as dependent variables. The optimized gel formulation was evaluated for various physical parameters. Mathematical models were applied to predict the mechanism of drug release.

Results: The optimized gel passed the evaluation tests. A marked effect of independent variables (concentration of carbopol-934 and Hydroxypropyl methylcellulose K4M) was observed on the values of percentage drug release (Q_8) and Viscosity. A drug release of 91.02±0.32 % was achieved after 8 hours. The optimised gel formulation followed first order kinetics. Stability studies indicated no changes in the formulation.

Conclusion: The study indicated that the polymer concentration significantly affects the drug release and rheological properties of the gel formulation. The study holds promise for further investigation in the development stable topical gels of clobetasol propionate.

Keywords: Clobetasol propionate, Topical, Gel, Formulation, Optimization, Evaluation

INTRODUCTION

Topical drug delivery can be defined as the application of a drug containing formulation to the skin to directly treat cutaneous disorders (e.g. acne) or the cutaneous manifestations of a general disease (e.g. psoriasis) with the intent of confining the pharmacological or other effect of the drug to the surface of the skin or within the skin. Topical activities may or may not require intra-cutaneous penetration or deposition [1]. Topical drug delivery systems include a large variety of pharmaceutical dosage form like semisolids, liquid preparation, sprays and solid powders. Most widely used semisolid preparation for topical drug delivery includes gels, creams and ointments [2]. Topical preparations are used for the localized effects at the site of their application by virtue of drug penetration into the underlying layers of skin or mucous membranes. The main advantage of topical delivery system is to bypass first pass metabolism. Avoidance of the risks and inconveniences of intravenous therapy and of the varied conditions of absorption, like pH changes, presence of enzymes, gastric emptying time are other advantage of topical preparations [3,4]. Semi-solid formulation in all their diversity dominate the system for topical delivery, but foams, spray, medicated powders, solution, and even medicated adhesive systems are in use. The topical drug delivery system is generally used where the other systems of drug administration fail or it is mainly used in pain management, contraception, and urinary incontinence.

A gel consists of a natural or synthetic polymer forming a three dimensional matrix throughout a dispersion medium or hydrophilic liquid. After application, the liquid evaporates leaving the drug entrapped in a thin film of the gel – forming matrix physically covering the skin [5].The presence of a network formed by the interlocking of particles of the gelling agent gives rise to the rigidity of a gel. The nature of the particles and the type of form that is responsible for the linkages determine the structure of the network and the property of the gel [6]. Gels have better potential as a vehicle to administer drug topically in comparison to ointment, because they are non-sticky, requires low energy during formulation, are stable and have aesthetic value. Clobetasol propionate belongs to the class of corticosteroids and is believed to have anti-inflammatory, antipruritic and vasoconstrictive properties [7]. The anti-inflammatory action of CP may be due to its binding to specific glucocorticoid receptors (GR), which through a cascade of events decreases the production of pro-inflammatory prostaglandins, leukotrienes and thromboxanes and leucocyte migration. It is the most potent of currently available topical steroids as predicted by the vasoconstrictor assay. In psoriasis, it has proved significantly more effective than class II steroids and as or more effective than the only marketed class I steroid. In the more steroid-responsive eczemas, the superior efficacy of clobetasol is also apparent, but less striking. Clobetasol prolongs remission rates, making intermittent treatment schedules feasible and minimizing inherent potential steroid side effects. Clobetasol may also be useful in the treatment of a myriad of other skin conditions [8]. 0.05% clobetasol propionate has been shown to be effective and convenient in treatment of moderate to severe scalp psoriasis [9, 10]. The aim of the study is to develop and evaluate a topical gel of clobetasol propionate using various polymers like Carbopol-934, HPMC K4M, Carboxymethylcellulose sodium and sodium alginate in different concentrations.

MATERIALS AND METHODS

Material

Different grades of Hydroxypropyl methylcellulose viz., HPMC K4M, K15M and K100 were gift samples from Colorcon Asia Private Limited, Goa. Carbopol-934 was purchased from loba chemicals, Mumbai, Ethanol was purchased from chamgshu yanguan chemical, China, hydrochloric acid was purchased from Fisher scientific, Mumbai, Propylene Glycol was purchased from Oswal scientific store, and Triethanolamine (TEA) was purchased from Magus Chemical and scientific equipments. All other chemicals used were of analytical grade. Double distillation water (DDW) was prepared using in – house distillation unit (fabricated at Jencons), Stability Chamber (Tanco, Dehradun)

Preparation of Gels

Various gel formulations were prepared using carbopol -934 and HPMC K4M as gelling agents. Required quantity of gelling agent was weighted and dispersed in a small quantity of distilled water to form a homogeneous dispersion. The drug was dissolved in suitable solvent (PG or ethanol) and added to the above solution. Other excipients (methyl paraben and propyl paraben) were also added

with continuous stirring. The pH of the gels was brought to skin pH by TEA. The final weight of the gel was adjusted to 50 grams with distilled water. The gels were stored in wide mouthed bottles. Entrapped air bubbles were removed by keeping the gels in vacuum oven for 2 hours. The composition of various gel formulations is shown in Table No.2

Optimisation of Gel formulation

The experimental design was a two factor three level (3^2) full factorial design (FD) and nine formulations were prepared. The amount of polymers X_1 (HPMC K4M) and X_2 (carbopol -934) were selected as independent variables. The amount of polymers was optimised for dependent variables: Drug release after 8 hours and viscosity of gels. The low (-1), medium (0) and high (1) are the values of X_1 (HPMC K4M) and X_2 (carbopol -934) respectively. Nine batches were formulated as shown in Table 2. In a full FD, all the factors are studied in all possible combinations, as it is considered to be most efficient in estimating the influence of individual variables and their interaction using minimum experimentation. In the present study the responses were analysed for ANOVA using design expert software (trial version 8.0.7). A mathematical equation was generated for each parameter. The mathematical model was studied for significance. Response surface plots were generated for each response to study the behaviour of the system.

Generation of statistical models

A statistical model, Y= incorporating interactive and polynomial terms was used to evaluate the responses; where Y is the dependent variable, is the arithmetic mean response of the nine runs and is the estimated coefficient for the factor X. The main effects (X_1 and X_2) represent the average result of changing one factor between two factors.

Optimum formulation for topical gel of clobetasol propionate

Gels were prepared as method described earlier. The composition of optimized formulation (F10) of the gel is tabulated in Table 8.

Development of optimized topical gel

The optimized gel was prepared with the best amount of polymers suggested by the design expert software (demo version 8.0.7). The prepared gels were evaluated for its physiochemical properties viz. Homogeneity, grittiness, spreadability, viscosity, Ph measurement, drug content and *In-vitro* drug diffusion studies. The procedures for the above mentioned properties are described below. The results are shown in Table 8 and 9.

Evaluation of Gels

A. pH Measurement [11]

The pH of various gel formulations was determined by using digital pH meter.1 g of gel was dissolved in 100 mL freshly prepared distilled water and stored for two hours. The measurement of pH of each formulation was done in triplicate and average values are calculated.

B. Homogeneity [12]

All developed gels were tested for homogeneity by visual inspection after the gels have been set in the container.

C. Grittiness [13]

Smears of gels were prepared on glass slide and observed under the microscope for the presence of any particle or grittiness.

D. Viscosity Measurement [12, 14]

Brookfield digital viscometer was used to measure the viscosity of prepared gel formulations. The spindle no. 6 was rotated at 10 rpm. The reading, near to 100 % torque was noted. Samples were measured at 30 ± 1 °C.

E. Spreadability [15]

One of the criteria for a gel to meet the ideal quantities is that it should possess good spreadability. It is the term expressed to denote the extent of area to which gel readily spreads on application. The therapeutic efficacy of a formulation also depends upon its spreading value. It was determined by wooden block and glass slide apparatus. Weights of about 2 g were added to the pan and the time was noted for upper slide (movable) to separate completely from the fixed slides. Spreadability was then calculated by using the formula:

$S = M.L / T$

Where,

S = Spreadability

M = Weight tide to the upper slide

L = Length of a glass slide

T = Time taken to separate the slide completely from each other.

F. Drug content [16, 17]

A specific quantity (1 g) of developed gel was taken and dissolved in 100mL of phosphate buffer of pH 7.4. The volumetric flask containing gel solution was shaken for 2 h on mechanical shaker in order to get complete solubility of drug. The solution was filtered through 0.45 µm membrane filter and estimated spectrophotometrically at 293 nm using phosphate buffer (pH 7.4) as blank.

G. In-vitro Drug Diffusion Study [18]

In-vitro drug release studies were performed by using a modified Franz diffusion cell with a receptor compartment capacity of 20 ml. The synthetic cellophane membrane was mounted between the donor and receptor compartment of the diffusion cell. The formulated gels were weight up to 1 g and placed over the drug release membrane and the receptor compartment of the diffusion cell was filled with phosphate buffer pH 7.4. The whole assembly was fixed on a magnetic stirrer, and the solution in the receptor compartment was constantly and continuously stirred using magnetic beads at 50 RPM; the temperature was maintained at 37 ± 0.50 °C. The samples of 1 mL were withdrawn at time interval of 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330, 360, 390, 420, 450 and 480 minutes and analysed for drug content spectrophotometrically at 240 nm against blank. The receptor phase was replenished with an equal volume of phosphate buffer at each time of sample withdrawal. The cumulative amounts of drug diffused from gels were plotted against time.

Mechanism of Drug Release [19]

Various models were tested for explaining the kinetics of drug release. To analyse the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, Hixon- Crowell model and Korsmeyer-Peppas release model.

Zero order release rate kinetics

To study the zero–order release kinetics the release rate data are fitted to the following equation.

$F = K0.t$ ..... **(Eq. 1)**

Where 'F' is the drug release, 'K0' is the release rate constant and 't' is the release time. The plot of percentage drug release versus time is linear.

First order release rate kinetics

The release rate date are fitted to the following equation

$Log (100 – F) = K t$ ..... **(Eq. 2)**

A plot of log % drug release versus time is linear.

Higuchi release model

To study the Higuchi release kinetics, the release rate data were fitted to the following equation, where, 'k' is the Higuchi constant. In higuchi model, a plot of percentage drug release versus square root of time is linear.

Hixon-Crowell model

To study the Hixon-Crowell release kinetics, the release rate data were fitted to the following equation,

$W_0^{1/3} - Wt^{1/3} = k\,t$…… **(Eq. 3)**

Where, 'Wo' is the original mass/weight of drug, 'Wt' is the mass/weight at't' time, 'k' is Hixon-Crowell constant. In this model ($Wo^{1/3} - Wt^{1/3}$) versus time is linear.

Korsmeyer and Peppas release model:

The release rate data were fitted to the following equation, Where, Mt /Mμ is fraction of drug released 'k' is the release constant, 't' is the release time, 'n' is diffusion exponent, if n is equal to 0.89, the release is zero order. If n is equal to 0.45 the release is best explained by Fickian diffusion, and if 0.45 < n < 0.89 then the release is through anomalous diffusion or non-fickian diffusion (swellable and cylinder Matrix). In this model, a plot of log (Mt/Mμ) versus log (time) is linear. The data from *In-Vitro* Drug diffusion studies of gels was fitted to Zero-order, First order, Higuchi, Hixon- Crowell, and Korsmeyer- Peppas model to study the kinetics of drug release.

Stability Study [20, 21]

In order to access the long term stability, the optimised gel of clobetasol propionate was packed in aluminium collapsible tubes and stored at (40 ± 2ºC/75 ±5% RH) for a period of three months. The test conditions are given in Table 1.

The gels was withdrawn after a period of 15 days and analysed for physical characterisation and drug content spectrophotometrically at 240 nm. The data obtained was fitted into the first order equations to determine the kinetics of degradation. The diffusion profile of optimised gels was also compared. The diffusion similarity factor (f2) was also calculated to compare before and after storage diffusion profile. In recent years, FDA has placed more emphasis on diffusion profile comparison in the area of post-approval changes and bio waivers. Under appropriate test conditions, a diffusion profile can characterise the product more precisely than a single point diffusion test. A diffusion profile comparison between pre-change and post- change products for Scale-up and post approval changes SUPAC related changes, or with different strengths, helps assure similarity in product performance and signals bioequivalence.

Among several methods investigated for diffusion profile comparison, f2 is the simplest.

$f1 = \{[\sum_{t=1}^{n} | R_t - T_t |] / [\sum_{t=1} n R_t]\}.100$…… **(Eq. 4)**

$f2 = 50.\log\{[1+1/n] \sum_{t=1}^{n} (R_t - T_t)^2]^{-0.5}.100\}$……**(Eq. 5)**

Where, R1 and T1 are the cumulative percentage dissolved at each of the selected n time points of the reference and test product respectively. When the two profiles are identical, *f2* = 100. An average difference of 10 % at all measured time points result in an f2 value of 50. FDA has set a public standard of an f2 value of 50 to 100 which indicates similarity between two diffusion profiles.

Table 1: It shows test conditions for stability studies

Accelerated stability	Testing conditions
Temperature conditions* (º)	40±2
Relative humidity conditions* (%)	75±5
Frequency of testing samples	0, 15, 30, 45, 60, 75 and 90 days

º denotes degree Celsius, % is percentage. * indicates Value ± SD where S.D = standard deviation

RESULTS AND DISCUSSION

The results shown in Table 4 clears that the Q_8 and viscosity have a significant effect on the gels prepared. The use of carbopol-934 and HPMC K4M in combination resulted in better drug release and viscosity profiles of gels were also improved. By evaluating these gels, the levels for the optimisation of the independent factors were to be set. The three levels (-1, low: 0, medium: +1, high) of carbopol-934 and HPMC K4M were selected.

Table 2: It shows formulations according to factorial design level

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Carbopol - 934	0.5	0.5	0.5	1.0	1.0	1.0	1.5	1.5	1.5
HPMC K4M	0.5	1.0	1.5	0.5	1.0	1.5	0.5	1.0	1.5
Propylene glycol	15	15	15	15	15	15	15	15	15
Ethanol	40	40	40	40	40	40	40	40	40
Methyl paraben	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Propyl paraben	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Triethanolamine	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S

*All Quantities are in percentage (%); Q.S is Quantity sufficient.

Table 3: It shows characterization of gels (F1 – F9)

Parameters → / Formulations ↓	Homogeneity	Grittiness	pH
F1	+++	-	6.9
F2	+++	-	7.1
F3	+++	-	7.0
F4	++	-	7.0
F5	+++	-	7.2
F6	++	-	6.9
F7	++	-	7.0
F8	++	-	6.9
F9	++	-	7.1

+ Satisfactory, ++ good, +++ Very good; - no grittiness

Table 4: It shows characterization of gels (F1 – F9)

Parameters* → Formulations ↓	Spreadability (g.cm/s)	Percentage Drug Content	Percentage Drug Release after 8 hours (Q_8)	Viscosity (cps)
F1	38.98±0.56	99.6±0.2	93.56±2.7	18980±19
F2	36.26±0.68	99.3±0.2	88.98±2.1	23039±17
F3	33.29±1.89	98.9±0.5	85.69±2.0	24129±13
F4	32.65±1.14	99.1±0.2	79.61±2.6	26374±10
F5	31.25±0.62	98.6±0.1	78.47±3.1	27324±14
F6	28.97±0.29	99.2±0.3	76.39±2.2	28926±23
F7	27.49±0.48	99.7±0.1	73.26±2.5	32386±15
F8	26.54±0.32	99.1±0.3	71.15±3.2	34248±22
F9	25.78±0.58	98.6±0.4	69.89±2.4	35390±24

* means that each value is average of three independent determinations and is presented as Mean ±S.D. S.D= standard deviation; g.cm/s = grams centimetre per second; cps = centipoise

Batch no. F1 – F9 were prepared using different concentrations of carbopol-934, HPMC K4M in the concentration range of 0.5-1.5 %. The data for physiochemical characterization of these batches is shown in Table 3 and 4.

In order to investigate the factors systematically and optimize the gels for Percentage drug release after 8 hours (Q_8) = 91 %, viscosity = 20000 cps, a factorial design is applied in the present investigation. The amount of carbopol-934 and HPMC K4M was chosen as independent variables in a 3^2 full factorial design (FD). A statistical model incorporating interactive and polynomial terms was used to evaluate the responses.

$$Y=b_0 + b_1X_1 + b_2X_2$$

The Q_8 and viscosity for the 9 batches (F1 –F9) shown in table 4 showed a wide variation. The data clearly indicates that the percentage release and viscosity values are strongly dependent on the selected independent variables. The fitted equation relating the responses percentage release and viscosity to the transformed factors are shown in Table 6.

Table 5: It shows factorial design based gel formulation of clobetasol propionate

Formulation code	X1(%)	X2(%)	Percentage drug release at 8 hours (Q_8)	Viscosity (cps)
F1	-1	-1	93.56	18980
F2	-1	0	88.98	23039
F3	-1	1	85.69	24129
F4	0	-1	79.61	26374
F5	0	0	78.47	27324
F6	0	1	76.39	28926
F7	1	-1	73.26	32386
F8	1	0	71.15	34248
F9	1	1	69.89	35390
Coded values	**Actual Values**			
	X1	**X2**		
-1	0.5	0.5		
0	1	1		
1	1.5	1.5		

X1 indicates amount of Carbopol-934(mg), X2 indicates amount of Hydroxypropyl methylcellulose (HPMC K4M K4m)

The polynomial equations can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries (i.e. positive or negative).Table 7 shows the results of ANOVA, which was performed to identify insignificant factors. The values of correlation coefficient for percentage release, 0.9669 and viscosity, 0.9831 (Table 7) indicate good fit. The F-value is the ratio of model mean square to the appropriate error (i.e. residual) mean square. The larger the F-Value and the more likely that variance contributed by model are significantly larger than random error. If the F ratio, the ratio of variances lies near the tail of the (F) distribution then the probability of a larger F is small and the variance ratio is judged to be significant. Usually, a probability less than 0.05 is considered significant. Values of 'p' less than 0.05 indicate model terms are significant. In this case both the models generated for percentage release and viscosity were significant. As there were no insignificant terms, model reduction is not required. The F value distribution is dependent is dependent on the degrees of freedom (DF) for the variance in the numerator and the <DF> of the variance in the denominator of the F ratio. The model F value of 87.63 for Q_8 and 174.06 for viscosity and high R^2 values suggested that these models are significant. PRESS (predicted residual sum of squares) is a measure of how well the model fits each point in the design. The model is used to estimate each point using all of the design points except that one. The difference between the predicted value and actual value at each point is squared and summed over all of the points. Small values for the same in these models show a good fit of the data points. Adequate precision measures the signal to noise ratio. A ratio greater than 4 is desirable the ratios of 22.932 and 32.830 respectively for Q_8 and viscosity models indicated an adequate signal for each. These models can be used to navigate the design space.

Table 6: It shows fitted equation for percentage drug release after 8 hours and viscosity

Coefficient	b_0	b_1	b_2
Q_8	79.67	-8.99	-2.41
Viscosity	27866.22	5979.33	1784.17

b_0, b_1 and b_2 represent polynomial terms.

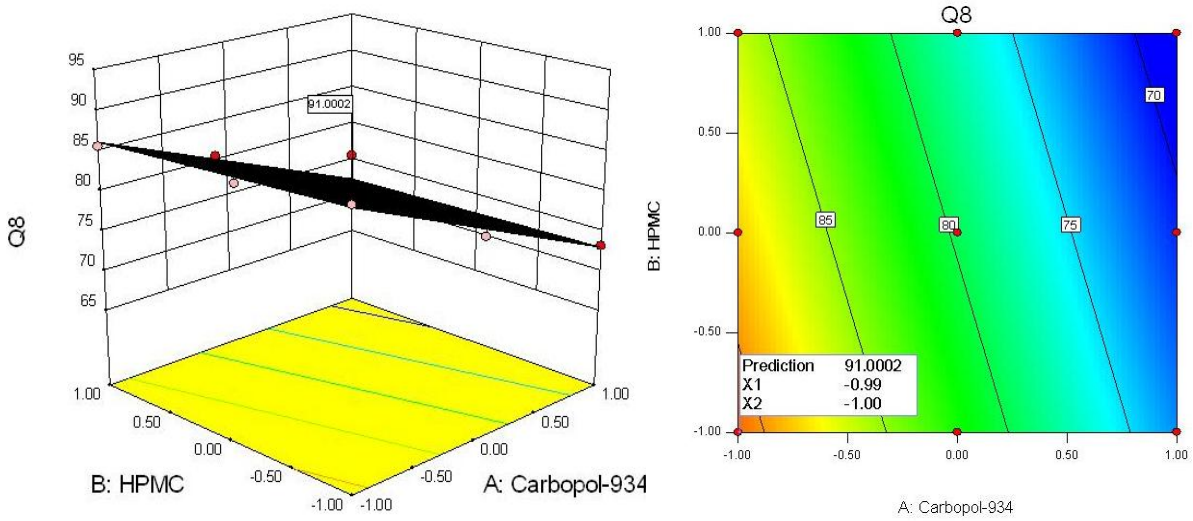
Table 7: It shows ANOVA for testing the models in portions

Response model	Percentage drug release after 8 hours (Q_8)	Viscosity
Sum of squares	519.59	2.336E+008
Degrees of freedom	2	2
Mean square	259.79	1.168E+008
Model F Value	87.63	174.06
P Value	<0.0001	<0.0001
R^2	0.9669	0.9831
Adequate Precision	22.932	32.830
PRESS	45.33	9.688E+006

PRESS is predicted residual sums of squares, R^2 is correlation coefficient

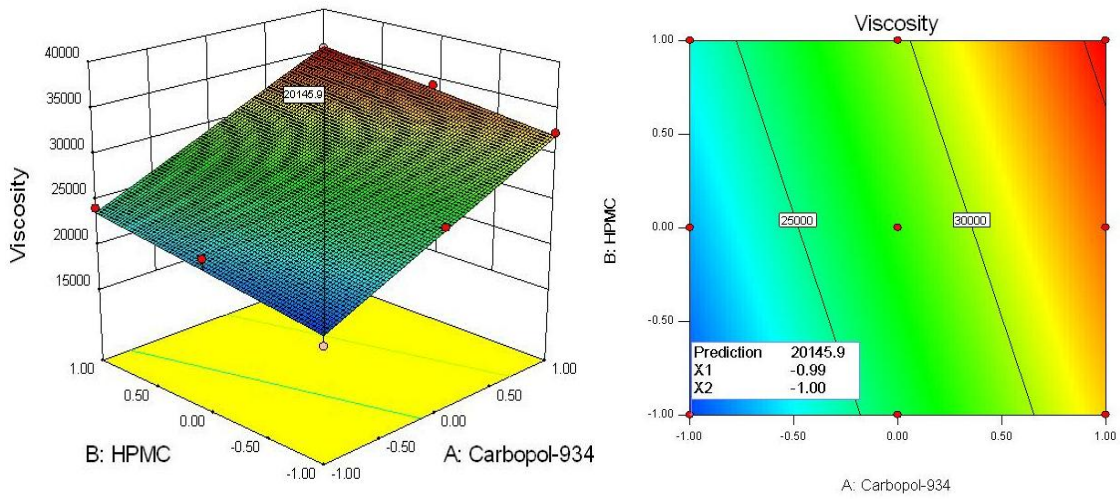
The results of multiple linear regression analysis reveal that, on increasing the concentration of either carbopol-934 or HPMC K4M, a decrease in Q_8 was observed; both the coefficients b1 and b2 bear a negative sign. Gelling agents undergo a high degree of cross-linking or association when hydrated and dispersed in the dispersing medium, or when dissolved in the dispersing medium. This cross-linking or association of the dispersed phase will alter the viscosity of the dispersing medium. The movement of the dispersing medium is restricted by the dispersed phase, and the viscosity is increased. When higher percentage of carbopol-934 or HPMC K4M was used, the viscosity of the gel formulation increases. This phenomenon may be attributed to the increase in number and size of micelles formed at higher polymer concentration, which causes a greater tortuosity in the aqueous phase of the gel structure. Viscosity plays a vital role in the dispensing and formulation of topical gels. Depending on the need, gels with good rheological properties can be prepared using different gelling agent in variable concentrations.

Results were shown in response surface plot and a contour plot for Q8 and Viscosity (Fig 1 and Fig 2).



(A) **(B)**

Fig. 1: It shows response surface (A) and contour (B) plots for percentage drug release after 8 hours (Q_8)



(A) **(B)**

Fig. 2: It shows response surface (A) and contour (B) plots for viscosity

The optimization of the gel was decided to target Q_8 of 91 % and Viscosity of 20000 cps. The optimized concentration was obtained by using design expert software (Demo version 8.0.7.1) as clears in the response surface prediction curves. A checkpoint batch was prepared at X_1 = 0.495 level and X_2 = 0.5 level. From the full model, it was expected that the Q_8 value should be 91 % and the value of viscosity should be 20145 cps. Table 8 indicates that the results were as expected. Thus, we conclude that the statistical model is mathematically valid. The optimized formulation was characterized for gel characterization.

In vitro Drug release Studies

In-vitro drug release experiments were performed at 37±0.5ºC using a modified Franz diffusion cell fir the optimized formulation. The drug release at the end of 480 min for the optimized formulation was 91%. The results of dissolution profile for the optimized formulation are shown in Table 9.

Stability studies

No significant difference was observed in the release profile of optimized formulation (F10) indicating that the fabrication process employed was reliable and reproducible. Further there was no change in physical appearance at the end of 90 days storage period at accelerated conditions (40±2º C/75 ± 5% RH). The optimized formulation was also subjected for the estimation of drug content and *in-vitro* drug release as reported in table 10 and 11.

Thus results implied good stability of different products at short term storage. The value of similarity (f2) and dissimilarity (f1) factor for *in-vitro* release study suggest that profile of optimized gel formulation (F10) matches with that of theoretically predicted ; since f1 and f2 was less than 15 and greater than 50 were obtained. Therefore, it can be concluded that the selected formulation is stable for 90 days w.r.t appearance, pH, homogeneity, grittiness, spreadability, drug content, % drug release after 8 hours (Q_8) and Viscosity.

Table 8: It shows composition and evaluation results of optimized gel formulation (f10)

Ingredients	**Amounts (%)**
Clobetasol propionate	0.05
Carbopol-934	0.495
HPMC K4M	0.5
Propylene glycol	15
Ethanol	40
Methyl paraben	0.3
Propyl paraben	0.6
Triethanolamine	Q.S
Distilled water	Q.S
Parameters	**Results**
pH	7.0
Homogeneity	**+++**
Grittiness	**-**
Spreadability* (mg.cm/s)	39.24±0.47
Percentage Drug content**	99.6±0.2
Percentage release after 8 hours (Q8)***	91.02±0.32
Viscosity (cps)	20145

+ Satisfactory, ++ good, +++ Very good; - no grittiness; mg.cm/s = milligram.centimeters per second; *, **, *** indicate that value are presented as Mean ±S.D where S.D= standard deviation.

Table 9: It shows percentage drug release of optimised gel formulation

Time(min)	**Cumulative mean percentage drug released***
0	0
30	15.25±1.33
60	25.23±1.13
90	32.64±1.18
120	38.36±1.07
150	47.14±0.87
180	52.14±1.30
210	61.59±1.45
240	68.66±1.31
270	72.23±0.62
300	77.69±1.60
330	81.06±0.73
360	84.81±0.72
390	86.32±0.35
420	88.20±0.31
450	89.21±0.49
480	91.02±0.32

Min =minutes; * Indicates that value are presented as Mean ± S.D where S.D is standard deviation

Table 10: It shows effect of storage conditions on optimized formulation at accelerated storage conditions (40±2º /75 ±5% RH)

Time Interval (Days)	**Physical appearance**	**pH**	**Homogeneity**	**Grittiness**
0	White colour	6.9	+++	-
15	White colour	7.1	+++	-
30	White colour	7.2	+++	-
45	White colour	7.0	+++	-
60	White colour	7.1	+++	-
75	White colour	7.0	+++	-
90	White colour	6.9	+++	-

º is degree Celsius, R.H is relative humidity; + Satisfactory, ++ good, +++ Very good; - no grittiness

Table 11: It shows effect of storage conditions on optimized formulation at accelerated storage conditions (40±2º c/75 ±5% RH)

Time Interval (Days)	Spreadability (gm.cm/s)*	Percentage Drug content**	Percentage Drug release after 8 hours (Q_8)***	Viscosity (cps)****	f2	f1
0	39.16±0.26	99.6±0.2	91.04±1.20	20018±21	92.36	1.96
15	39.25±0.11	99.6±0.1	91.06±1.32	20026±36		
30	39.17±0.08	99.5±0.1	91.04±0.87	20007±14		
45	39.24±0.21	99.5±0.1	90.9±1.17	200024±29		
60	39.29±0.32	99.4±0.1	90.9±1.19	20011±13		
75	39.05±0.24	91.0±0.2	90.8±1.31	20023±15		
90	39.35±0.13	90.85±0.2	91.01±0.98	200027±23		

º is degree Celsius, R.H is relative humidity; mg.cm/s is milligram.centimeters per second; cps is centipoise; *, **, ***, **** indicates that values are presented as Mean ±S.D where S.D is standard deviation

Mathematical Model for Optimized gel formulation

Various release kinetics equations in which the experimental data can be fitted and the drug release can be predicted as a function of some variable (e.g. time) are described below. The suitability of equation is judged on the basis of best fit to the equation using statistical indicators like r^2 values.

The release data obtained was subjected to kinetic treatment to know the type and order of drug release. The data obtained from *in-vitro* drug release study is tabulated as shown in Table 9.It was found that the release from the gels follow first order kinetics as predicted by their higher correlation coefficient value (R^2) as shown in Table 12.The various release profiles are shown in Figure 3, 4, 5, 6 and 7).

- Cumulative percentage drug released v/s Time (Zero order release kinetics)
- Log cumulative percentage drug remaining v/s Time (First order release kinetics)
- Cumulative percentage drug release v/s Square root of time (Higuchi model)
- Cube root of drug percentage remaining v/s Time (Hixen-crowell)
- Log of percentage drug released v/s Log of time (Korsmeyer and Peppas model)

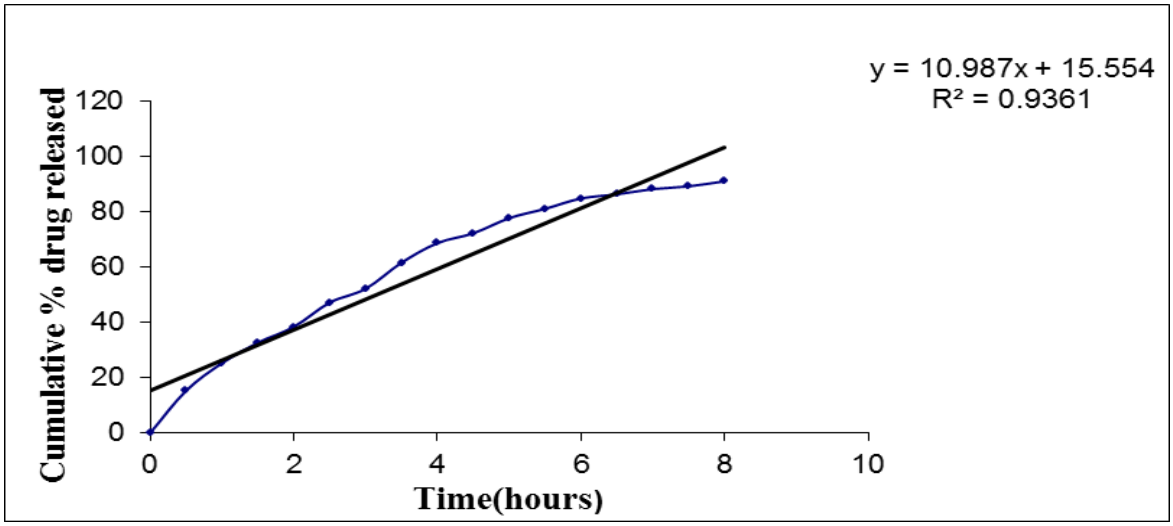


Fig. 3: It shows zero order drug release for optimised gel formulation (F10)

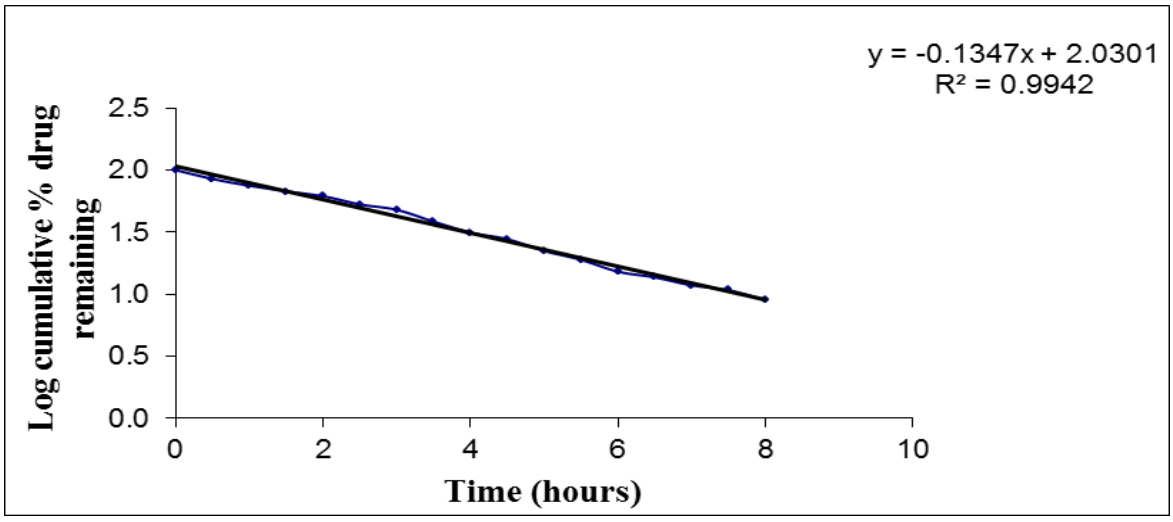


Fig. 4: It shows first order drug release for optimised gel formulation (F10)

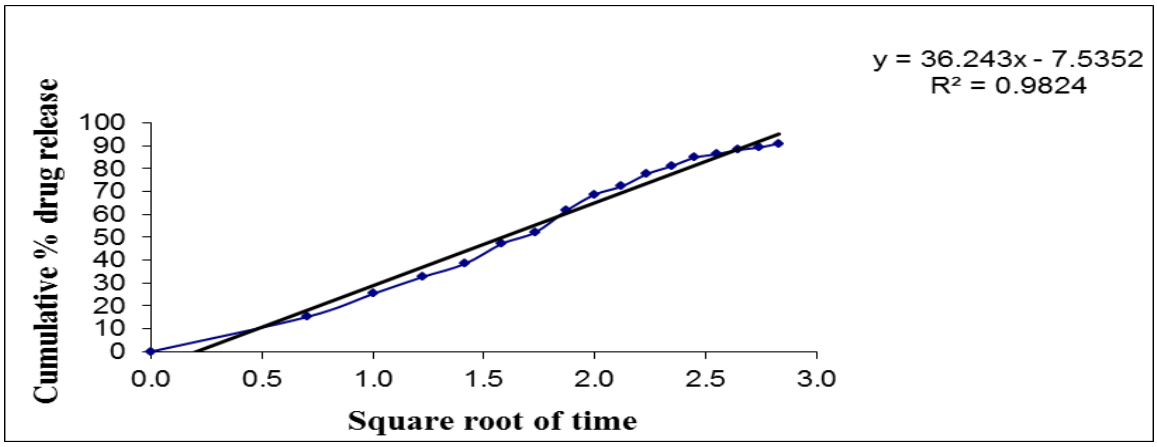


Fig. 5: It shows higuchi model drug release for optimised gel formulation (F10)

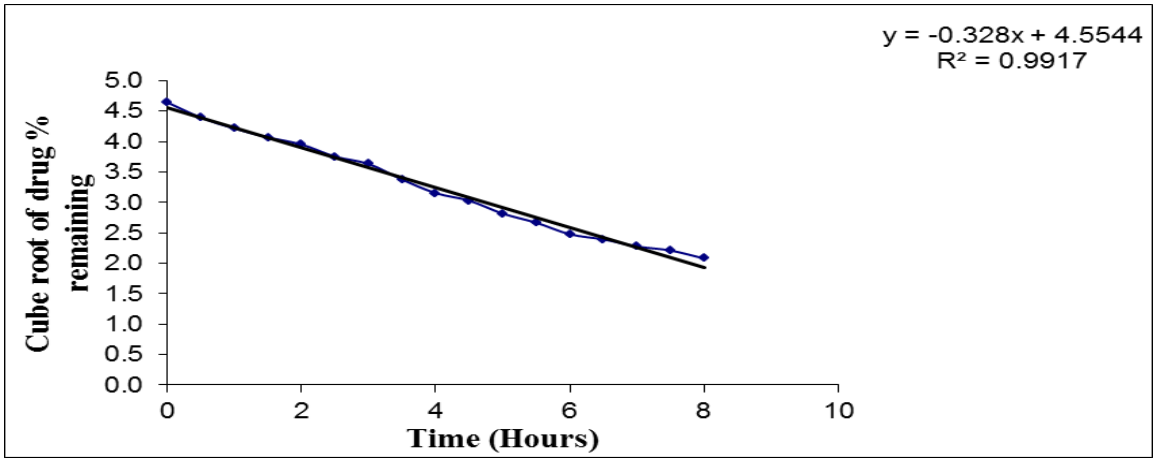


Fig. 6: it shows hixon-crowell model drug release for optimised gel formulation (F10)

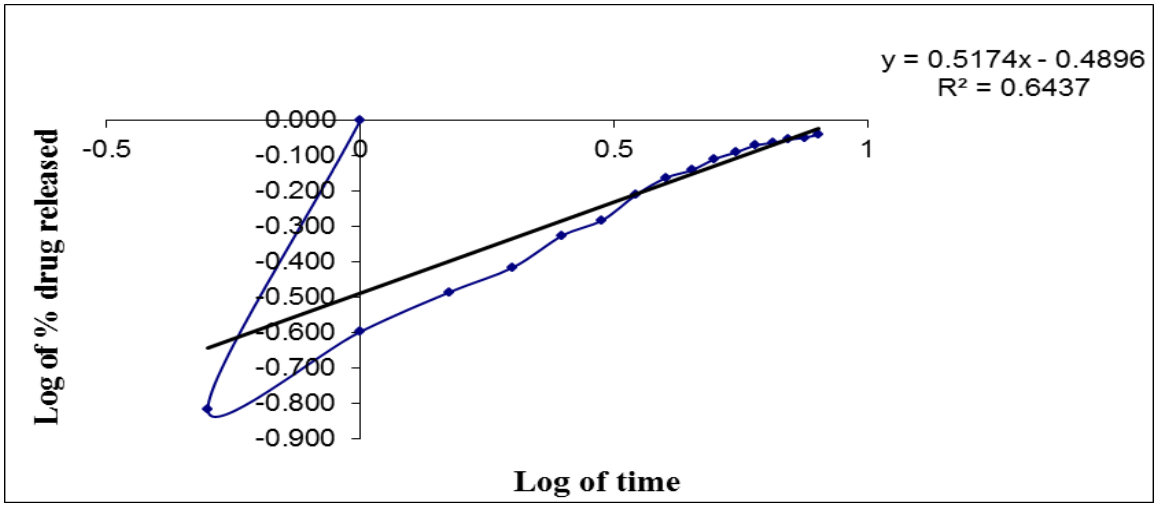


Fig 7: It shows korsmeyer and Peppas model drug release for optimised gel formulation (F10)

Table 12: It shows fit of various kinetic models for the optimized formulation (F10)

Formulation Code	Zero order		First order		Higuchi		Hixen-crowell		Korsmeyer and Peppas	
	R2	Slope	R2	Slope	R2	Slope	R2	Slope	R2	n
F10	0.9361	10.987	0.9942	-0.1347	0.9824	36.243	0.9917	-0.328	0.6437	0.5174

R^2 is correlation coefficient.

Drug release mechanism using drug release data for formulation F32 was further analysed for curve fitting based on power law. The value of n=0.5174 and R^2=0.6437 confirmed that release of clobetasol propionate from the formulation F10 followed anomalous transport (0.5 > n < 1.0) indicating that more than one type of release phenomenon could be involved.

CONCLUSIONS

Results indicated that the concentration of carbopol-934 and HPMC K4M significantly affects drug release and rheological properties of the gels. The viscosity of carbopol-934 gels was very high as compared to HPMC K4M gels but both gels showed decrease in drug release with increase in polymer concentration. Thus, clobetasol propionate gels can be successfully prepared using carbopol-934 and Hydroxypropyl methylcellulose K4M as gelling agents. The study holds promise for further investigation in the development stable topical gels of clobetasol propionate.

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