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Preparation And Characterization Of Dapsone Hydrogel Using Quality By Design

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ABSTRACT:

The present study work undertaken with the intend to develop a topical hydrogel formulation of dapsone 7.5% which would attenuate the first pass metabolism associated with an oral administration. Dapsone has low solubility and low permeability and classified as BCS class II drug as per biopharmaceutics classification system. The dapsone is formulated as hydrogel which premeditated to application by topical route for the treatment of skin disease acne vulgaris. The QTPP was define considering the product quality and efficacy. CQAs are drug product quality metrics and identified for process validation. The hydrogel formulation containing dapsone was optimized by using central composed design (CCD). Concentration of polymer's and concentration of pH modifier were identified as independent variables and drug release, pH measurement, viscosity and extrudability were dependent variables. Hydroxypropyl methyl cellulose (HPMC) with concentration of 5 – 10 %, Sodium Carboxymethyl Cellulose (Sod. CMC) with 5 – 10 % as pH modifier Triethanolamine (TEA) with 2.5 – 7.5 %. The optimization study confirms with 20 runs which designate a high level of prognostic skill of response surface methodology. The formulations characterized by drug content, pH, extrudability, residence time, drug release and viscosity. From the obtained results of drug release it was concluded that an optimized formulation shows a complete drug release. An accelerated stability study analysis showed acceptable results for an optimized trial formulation.

Keywords: Hydrogel, CCD, dapsone, extrudability, etc

Introduction:

The administrations of topically applied drugs are considered as local drug delivery method everywhere on body such as skin, vaginal, rectal, ocular and topical route. Dermal layer is the major way of drug delivery system for topical administration because skin is one of the largest and most easily available organ on the human body. Skin plays a major obstruction for access of many substances and this is mostly because of stratum corneum of the skin, it allows only small molecules to penetrate over a period of time into a systemic circulation.

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Averting of risk, annoyance of injectable delivery and varied physiological condition like gastric emptying time, pH change, absorption, presence of enzyme are advantages of drug delivery by topical route. The topical delivery systems normally used whenever the other drug delivery systems not possible or feasible, mostly uses in the treatment of pain, acne and contraception. TDDS well-defined as an appliance of drug comprising preparation onto body skin which unswervingly delight cutaneous maladies (e.g. acne) or cutaneos appearances of common ailment (e.g. psoriasis) with intention of restricting the pharmacological or further consequence of the active ingredient to apparent surface of the dermis or inside the skin. [1,2,3].

Active moiety penetrates the skin through tortuous and continueous intercellular path. By addition of permeation enhancer and solvents in the topical formulation the drug can transport by hair follicles, a transcellular route and sweat ducts [4].

Previously it was considered that, the skin is an impervious shielding barrier but then an investigation proves that the skin will be used as route of systemic administration [5]. Absorption of drug may occur through following three major routes:

1. Transcellular Route: The drug may transport through keratin crowded corneocytes by way of partitioning into and away from the cell membrane.
2. Intercellular Route: The transportation in lipid loaded extracellular region about the corneocytes.
3. Transappendageal Route: The shunt transport by hair follicles, sebaceous and sweat glands.[6]

Now a days hydrogels are interesting method of preparation of gels in dermatology and cosmeticology. Hydrogels can fabricate through physical or chemical cross-linking, which endow with physical stability and networked structure. These material cross-links comprise Van Der Waals, entanglements, hydrogen bonding or crystallites. Hydrogels identified as physical, reversible or hydrogels which formed from physical cross-links and are identified as permanent or chemical gels which are produced through covalent bond cross-linked network. [7,8,9,10,11]

The different mechanism governs release of drug through hydrogels i.e. chemical stimulation or duffusion. Drug releases by diffusion mechanism with bulk erosion or through matrix of polymer of the hydrogels, whereas, the entrapped drug releases through their pores by chemical stimulation an enzymatic action, temperature or pH of the external cues are accountable for swelling of hydrogel.[12] Because of materials cross-linking hydrogels absorbs much quantity of water and this potential arises by attachment of hydrophilic functional groups to the backbone of polymer while their confrontation to drug release arises from cross-links among network chains. The water inside of hydrogel allows diffusion of drug whereas, the polymer matrix holds the water together. [13]

Acne vulgaris is a multifactorial provocative dermal disease which mostly affects young adults and adolescents. The presently available marketed 5% dapsone gel was introduced to lessen systemic absorption and hence improve the acceptability of drug; on the other hand, it requires two times application in a day and which is inconvenience to patients. An increased

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dose of 7.5% dapsone gel is at the present permitted in US for once-daily topical treatment of acne in ≥12 years of age patients. [14]

The aim of present study to develop hydrogel formulation of dapsone using Hydroxypropyl methylcellulose (HPMC K15M Premium) and Sodium Carboxy Methyl Cellulose (Sod. CMC) as polymer and Triethanolamine (TEA) as pH modifier and optimizes the formulation by means of response surface methodology (RSM). Exercise of RSM has been proved to be functional instrument in the development and optimization. The formulated hydrogel was evaluated for physical characteristics, pH, extrudability, viscosity, drug content and drug release. Accelerated stability study was performed on optimized formulation.[15,16,17]

Methodology:

Preparation of Dapsone 7.5% Hydrogel:

Fourteen formulations were executed using different concentration of polymers and pH modifier. The hydrogel was formulated by dissolving dapsone API in ethanol and propylene glycol was added to it in beaker. HPMC K15M Premium and sod. CMC were dissolved in purified water under continueous stirring for 1 hour, pH was maintained 4.5 to 5.5 using triethanolamine as pH modifier, glycerin, methyl paraben and propyl paraben were added to it. The prepared drug solution was added to polymer solution with stirring and water was added to make final weight.[18,19] The formulations were executed and optimization done by a response surface methodology i.e using central composite design (CCD). Fourteen runs were executed with 6 center point run and characterization done.[20,21]

Experimental Design:

The dapsone hydrogel was optimized by using central composite design with three independent variables to estimate the different parameters, their interactions and evaluation of quadratic effects of excipients on dapsone hydrogel by constructing replica using Design Expert (version 13, Stat-Ease Inc., Minneapolis, Minnesta). The quadratic equation generated by CCD experimental design is as follows:[20,21,22]

$$Y = a_0 + a_1X_1 + a_2X_2 + a_3X_3 + a_{12}X_1X_2 + a_{23}X_2X_3 + a_{13}X_1X_3 + a_{11}X_1^2 + a_{22}X_2^2 + a_{33}X_3^2$$

Where,

a is regression co-efficient

X_1, X_2, X_3 are main effect terms

X_1X_2, X_1X_3, X_2X_3 are interaction terms

X_1^2, X_2^2, X_3^2 are quadratic term

20 runs were generated for the responses having a concentration of the factors ranging from minimum to maximum concentrations as depicted in below table:

Table 1: Full Factorial Design Layout

Factor	Name	Units	Type	SubType	Minimum	Maximum	Coded Low	Coded High	Mean	Std. Dev.
A	HPMC	%	Numeric	Continuous	3.30	11.70	-1 ↔ 5.00	+1 ↔ 10.00	7.50	2.12
B	Sod. CMC	%	Numeric	Continuous	3.30	11.70	-1 ↔ 5.00	+1 ↔ 10.00	7.50	2.12
C	Triethanolamine	%	Numeric	Continuous	0.7955	9.20	-1 ↔ 2.50	+1 ↔ 7.50	5.00	2.12

Evaluation Parameters for Hydrogel [23,24,25,26,27]:

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1. **Physical Characteristics:** The small quantity of formulation should have to rub on the back side of hand skin and presence of agglomerate or feeling of grittiness can be checked. Colour and phase separation were examined by visual observation.

2. **Spreadability:** It expresses in the term of time take by 2 slides in seconds to slide from formulations which place between 2 slides beneath the application of a definite weight, the shorter the time taking apart of 2 slides indicates enhanced spreadability.

   Procedure: The apparatus typically comprise of a wooden block with pulley at one side. Take two glass slides of size 6 cm x 2 cm. Place the formulation on one slide which is being to be tested. Place second slide on it in such a technique that the preparation will be sandwiched between both the slides. Place 100 g weight on upper slide about approximate 5 min to expel the air, the excess gel will come out from the slide has to be removed after removal of weight. Fix the lower slide on apparatus and tie the upper slide with a string and apply 20 g of load with facilitated by pulley. The time required to separate both the slides should be note down.

   Spreadability = M * L / T

   Where,

   M = Weight which is attached to upper slide (e.g. 20 g)

   L = Glass slide's length (e.g. 6 cm)

   T = Separation time of two slides (seconds)

3. **Content of Drug:** Dissolve known quantity of hydrogel formulation in pH 5.5 phosphate buffer by sonication and filter it to get clear solution. Absorbance of solution measures with the help of UV spectrophotometer at 256 λmax. Prepare calibration curve by using aliquots of different concentration solutions and determine the content of drug using formula, which accomplished by linear regression analysis of calibration curve.

4. **pH measurement:** The 1% aqueous solution of hydrogel formulation should be prepare and keep for two hours then measure for pH value by pH meter.

5. **Extrudability:**

   The hydrogel formulations filled in aluminum collapsible tubes and sealed with crimping of the tube end. The filled tubes weighed and weight recorded. The filled tubes were holds between 2 glass slides which was clamped. The cap was removed after placing the weight of 0.5 Kg on the slides, because of resultant weight the hydrogel comes out from the opening. This extruded quantity was collected and weighed.

6. **Viscosity:**

   The viscosity is an important rheological parameter of the hydrogel, which plays an imperative role in the administration and preparation of topical hydrogel formulations. It is allied to physical and mechanical properties like hardness, consistency and spreadability of the formulation which mostly associated to effortlessness of application on the intended surface, ease of removal of formulation from the container and product sense on the relevant

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site. All the propose design points exhibits a shear-thinning behavior while the viscosity decreases with the increase in shear rate. This is an enviable property in gel formulation because it should be thin during an application. The reason behind pseudoplastic flow revealed by gels may be due to progressive split of the internal structure of preparations and its afterward re-enactment by means of Brownian movement.

Viscosity determinations of the prepared hydrogel were carried out using a rotational viscometer with 'T' shaped special spindles exerting minimal disturbance to sample at room temperature. A typical run will comprise a velocity from 0.4 to 12 rpm with 10 sec between each two successive speeds. Equilibration of the sample for 5 min was made following loading of the viscometer. The reading for each viscosity stage was done at least after 20 sec of run. The average of three readings was used to calculate the viscosity.

7. *In-vitro* Release Study:

Active moiety release from gel can be evaluated in-vitro by using egg membrane which exhibits stratum corneum of human and mainly consists of keratin. Put a fresh egg into concentrated HCl for 15 min and then in fresh water for 5 min and then remove the egg membrane. The resultant egg membrane should be carefully fitted with clamp among receptor as well as donor chamber of Franz diffusion unit. Apply known quantity of gel on to the egg membrane. Prepare fresh pH 5.5 phosphate buffer solution and fill into receptor chamber which may solubilizes drug. Solution of receptor compartment should be stirred continuously with magnetic stirrer and 5 mL of aliquant withdrawn at appropriate time intervals. Analyze the formulation for active content with the help of UV spectrophotometer with required reduction in concentrations.

8. Stability Study: The drug degradation was mostly seen under stability which may results due to instability of prepared formulation and/or decrease in the concentration of active ingredient in the formulation. The finalized hydrogel formulation was studied for accelerated (40 ± 2°C/ 75 ± 5% RH) and long term (25 ± 2°C/ 60 ± 5% RH) stability study as per ICH guideline for 3 months and analyzed to check changes in physical appearance, drug content and extrudability.

Response Analysis for Optimization:

Statistical substantiation of polynomial equation obtained by Design Expert® was recognized on the basis of ANOVA present in the software. Total 14 runs with 6 center points were generated by using central composite design (CCD). Validation of response surface methodology results was performed to find the compositions of optimized formulations over the whole experimental region.

Results and Discussion:[23,24,25,26,27,28]

Evaluation Parameters:

A) Physical Characteristics:

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The prepared hydrogels were evaluated for its physical appearance, grittiness, colour and phase separation after 24 hours of formulation. All were observed as off-white coloured with uniform appearance.

B) Spreadability:

An absorption of drug through dermis layer from a topical gel formulation is depends on its spreadability on the skin and is measured on the basis of 'Slip and Drag' characteristics of hydrogel. The results are portrayed in below Table 2.

C) Drug Content:

The drug contents of all the hydrogel formulations were observed between 98.53% and 101.23% of the labeled claim. Hence, it can be assumed that the prepared hydrogel formulations were suitable for the application on to the skin.

Table 2: Observation of Physical characteristics, Spreadability and Drug Content of hydrogel formulations

Formulation	Grittiness	Colour	Phase Separation	Spreadability (g.cm/sec)	Drug Content
1	No	Off-white	No	13.3	99.36
2	No	Off-white	No	2.5	98.53
3	No	Off-white	No	6.7	100.61
4	No	Off-white	No	0.7	99.89
5	No	Off-white	No	10.0	101.23
6	No	Off-white	No	7.1	100.55
7	No	Off-white	No	8.0	98.59
8	No	Off-white	No	3.4	98.63
9	No	Off-white	No	4.3	98.79
10	No	Off-white	No	2.6	99.36
11	No	Off-white	No	10.9	99.28
12	No	Off-white	No	4.0	100.74
13	No	Off-white	No	3.0	99.79
14	No	Off-white	No	2.2	99.88
15	No	Off-white	No	2.4	100.22
16	No	Off-white	No	2.9	99.41
17	No	Off-white	No	5.5	98.65
18	No	Off-white	No	6.3	99.44
19	No	Off-white	No	3.3	100.27
20	No	Off-white	No	3.4	99.72

D) pH Measurement:

The pH values of formulated hydrogels observed in the range of 3.11 to 6.78 which can be considered good enough to circumvent the risk of irritation which occurs by application onto the dermal layer. The results are portrayed in Table 3.

The model projected the subsequent polynomial equation for viscosity of hydrogel:

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$pH = +4.74 -0.0630A -0.0795B +0.8941C +0.0562AB +0.2063AC +0.1488BC -0.4502A^2 +0.1049B^2 +0.1420C^2$

Where, A is an amount of HPMC K15M Premium, B is an amount of Sod. CMC and C is an amount of Triethanolamine.

pH of twenty formulations was found within range of 3.11 – 6.78. The increase in concentration of triethanolamine increases the pH of the formulation, whereas the HPMC K15M Premium and Sodium CMC has no impact on pH. The model F value of 10.24 implies the model is significant. P values less than 0.0500 indicate model terms are significant which is observed as 0.0006.

The lack of fit F value of 0.83 implies the lack of fit is not significant relative to the pure error. There is a 57.61% chance that a lack of fit F-value this large could occur due to noise. The effect of polymers and triethanolamine on the pH the formulation shows in Figure 1 and Figure 2.

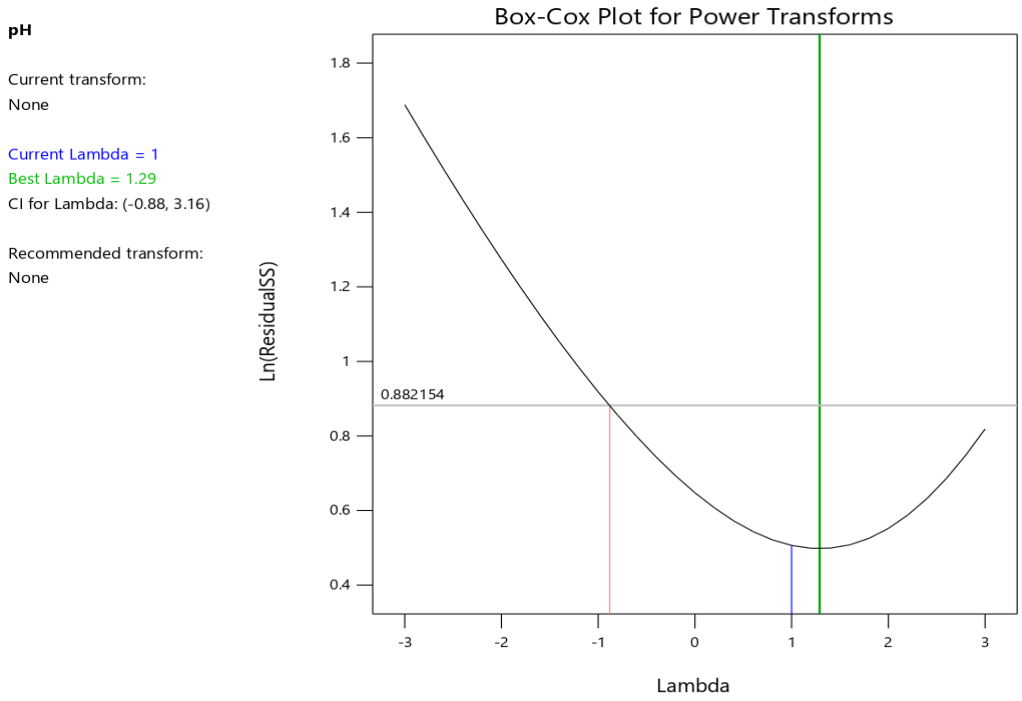

Figure 1: Box-Cox Plot for Power Transforms for pH of the Hydrogel Formulations

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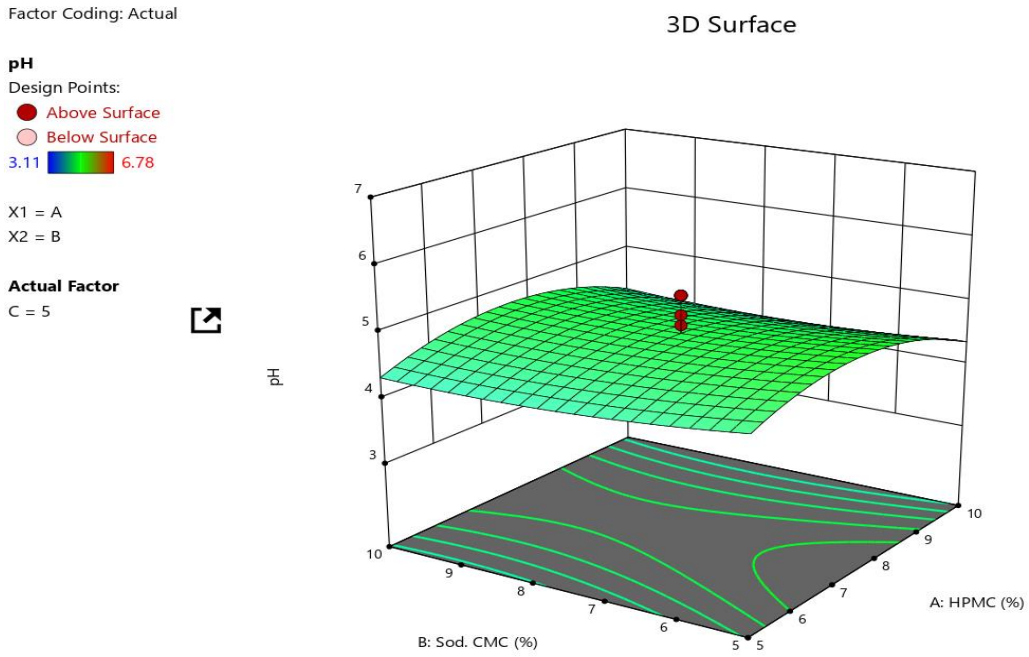

Figure 2: 3D Response Surface Plot for the effect of selecetd factors on pH

E) Extrudability:

Extrudability was performed for all hydrogel formulations as per the method described and results were portrayed in Table 3.
The model projected the subsequent polynomial equation for viscosity of hydrogel:

Extrudability = +2.77 -0.7823A -0.7632B +0.2658C +0.0563AB +0.3513AC -0.0462BC -0.0239A^2 -0.0345B^2 -0.3669C^2
Where, A is an amount of HPMC K15M Premium, B is an amount of Sod. CMC and C is an amount of Triethanolamine.

Extrudability of twenty formulations was found within range of 0.33 – 4.35 g. The increase in concentration of HPMC K15M Premium and sodium CMC decreases the extrudability and triethanolamine does not have impact on extrudability. The model F value of 32.84 implies the model is significant. P values less than 0.0500 indicate model terms are significant which is observed as <0.0001.

The lack of fit F value of 3.72 implies there is a 8.78% chance that a lack of fit F-value this large could occur due to noise. The predicted R^2 of 0.7904 is in reasonable agreement with the adjusted R^2 of 0.9378 i.e. the difference is less than 0.2. The effect of polymers on extrudability of the formulation shows in **Figure 5** and **Figure 6**.

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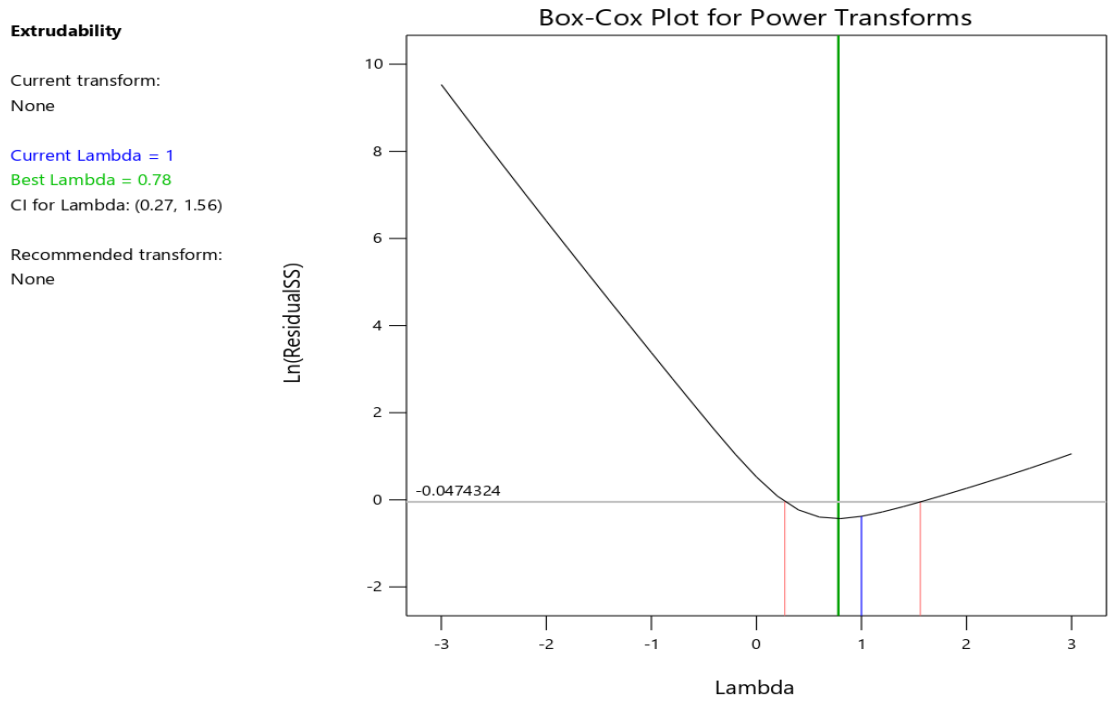

Figure 3: Box-Cox plot for power transforms for Extrudability

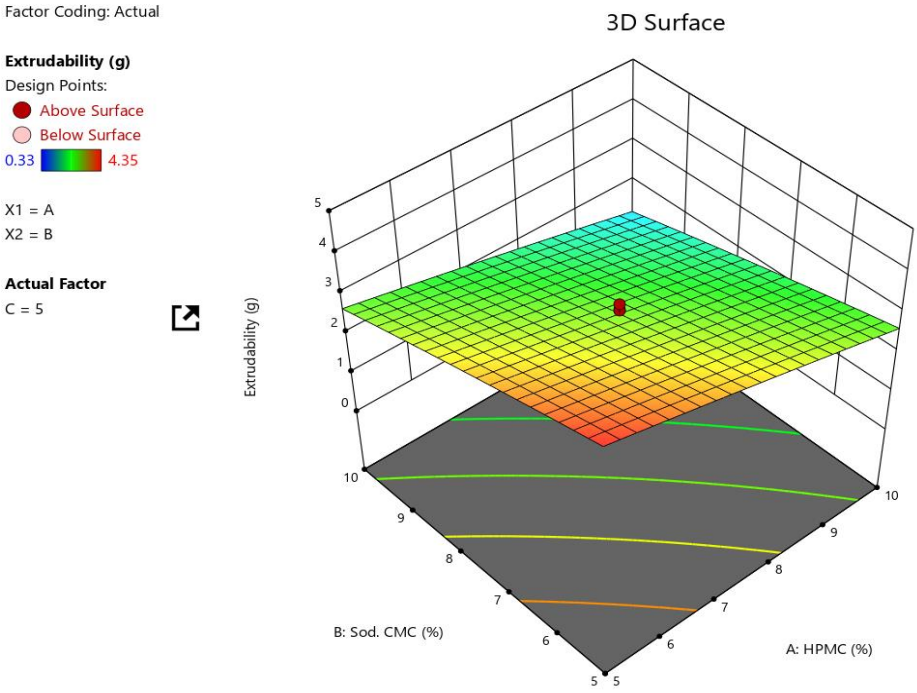

Figure 4: 3D Response Surface Plot for Extrudability

Table 3: Results for Drug Release, pH, Viscosity and Extrudability

Formulation	Drug Release (%)	pH	Viscosity (cps)	Extrudability (g)
1	99.9	4.51	3000	4.35
2	85.77	3.45	30800	1.74

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3	99.95	3.87	35300	2.39
4	56.15	3.12	85500	0.33
5	98.98	5.41	10300	4.01
6	83.75	5.26	47700	3.13
7	100.88	5.45	23450	2.19
8	57.55	5.44	90500	1.21
9	100.01	3.11	10600	3.83
10	48.78	3.77	90500	1.36
11	98.79	5.11	18750	3.55
12	75.75	4.91	80300	1.58
13	98.79	3.45	20200	1.06
14	99.65	6.78	20750	2.19
15	98.91	4.87	24300	2.87
16	100.22	4.55	20500	2.53
17	99.67	5.03	24000	2.85
18	99.23	5.33	21850	3.01
19	100.11	4.11	23600	2.73
20	99.5	4.59	22500	2.66

F) Viscosity:

The model projected the subsequent polynomial equation for viscosity of hydrogel:

Viscosity = +22805.21 +23198.99A +18046.93B +1338.15C +6506.25AB +3306.25AC -3881.25BC +9725.51A^2 +9363.12B^2 -907.60C^2

Where, A is an amount of HPMC K15M Premium, B is an amount of Sod. CMC and C is an amount of Triethanolamine.

Viscosity of twenty formulations was found within range of 3000 - 90500 cps. The increase in concentration of HPMC K15M Premium and Sod. CMC increases the viscosity and the triethanolamine does not have any impact on the viscosity of the hydrogel formulations. The model F value of 476.36 implies the model is significant. P values less than 0.0500 indicate model terms are significant which is observed as <0.0001. In this study HPMC K15M Premium and Sod. CMC having significant effect on viscosity of the preparations.

The lack of fit F value of 2.27 implies the Lack of Fit is not significant relative to the pure error. There is a 19.51% chance that a lack of fit F-value this large could occur due to noise. The predicted R^2 of 0.9860 is in reasonable agreement with the adjusted R^2 of 0.9956 i.e. the difference is less than 0.2. The effect of polymers on viscosity of the formulation shows in **Figure 5** and **Figure 6**. The viscosity of the formulation is directly proportional to the polymer concentration, as the concentration of polymer increases, viscosity increases.

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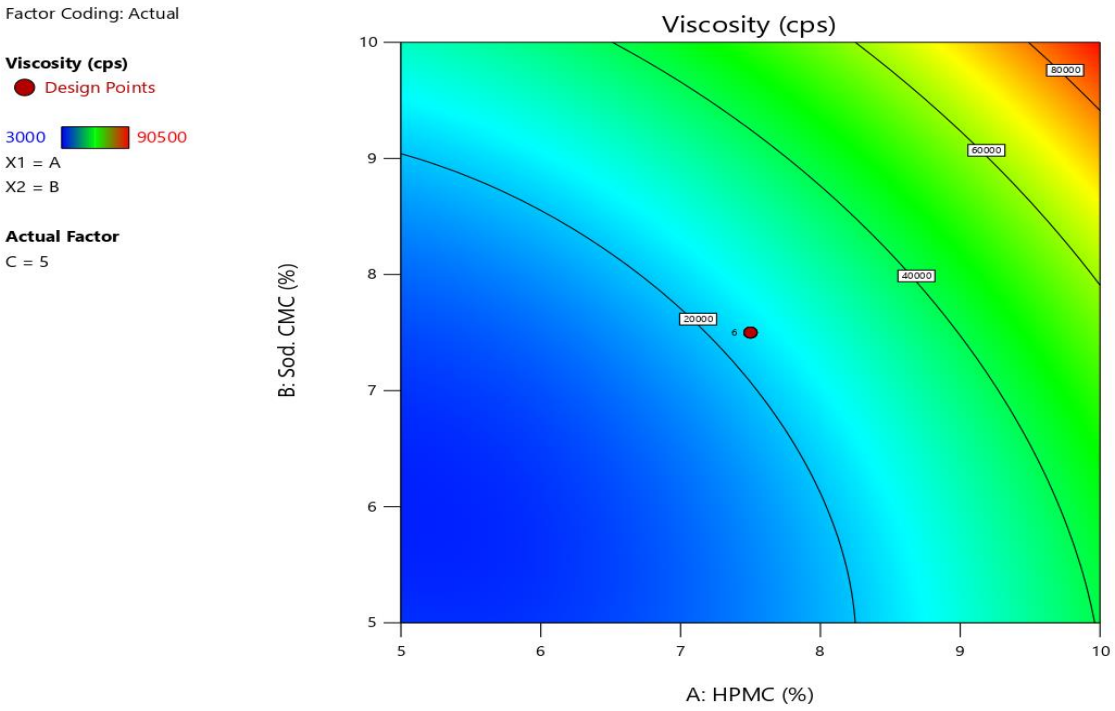

Figure 5: Contour Response Surface Plot for Viscosity

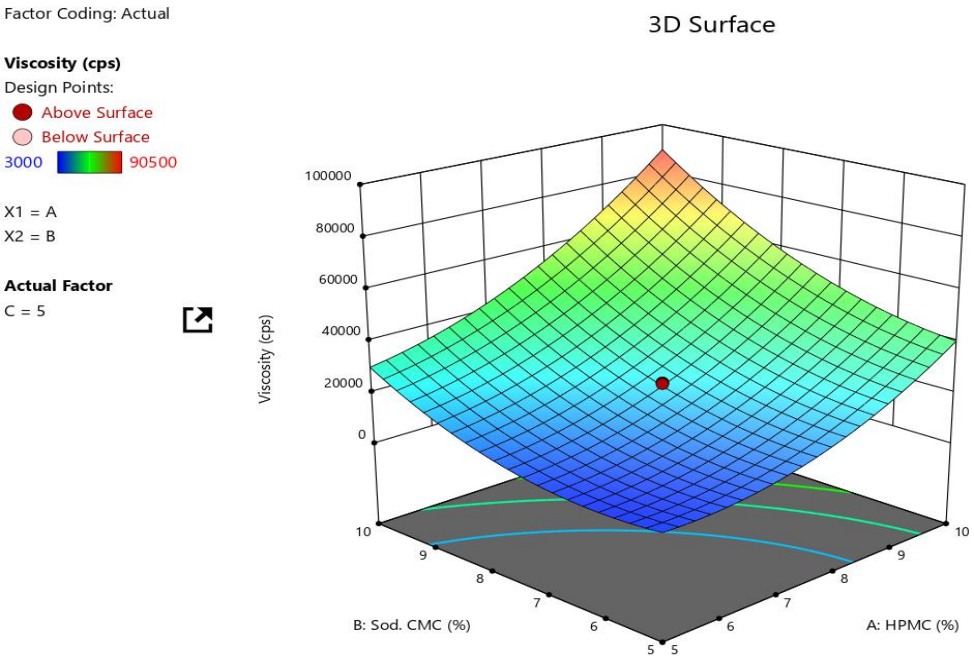

Figure 6: 3D Response Surface Plot for Viscosity

G) In-vitro Drug Release Study:

The model projected the subsequent polynomial equation for drug release of hydrogel:

Drug Release = +99.63 -14.84A -6.78B +0.0612C -7.22AB -0.0787AC +0.6587BC -9.09A^2 -4.54B^2 -0.3115C^2

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Where, A is an amount of HPMC K15M Premium, B is an amount of Sod. CMC and C is an amount of Triethanolamine.

The model F value of 1068.75 implies the model is significant. P-values less than 0.0500 indicates model terms are significant which is observed as <0.0001. The lack of fit F-value of 3.45 implies there is a 9.99% chance that a lack of fit F-value this large could occur due to noise.

The predicted R^2 of 0.9935 is in reasonable agreement with the adjusted R^2 of 0.9980 i.e. the difference is less than 0.2. HPMC K15M Premium and Sodium CMC having high significance on the drug release **Figure 7** and **Figure 8**.

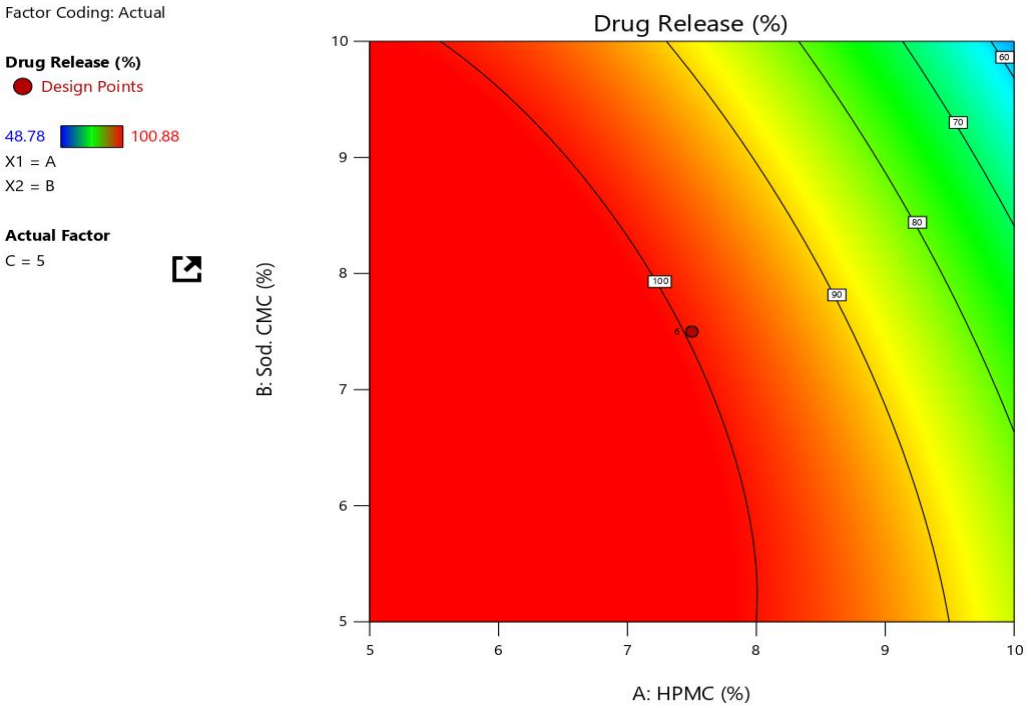

Figure 7: Contour Response Surface Plot for Drug Release

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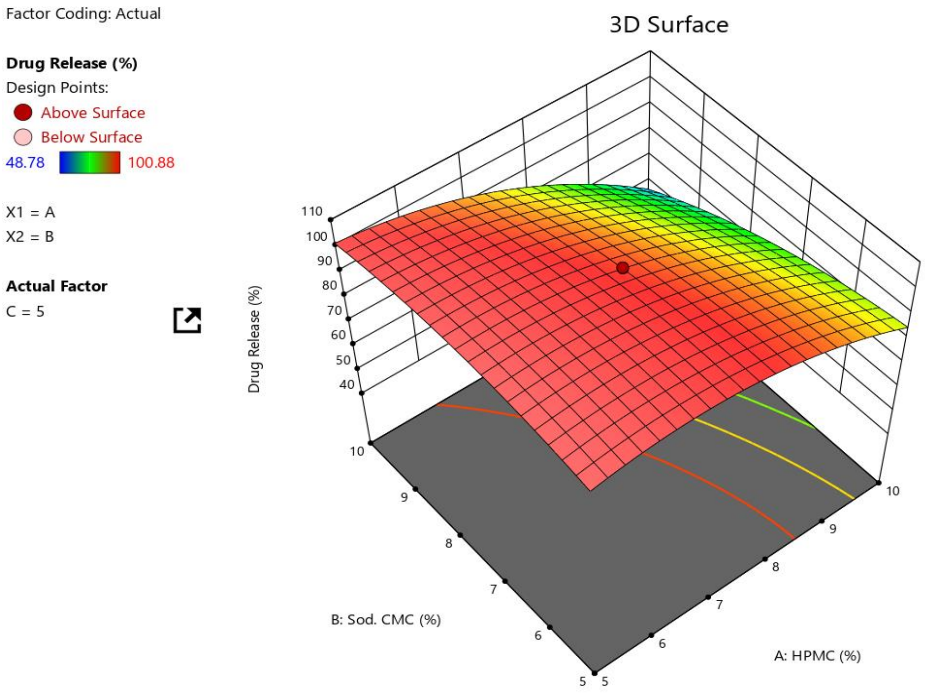

Figure 8: 3D Response Surface Plot for Drug Release

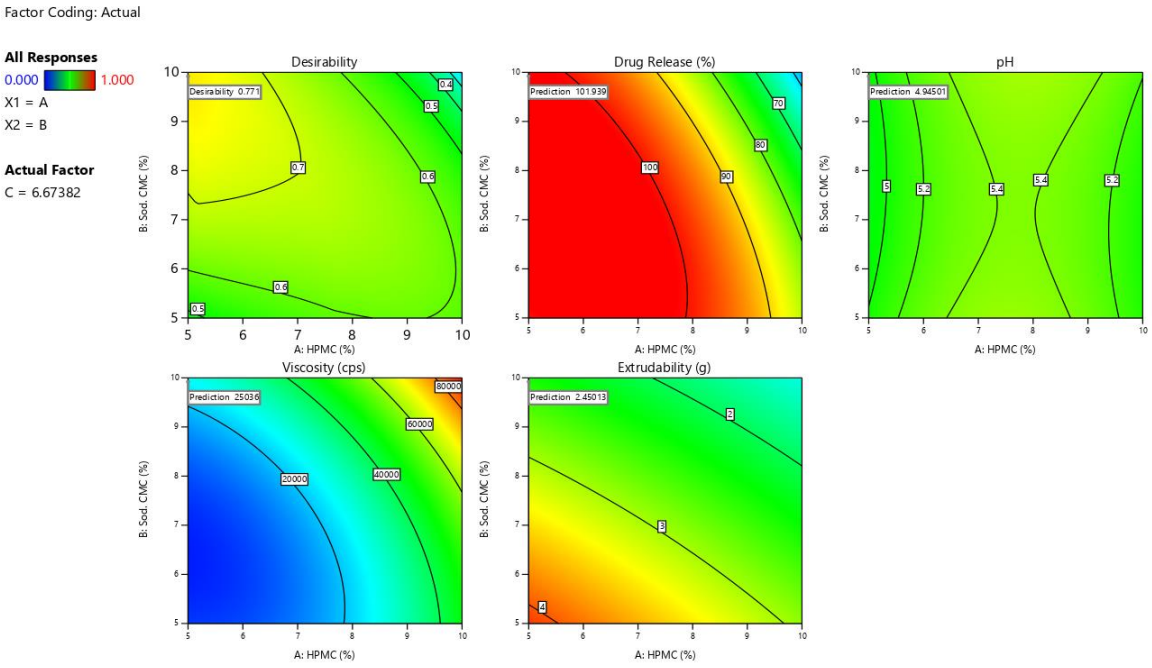

Figure 9: Desirability plot for all responses

H) Stability Studies:

The hydrogel formulations optimized from CCD by using Design Expert ® software and the final formulation of hydrogel was kept for stability study. The hydrogel formulation was studied for accelerated (40 ± 2°C/ 75 ± 5% RH) and long term (25 ± 2°C/ 60 ± 5% RH) stability study as per ICH guideline for 3 months and analyzed to check changes in physical characteristics and drug content. After stability results are depicted in the **Table 4**. The

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appearance of all formulations remained same as compared to initial observations. Stability study result shows no any drastic change in the pH, drug content and physical characteristics.

Table 4: Results of Physicochemical Evaluations of Stability Testing

Formulation	Gritiness	Phase Separation	Drug Content	pH
DH1	No	No	99.77	4.98

Confirmation of factors by post analysis: The confirmation was done by applying the constraints to the responses, as drug release should be maximum, viscosity should be minimum, extrudability should be minimum, pH is in the target of 4.945. Then, from the given solutions, the most desirable formulation was selected, HPMC K15M Premium with 5.0 %, Sodium CMC with 9.92 % and Triethanolamine with 6.67 %, the desirability graph shown in . The results are depicted in **Table 5**.

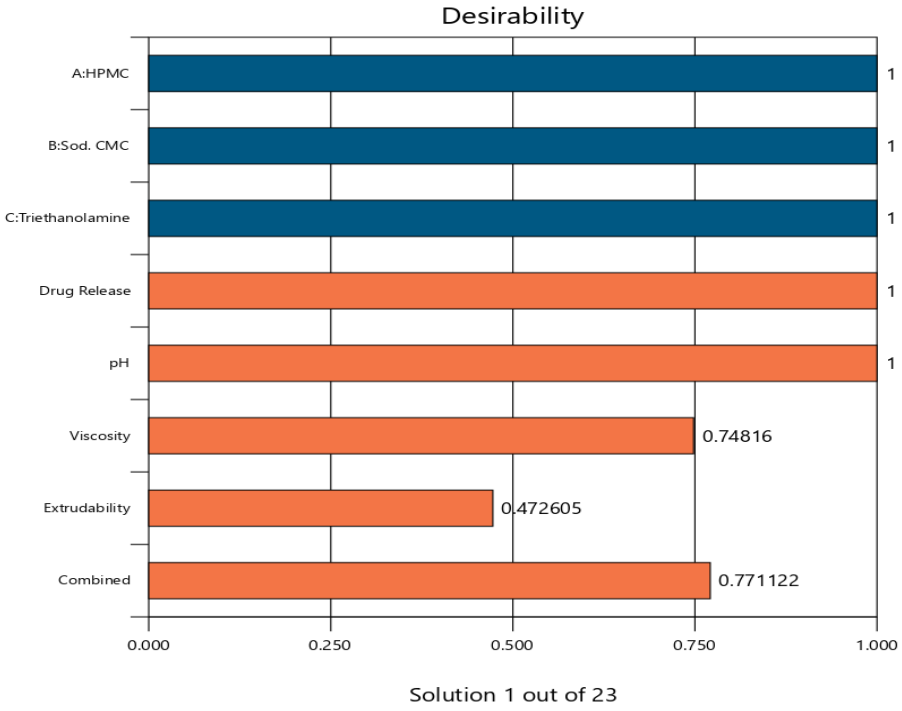

Figure 10: Graph of Desirability

Table 5: Point Prediction

Solution 1 of 23 Response	Predicted Mean	Observed	Std Dev	SE Mean	95% CI low for Mean	95% CI high for Mean	95% TI low for 99% Pop	95% TI high for 99% Pop
Drug Release	101.939	99.89	0.752789	0.513254	100.796	103.083	97.92	105.959
pH	4.94501	5.06	0.407356	0.277736	4.32617	5.56384	2.77005	7.11997
Viscosity	25036	22360	1861.75	1269.35	22207.7	27864.3	15095.7	34976.3
Extrudability	2.45013	2.2	0.26176	0.178469	2.05247	2.84778	1.05253	3.84772

Conclusion:

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Dapsone 7.5% gel is recently launched in market with an indication for once-daily topical treatment of acne vulgaris in patients aged ≥ 12 years. This increased dose formulation reduced acne severity (as per the Global Acne Assessment Score) and lesion counts versus vehicle. The present study demonstrates that the formulated Dapsone 7.5% hydrogel using central composite design. The quantitative responses drug release, pH, viscosity and extrudability of hydrogel for diverse combination of independent variables were obtained experimentally and the outcome were pragmatic to fit in the premeditated form. The investigational responses of the optimized formulation was found to be near to the predicted responses having a correlation coefficient value 1, which indicates that the CCD is a very useful tool in pharmaceutical formulation studies. QbD approach to the gel preparation gives safe, effective and quality medicated dosage form for treatment of locally. QbD approach minimizes the cost on research and ultimately dosage form available at affordable cost. The present hydrogel formulation revealed to be stable up to 3 months and having desired quality attributes which can meet the current market need.

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