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A QUALITY BY DESIGN APPROACH: DEVELOPMENT AND EVALUATION OF HERBAL HYDROGEL

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CADD (Cumulative Amount of Diffused Drug), QbD (Quality by Design), QTPP (Quality Target Product Profile), Critical Quality Attributes (CQA)

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ABSTRACT: The current study was undertaken to formulate and evaluate herbal hydrogel containing ethanolic seed extract of plant *Coix lacryma jobi* L. Hydrogel was prepared by ethanolic seed extract, carbapol 934p, aloevera gel extract, triethanolamine and methylparaben. The effects of critical parameters (concentration of Carbapol 934p and Aloe vera gel extract) were investigated by executing design of the experiment using 3^2 factorial designs through Design Expert 12 version software. All the formulations were developed and evaluated for visual inspection, pH, viscosity, spreadability, drug release and drug content. Optimized formulation was subjected to *in-vitro* antifungal activity against *Candida albicans*. It was observed that formulation variables X_1: Carbapol 934p and X_2: Aloeveragel extract significantly affected the response Y_1: Viscosity (cp) and Y_2: Drug release (% Drug release). Stability studies conducted under accelerated conditions and at room temperature were shown acceptable results. It was concluded that hydrogel containing coix ethanolic seed extract showed good consistency, spreadability, homogeneity, and stability. This study confirmed that quality by design is an effective approach for understanding the quality parameters for optimizing Hydrogel formulation.

INTRODUCTION: Herbal medicinal system is old and has been practiced since mankind [1]. According to the World Health Organization (WHO), about 80 % of the world's population uses herbs and other traditional medicines. They are known for their safety, efficacy, cultural acceptability and lesser side effects [2]. *Coix lacryma jobi* L. belongs to Poaceae or Gramineae family. Coix plant is a grass crop that is used in traditional Chinese medicine.

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Adlay seeds **Fig. 1** are the major medicinal part that contains a range of phytoconstituents such as Polysaccharides, Coixol, Coixenolide, Protein, Lipid, Phytosterol and Polyphenols. Several studies have demonstrated that coix seeds have antimicrobial, anti-diabetic, anti-inflammatory, anti-obesity, anti-cancer activity, and other beneficial effects on humans [3-5].

FIG. 1: COIX SEED

Topical drug delivery system is widely used for skin diseases like bacterial, fungal, eczema, *etc*. Topical drug application has the advantage of directly delivering the drug to the site of action. The advantages of topical formulations are avoidance of first-pass metabolism, avoiding inter-intra-patient variation, convenience, and easy application, *etc* [6]. Hydrogels are three-dimensional, cross-linked networks of water-soluble polymers. It is a semi-occlusive film over the skin and releases the drug in a controlled manner. Hydrogels are flexible like natural tissue due to their significant water content and good transport properties. Hydrogel are biocompatible, easy to modify, and time release growth factor [7, 8].

There was no report on the formulation containing extract of coix seed. Hence, the present study will design, formulate and evaluate hydrogel containing ethanolic extract of adlay seed.

To document product development (ICH guideline (Q9)) report by "Quality by Design" approach for Hydrogel formulation. The product development report aims to present the quality by design aspect for gel-based formulations. The elements of quality by design are examined, and a consistent nomenclature is proposed with the help of Quality Target Product Profile (QTPP), Critical Quality Attribute (CQA), Critical Process Parameter, Critical Material Attribute (CMA), risk assessment, and control strategy [9, 10].

Quality by design is a structured, organized method for determining the relationship between factors affecting a process and the output of that process based on quality risk management, ICHQ8 (R2) guideline.

MATERIALS AND METHODS: Ethanolic extract of Coix seed was purchased from Shannxi Green Bio-Engineering Co. Ltd., China. Aloevera gel extract was obtained from Arogya Jyoti Pharmacy, New V.V. Nagar as a gift sample. Carbapol 934p (gel base), Triethanolamine (pH adjust), and Methylparaben (preservative) were used in the preparation of hydrogel.

Quality Target Product Profile (QTPP): The Quality Target Product Profile as described in International Council for Harmonization (ICH) Q8 is an essential element of a QbD approach. The QTPP includes all product attributes that are needed to ensure equivalent safety and efficacy. QTPP for herbal hydrogel has been developed by considering the elements of the important drug product quality attributes. The initial QTPP and CQAs for formulation are shown in **Table 1.**

TABLE 1: QTPP FOR HYDROGEL

Parameters	QTPP element	Justification	Critical Quality Attributes		
			Low	Medium	High
Dosage form	Hydrogel	Topical application	√		
Dosage design	Controlled release	Better for topic application	√		
Strength	5 %	Effective dose			√
Assay	95 % - 105 %	Affect on safety and efficacy			√
pH	6 – 7	Compatible with skin			√
Viscosity	Medium	Impact on drug release			√
Spreadability	Good	Uniformity on skin		√	
Drug release	Permeation	Impact on therapeutic point of view			√
Packaging materials	Amber color jar	Protect for photolytic degradation			√

Critical Quality Attributes (CQA): Critical quality attribute (CQA) is "a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.

The initial CQA was defined from QTPP to identify the satisfactory quality of the product. The potential CQA of excipients required for the development of herbal hydrogel [11].

Risk Assessment: A risk assessment was conducted to identify all the potential high risk factors for further study. Risk Priority Numbers (RPN) was mapped into three categories (high, medium and low) in the risk assessment process. The initial risk assessment for critical input material and formulation components and their impact on the product quality was determined [12].

Design of Experiment (DoE): DoE is a structured, organized method for determining the relationship

between factors affecting a process and the output of that process. Design expert version 12 software (Stat-Ease Inc., Minneapolis, MN, USA) was used for formulation design. A 3^2-factorial design was employed where the amount of two factors varied at three levels (-1, 0 and +1) as hypothesized by the design. In this design, two factors, Carbapol 934p and Aloevera gel extractin each in three levels were evaluated and experimental trials were performed in all 9 possible combinations. Carbapol 934p and Aloevera gel extract were selected for independent variables, and viscosity and drug release were selected for dependent variables. The formulation run was executed by a design expert and are shown in **Table 2.**

TABLE 2: FORMULATION TRIAL BATHCES OF HERBAL HYDROGEL

Ingredients	FB1	FB2	FB3	FB4	FB5	FB6	FB7	FB8	FB9
Seed extract	5	5	5	5	5	5	5	5	5
Carbapol 934p	1.5	1	2	2	2	1	1	1.5	1.5
Aloevera gel extract	2	1.5	1.5	2	1	1	2	1	1.5
Triethanolamine	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Methyl paraben	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Distilled water (ml)	100	100	100	100	100	100	100	100	100

Concentration of each ingredient is expressed in % w/v.

Drug Excipient Compatibility Studies: A Fourier-transform infrared (FT-IR) was used to identify if any interaction existed between the seed extract and the excipients. The samples were analyzed via potassium bromide pellet method in the region 4000-400 cm^{-1} [13].

Formulation of Hydrogel: Weighed accurately amount of Carbapol 934p and dissolved in water using a magnetic stirrer. Keep the mixture for overnight. Coix seed extract, Aloevera gel extract and Methylparaben were added to the gel base. Triethanolamine was added to adjust the pH of hydrogel between 6.0 to 7.0 with constant stirring.

Evaluation of Hydrogel Formulation: The formulated gel was evaluated for physical examination. The characterization and response in the design of the experiments conducted on the gel preparations include pH, spreadability, homogeneity, viscosity, drug release, and drug content [14-16].

Spreadability: The gel was weighed as high as 0.5 g and then placed on glass plate. Then, put another other glass plates above the gel mass. The gel was spread over the slides. Then gel was spread uniformly over the glass plate.

Homogeneity: After the gels have been set in a container, all developed gels were tested for homogeneity by visual inspection. They were tested for their appearance and the presence of any aggregates.

Viscosity: A maximum of 100 g of gel was put into a container and then placed on a viscometer with spindle no. 64 installed. Then, the spindle was lowered onto the gel with 10 rpm speed.

Drug Content: 1 g of hydrogel was accurately weighed and dissolved in 80 ml Phosphate buffer (pH 6.8). Sonicated for 10 min. and made up volume up to 100 ml with Phosphate buffer. From this 1 ml was pipetted out and diluted to 10 ml same solvent. The absorbance was measured by UV spectroscopy at 286 nm against blank.

***In- vitro* Diffusion Study:** The diffusion studies of the prepared gels were carried out in Franz diffusion cell to study gels' release through a cellophane membrane. Place 1gm hydrogel was taken on cellophane membrane and the diffusion studies carried out at 37±1°C using Phosphate buffer (pH 6.8) as dissolution medium.

Threeml of each sample was withdrawn periodically up to 9 h. each sample was replaced with an equal volume of dissolution medium. The samples were analyzed for the drug content by using Phosphate buffer as blank. The absorbance was analyzed by UV spectroscopy at 286 nm.

Statistical Optimization: The model's fit quality was evaluated using the analysis of variance (ANOVA) technique. Based on a comparison of several statistical parameters, the best fit model was selected; the statistical parameters included the R^2 - coefficient of determination, Adjusted R^2,

Predicted R^2, p-value provided by the software. The relationship between the dependent and independent variables was demonstrated using response surface plots, *i.e.,* Contour and 3D surface plots; these plots were used to study the effect of various factors on the response. Optimized formulations were run for triplicate and evaluated for pH, viscosity, drug content and dug release.

Anti-bacterial Activity: Optimized formulation was subjected to perform *in-vitro* anti-fungal activity. Facility provided by Vasu Research Center, Baroda.

Stability Study: Stability studies were carried out for statistically optimized formulation according to the International Council for Harmonization (ICH) Q1A (R2) guidelines. The sample was stored in amber color bottle, which was maintained at room temperature and accelerated conditions 40°±2°/ RH 75±5 % for 3 months. The hydrogel formulation was withdrawn after 1, 2 and 3 months and evaluated for physical appearance, pH, viscosity and drug content [17].

RESULTS AND DISCUSSION: FTIR study showed no major change in the position of band obtained in the extract alone and in a physical mixture of formulation, indicating no distinct interaction. Based on results, all mentioned excipients were found to be compatible with seed extract. QTPP serves as a summary of a drug product's quality attributes that must be achieved to ensure its safety and efficacy. The QTPP for Herbal formulation consist of information regarding dosage form, dosage designand route of administration, dosage strength, and drug product quality attributes, and based on prior scientific knowledge and data an Initial Risk Assessment of drug substance (Herbal Extracts) and formulation variables (Excipients) was carried out to meet the quality target product profile (QTPP).

Concentration of Carbapol 934p (%) (X_1) and concentration of Aloevera gel extract (%) (X_2) were considered as the major formulation parameters for design of experimentation. A 3^2 full factorial design was employed for development and optimization of hydrogel. The experimental runs, with independent variables and measured responses for the developed hydrogel formulation.

The all prepared formulations were inspected visually for their color, homogeneity, and grittiness. It observed that all the formulations showed good homogeneity with no grittiness and brown in color. The formulation batches FB1-FB9 were subjected for physical characterization, pH, spreadability, viscosity, drug release and drug content. The evaluation parameters of all batches were shown in **Table 3.**

The pH of the hydrogel was found to be within 6.55 – 6.99. The viscosity of hydrogel prepared was in the range of 28092 – 34920 cp. The drug release of the hydrogel was found to be 75.65–84.85 % and Coixol content was within the range of 97.12 – 98.86 %.

TABLE 3: VARIABLES AND RESPONSE AS PER DESIGN EXPERT

Batch	Spreadability	pH	Viscosity (cp)	% Drug release/ 9 h	Drug content (%)
FB1	Good	6.72 ± 0.0208	32645 ± 8.0208	83.58 ± 0.1350	98.86 ± 0.1350
FB2	Good	6.99 ± 0.0351	28923 ± 7.0237	88.12 ± 0.0450	97.16± 0.0450
FB3	Average	6.83 ± 0.0251	32249 ± 7.5075	78.67 ± 0.0650	97.12± 0.0650
FB4	Average	6.78 ± 0.0251	34920 ± 5.5075	75.65 ± 0.3511	97.27± 0.0351
FB5	Average	6.95 ± 0.0577	33712 ± 6.5640	76.98 ± 0.3511	98.26± 0.0351
FB6	Good	6.77 ± 0.0208	28092 ± 6.5064	90.53 ± 0.0300	97.78 ± 0.0300
FB7	Good	6.89 ± 0.0251	32590 ± 2.8867	84.19 ± 0.0650	98.51± 0.0650
FB8	Excellent	6.96 ± 0.0152	30021 ± 9.5043	88.85 ± 0.0550	98.82± 0.0550
FB9	Excellent	6.90± 0.0208	30125 ± 4.5092	87.02 ± 0.0750	98.15± 0.0750

Statistical optimization of Herbal hydrogel was performed by comparison of several statistical parameters provided by Design-Expert® Software, Version 12. The values of the coefficients X_1, X_2, their interaction, and quadratic terms are related to the effect of these variables on the response. To demonstrate the influence of each factor on responses of viscosity graphically, the Contour plots and 3D surface plots were generated and shown in **Fig. 2** to **3,** respectively.

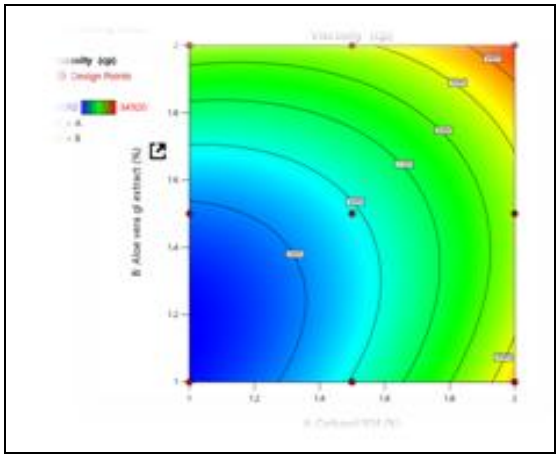

FIG. 2: COUNTER PLOT FOR RESPONSE Y_1

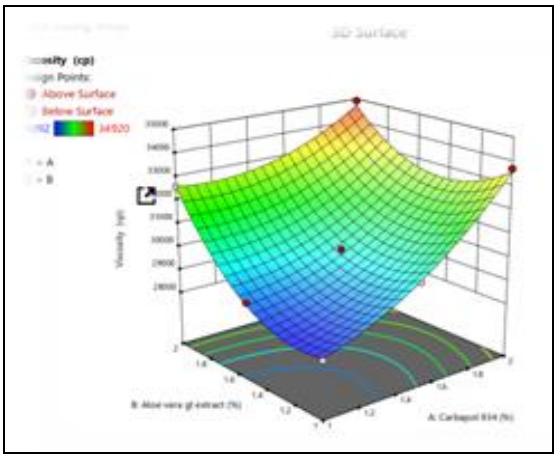

FIG. 3: 3D SURFACE RESPONSE FOR Y_1

The statistical data of response Y_1 and response Y_2 are shown in **Table 4.**

TABLE 4: ANOVA RESULT FOR RESPONSES Y_1 AND Y_2

ANOVA	Response Y_1 (Viscosity)	Response Y_2 (Drug release)
Significant Model	**Quadratic**	**Quadratic**
Polynomial equation	87.3544 + -5.25667 * A + -2.15667 * B + 1.2525 * AB + -4.12667 * A^2 + -1.30667 * B^2	29887.4 + 1879.33 * A + 1388.33 * B + -822.5 * AB + 817.333 * A^2 + 1564.33 * B^2
p - value	0.0019 (less than 0.05)	0.0019 (less than 0.05)
R^2	0.9932	0.9932
Adjusted R^2	0.9819	0.9819
Predicted R^2	0.9316	0.9316

From the counter-plot presentation, formulation no. 9 – was within this appropriate area, having a viscosity 30125 cp. Based on 3D surface plot concentration of Aloevera extract was increased the pH of hydrogel also increased, so to maintain pH requirement of Triethanolamine was more and increased viscosity. To increase the concentration of Aloevera gel extract in formulation pH decrease and to maintain pH need to add triethanolamine. So, it increased the viscosity of hydrogel. For responses to drug release, the Contour plots and 3D surface plots were generated and shown in **Fig. 4** and **5,** respectively. Formulation 9 was given adequate drug release from the graphical presentation, showing an effective counter-plot area. The normal probability plot for both responses, the residuals is normally distributed.

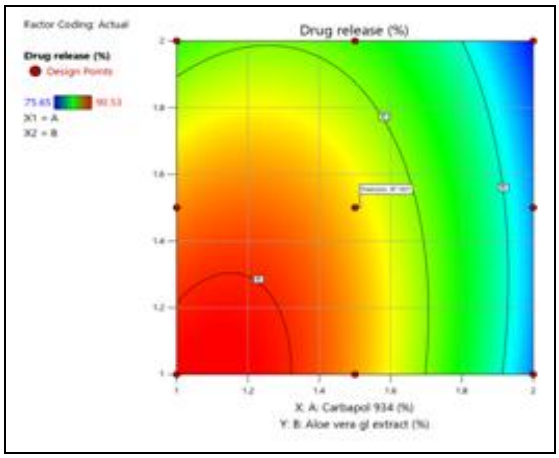

FIG. 4: COUNTER PLOT FOR RESPONSE Y_2

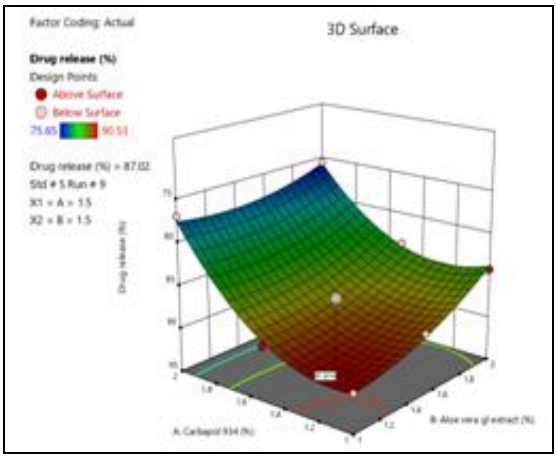

FIG. 5: 3D SURFACE RESPONSE FOR Y_2

From the Design Space, formulation batch FB9 falls under the region of successful operating ranges. Hence formulation FB9 (Carbapol 934p – 1.5 % and Aloeveragel extract -1.5 %) fulfills the criteria of QTPP and CQA for hydrogel formulation. Therefore FB9 formulation was

selected as optimized formulation. The optimized formulationas evaluated for physical appearance, spreadability, viscosity, drug release and drug content (n=3).

***In-vitro* Antimicrobial Study:** *In-vitro* antifungal activity performed by cylindrical plate method. *Candida albicans* (ATCC 10231) was used for antifungal activity. Sabroud dextrose agar with Chloramphenicol media was used to prepared agar plate. Four Derm Cream was used as a reference sample. The formulation showed antifungal activity having zone inhibition 20mm.

The results of zone of inhibition were shown in **Table 5**. The image of inhibition for sample and formulation shown in **Fig. 6** & **7** respectively.

TABLE 5: ZONE OF INHIBITION OF FORMULATION

Batch	Reference sample	Control	Formulation containing Aloe vera gel extract only	Formulation
Zone of inhibition	25 mm	10 mm	12 mm	20 mm

FIG. 6: ZONE OF INHIBITION OF REFERENCE SAMPLE

FIG. 7: ZONE OF INHIBITION OF HYDROGEL

The results obtained demonstrated that Hydrogel formulation has good anti-fungal activity. The present research work has demonstrated the successful implementation of QbD approach for the development of hydrogel formulation. The desired QTPP and CQA were predefined in order to obtain the final product with desired quality. Further it can also be concluded that formulation prepared within the design space will be able to accomplish CQAs in the drug product which further results into the product with desired QTPP.

Stability Studies: The stability of the hydrogel formulation was studied as per ICH Q2 (A) guideline. It was observed that there were no serious changes in the physical characterization of the formulation. These results indicated that the developed hydrogel formulation was pharmaceutically appear to be stable and retained their properties at various environmental conditions over a period of 3 months.

CONCLUSION: In the present study, efforts were made to develop and evaluate herbal hydrogel formulation containing seed extract of Coix lacryma jobi L. for anti-fungal activity. The collected plant was authenticated and it was found to be free from adulterants and substitutes. Ethanolic seed extract was purchased in ratio 10:1 and based on preliminary analysis, it contained alkaloid, phytosterol and phenolic compound. In vitro antimicrobial activity of seed extract revealed good results in fungal strains (*C. albians*). Extracts shows significant zone of inhibition.

The FT-IR study of extract and selected excipients for hydrogel formulation revealed they were physically compatible. Formulation of topical hydrogel was optimized with the help of 3^2 full factorial design using 2 variables and three levels. Total 9 batches were formulated as per design and all formulations were evaluated for various parameters like pH, homogeneity, spreadability, viscosity, drug content and percentage drug release. Formulation was optimized and statistical analysis was performed with the help of Design Expert® 12.

The formulation FB9 was optimized. The optimized formulation was subjected to in-vitro anti-fungal activity. The formulation was shown good anti-fungal activity against *Candida albicans* strain. The formulation was shown good stability in accelerated and room temperature up to 3 months.

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CONFLICTS OF INTEREST: Nil

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