Original Research Article

THE APPLICATION OF RESPONSE SURFACE METHODOLOGY (RSM) IN THE COMPUTATIONAL OPTIMIZATION OF SUSTAINED RELEASE (SR) FORPHENOTHIAZINE DERIVATIVE PROCHLORPERAZINE MALEATE (PCM) MATRIX TABLET

Abstract:

Introduction: This study explores the use of Response Surface Methodology (RSM), a statistical optimization technique, to optimize the SR properties of PCM matrix tablets. PCM is a phenothiazine derivative used for treating schizophrenia, nausea, and vomiting. Sustained release formulations offer extended drug delivery, potentially improving patient compliance and reducing side effects. RSM helps identify optimal combinations of critical formulation factors influencing drug release, such as polymer type and concentration, filler type, and drug/polymer ratio. The study likely involves; such designing experiments based on chosen RSM design (e.g., Box-Behnken) with varying factor levels. To Formulate SR tablets with different factor combinations. Evaluating drug release profiles of each tablet formulation. Analysing data using RSM software to build mathematical models relating factors to drug release and Identifying optimal factor combinations that maximize desired release characteristics (e.g., sustained release over a target duration).

Objective: The ongoing research purpose to improve the advancement of a sustained release tablet containing Phenothiazine derivative PCM loaded matrix. This is achieved by utilizing DoE as a computational method to statistically validate the formulation.

Methodology: Basically two methods involved in the formulation using direct compression; a simple and efficient method where all dry ingredients are blended and directly compressed into tablets.

Results: The obtained outcomes closely matched the anticipated values derived from the experimental setup. The enhanced PCM matrix tablets demonstrated a prolonged and uniform discharge of PCM over a span of 6 hours.

Conclusion: This studyBased on a 2^3FD, response surface methodology was used to successfully develop the current research of PCM matrix tablets for sustained release application. The corresponding contour plots and 3D response methodology represent the important variables for the optimisation process.

Keywords: sustained release; tablets; statistical analysis; contour plot; response surface methodology; optimization; antiemetic formulations; computational approach; factorial study; design of experiments; and designs.

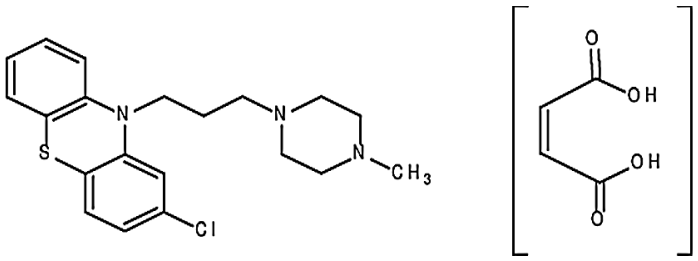
1. INTRODUCTION:

The matrix tablet formulated for sustained release refers to a specific type of medication where the active ingredient is dispersed throughout a solid, inert matrix. This matrix acts as a controlled-release mechanism, gradually releasing the drug over a longer period of time compared to a conventional immediate-release tablet [1-2]. The mechanism is the drug is physically dispersed within the matrix, usually composed of polymers and other excipients. The matrix allows for slow diffusion of the drug into the surrounding fluids, controlling the release rate.

RSM is a powerful statistical and mathematical tool widely employed in the pharmaceutical industry, particularly for optimizing the formulation of matrix tablets. It helps to identify the optimal combination of critical factors influencing the desired characteristics of the tablet, such as drug release rate, hardness, and disintegration time [3-4].DoE plays a crucial role in both formulation development and optimization. It helps researchers systematically explore the influence of various factors on desired responses, paving the way for efficient and effective formulation design.

PCM, also known by the brand name Compazine, is a medication belonging to the phenothiazine class. It acts primarily as an antiemetic (prevents nausea and vomiting) and an antipsychotic

(treats mental disorders like schizophrenia) [5]. The chemical structureof PCM shown in the given **Fig. 01** as below followings:



2-chloro-10-[3-(4-methylpiperazin-1-yl)propyl]phenothiazine maleate

Figure. 01: The chemical structure of prochlorperazine maleate (PCM) with its IUPAC name

Phenothiazines are a group of older antipsychotic medications with various applications. They share a similar chemical structure and mechanism of action, but differ in potency and side effect profiles. PCM is considered a first-generation phenothiazine, meaning it was developed earlier and has a higher risk of side effects compared to newer generations [6-7]. Overall, PCM is an effective medication for managing nausea and vomiting and short-term treatment of certain mental disorders. However, it's crucial to be aware of its potential side effects and use it only under the guidance of a healthcare professional [8].

Manufacturing a pharmaceutical formulation that delivers ideal quality quickly and with few trials is essential for creating a matrix tablet for continuous release, for example. Due to its ability to reduce the necessity for significant research, the RSM is a generally used strategy for creating and optimising diverse pharmacological formulations [8-10].

Table. 01: The PCM matrix tablet formulation batches for each suggested trial formulation

PreparationBatches	API (mg)	Calcium alginate (mg) (*M*)	EC(mg) (*N*)	Carbopol 971 (mg) (*R*)	Lactose (mg)	Mg-Stearate (mg)
RP1	25	16 (+1)	0 (−1)	0 (−1)	85	10.5
RP2	25	32 (-1)	25 (+1)	25 (+1)	85	10.5
RP3	25	32 (-1)	0 (−1)	0 (−1)	85	10.5
RP4	25	32 (+1)	25 (+1)	25 (−1)	85	10.5
RP5	25	16 (+1)	25 (+1)	25 (+1)	85	10.5
RP6	25	16 (−1)	0 (−1)	25 (+1)	85	10.5
RP7	25	32 (+1)	0 (−1)	25 (+1)	85	10.5
RP8	25	16 (1)	25 (+1)	0 (1)	85	10.5

Where; EC: Ethyl cellulose.

The primary objective of the ongoing research is to enhance the progress of a sustained release tablet that contains PCM loaded matrix. This goal is accomplished by employing DoE as a computational method to statistically validate the formulation.An investigation was conducted using a computer-aided optimization technique, specifically a 2^3FD, to analyze the impact of different amounts of hydrophilic polymers on the properties of PCM sustained release matrix tablets [10]. The three independent process variables, namely calcium alginate, EC, and Carbopol 971, were considered as factors in the polymer-blend. The study focused on evaluating the effects of these factors on drug release and tablet hardness [11-12].

2. METHODOLOGY/MATERIALS:

2.1.Chemical Agents: Lactose and prochlorperazine maleate (PCM) were acquired from Pvt. Ltd. in India. We bought carbopol 971, ethyl cellulose (EC), and calcium alginate from M.K. Specialties Pvt. Ltd. in India. Analytical grade reagents and chemicals were utilised in all other instances.

2.2.Formulation of PMC loaded Matrix Tablet:

PCM matrix tablets were prepared using the direct compression approach. In order to do this, different excipients were combined with hydrophilic polymers in the proper ratios to act as release modifiers. Using a #80 sieve, the medication, polymers, and excipients were filtered. After that, a single punch tablet machine from Pvt. Ltd., India was used to properly blend and compress the medicine together with all the other elements. For a batch size of 100 tablets, 6 mm round and flat punches were used to compress the material.

2.3.Experimental Design (2^3 Factorial Design): TheFD with three factors and two levels was employed to optimize the PCM matrix tablet. The independent variables, namely the amount

of calcium alginate (M), EC (N), and Carbopol 971 (R) in the polymer-blend, were varied at low and high levels. Several trial formulations of the PCM matrix tablets were created based on the FD's trial suggestion. The formulation chart for each suggested trial is shown in the table. The hardness (kg/cm^2) and cumulative drug release after 6 hours (R6h. %) were examined as dependent variables. Design-Expert 8.0.6.1 was utilized to construct and evaluate the statistical experimental design [13-15].This design matrix, which includes the investigated factors and responses, is shown in **Table. 02.**

Table. 02: The observed response values with drug contents in PCM matrix tablets and the 2^3 factorial designs (FD) are presented

Formulation Batches	Calcium alginate (mg) *M*	EC (mg) *N*	Carbopol 971 (mg) *R*	Observations	
				*R*6h (%)^x	Hardness (kg/cm^2)^y
RP1	16 (−1)	0 (−1)	0 (−1)	75.72 ± 3.37	4.20± 0.26
RP2	32 (+1)	25 (+1)	25 (+1)	57.25 ± 2.14	3.19± 0.16
RP3	32 (-1)	0 (−1)	0 (−1)	74.17 ± 2.55	4.53± 0.22
RP4	32 (+1)	25 (+1)	0 (-1)	62.42 ± 3.26	3.85± 0.17
RP5	16 (−1)	25 (+1)	25 (+1)	51.49 ± 2.18	4.12± 0.12
RP6	16 (+1)	0 (+1)	25 (-1)	63.44± 1.83	3.89± 0.35
RP7	32 (-1)	0 (−1)	25 (+1)	56.86± 2.33	4.92± 0.14
RP8	16 (−1)	25 (_1)	0 (+1)	60.16± 1.74	3.42± 0.26

The cumulative drug release after 6 hours is denoted as x R 6h (%). The mean value, represented by y, is accompanied by the standard deviation (S.D.) and is based on a sample size of 6 (n = 6). The main effects (factors) are represented by A, B, and C. A higher value is indicated by (+1), while a lower value is indicated by (−1)

2.4.Determination of Drug Content:

Twenty tablets from each batch of formulation were weighed and crushed to a fine powder. The powder equivalent to 20 mg of PCM was then transferred to a 100 mL volumetric flask. In order to ensure complete dissolution, the flask was filled up to the 100 mL mark with 0.1 N HCl, while vigorously shaking the contents. The resulting mixture was filtered using filter paper no. 40. Following appropriate dilution, the absorbance values were measured at the maximum λ max of 254.5 nm using a UV-VIS spec. [16-17].

2.5.Weight variation Test: From each batch, twenty tablets were selected, and an electronic analytical balance was used to measure the tablets precisely. Next, the percentage of weight fluctuation was computed.

$$\textbf{Weight variation (\%)} = \frac{\textbf{Standard Deviation}}{\textbf{Mean Weight}} \textbf{ x 100}$$

2.6.Hardness test:

The PCM matrix tablets' hardness was assessed using the Pfizer hardness tester. Initially, the tester was adjusted to zero and the tablets were placed between two jaws. The tablet was then forced to shatter into smaller pieces. The tester's scale was examined to determine the kilogram-level pressure needed to break the pill [18].

2.7.*In-Vitro* Drug Release (DR) Evaluation:

The *in-vitro*DR studies were conducted using the USP dissolution apparatus, specifically the basket type manufactured by Campbell Electronics in India. The experiments were performed at a speed of 50 rpm and a temperature of 37 ± 0.5◦C. PCM matrix tablets were placed in the basket and the dissolution process involved using 900 mL of 0.1 N HCl (pH 1.2) for the initial 2 hours, followed by 900 mL of phosphate buffer (pH 7.4) for the remaining duration. To keep track of the PCM release, 5 mL portions were taken out from the disso.Container at specific time intervals and replaced with the same amount of new solution. The gathered samples were then filtered using Whatman filter paper (no. 40) and analyzed for PCM content using a UV-VIS spec. made by Thermo Spectronic in the USA, at a wavelength of 254.5 nm [19-21].

2.8.Kinetic Analysis of Release Data:

In order to examine how drugs are released from PCM matrix tablets, the in vitro dissolution data was analyzed using different mathematical models [22-23]. These models include the zero-order, first-order, Higuchi, and Korsmeyer-Peppas models as in **Table. 03** as below followings:

Table. 03: The various models with their formula, description and various applications

Model	Description	Formula	Application
Zero-Order	Constant drug release rate, independent of drug concentration	$Qt = k_0\ t$	Matrix tablets with low soluble drugs, osmotic systems, transdermal systems
First-Order	Release rate proportional to remaining drug concentration	$\log(Qt) = kt/2.303$	Water-soluble drugs in porous matrices
Higuchi	Release rate controlled by diffusion through a dissolving matrix	$Qt = kH\sqrt{t}$	Matrix tablets, coated pellets, transdermal patches
Korsmeyer-Peppas	Release mechanism involves both diffusion and erosion	$Mt/M\infty = kt^n$	Polymeric systems, swelling devices, capsules

The Korsmeyer-Peppas model has once again been used to analyze drug release behavior in different pharmaceutical formulations. Its purpose is to distinguish between various releases mechanisms like Fickian release, non-Fickian release, and case-II transport. Fickian release

occurs when the value of n is 0.5 or less [24]. Non-Fickian release is defined when the value of n is between 0.4 and 1.0. On the other hand, case-II transport happens when the value of n is 1.0 or greater, involving polymer dissolution and polymeric chain enlargement or relaxation.

2.9. Statistical Analysis (SA): The SAis the science of collecting, examining, and interpreting data to uncover patterns, trends, and relationships. It's a powerful tool used in various fields, from scientific research and social sciences to business and healthcare.The statistical optimization was conducted utilizing Design-Expert 8.0.6.1 software developed by Stat-Ease Inc. Simple statistics were employed to analyze all other data [24-26].

3. OPTIMIZATION OF RECEPTOR AND LIGANDS FOR PCM:

A phenothiazine derivative belonging to the class of atypical antipsychotics. Primarily used to treat nausea, vomiting, and vertigo associated with motion sickness and chemotherapy.Also prescribed for schizophrenia, anxiety, and other psychiatric disorders.

3.1. PCM and its Receptor Binding:PCM interacts with various receptors in the central nervous system, including dopamine D2, serotonin 5-HT2, and histamine H1 receptors.

The antiemetic effects are mainly attributed to dopamine D2 receptor antagonism in the chemoreceptor trigger zone (CTZ).Antagonism of serotonin 5-HT2 receptors contributes to its antipsychotic and anxiolytic properties [26-27].

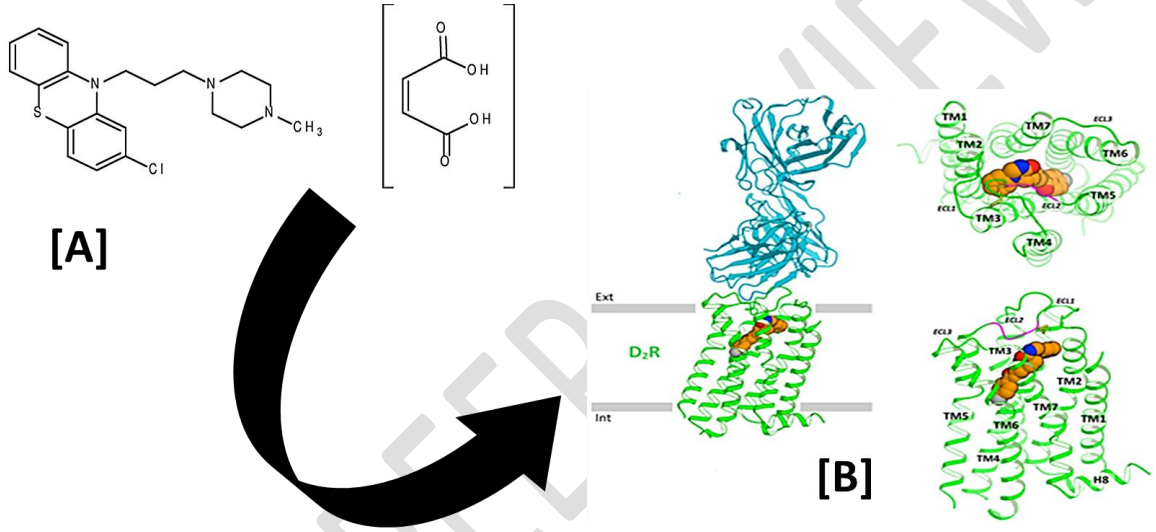


Figure. 02: The Structure of the dopamine D2 receptor in complex with the PCM drug [A]. Chemical structure of PCM and [B]. The docking of PCM

3.2. Optimization of Receptor and Ligands for PCM:Receptor optimization aims to improve the binding affinity and selectivity of PCM towards its target receptors. This can be achieved through:

- **Structure-based drug design:** Utilizing computational modeling and structural information of the receptors to design PCM analogs with enhanced binding properties.
- **High-throughput screening:** Identifying new ligands from large compound libraries that bind more potently and selectively to the desired receptors [28].

3.3. Ligand optimization focuses on modifying the chemical structure of PCM to:

- Increase its binding affinity to the target receptors.
- Improve its selectivity over other receptors, minimizing side effects.
- Enhance its pharmacokinetic properties, such as oral bioavailability and blood-brain barrier penetration.

4. RESULTS & DISCUSSION:

4.1. Optimization of PCM Matrix Tablet:

Pharmaceutical formulators traditionally create different formulations by changing one factor at a time, which is a time-consuming method. However, this approach often leads to unsuccessful experiments due to poor planning and design. A lack of appropriate planning cannot be compensated for, not even with extensive data analysis. Consequently, it is critical to comprehend how formulation parameters impact the calibre of formulations that require few experimental trials. As a result, the selection of formulation variables should be based on established statistical tools for optimization. In the case of PCM matrix tablets, a total of 8 trial formulations were proposed using a 2^3 FD. These formulations involved three independent variables: the amounts of calcium alginate (M), EC (N), and Carbopol 971 (R), considered in mg quantity, which were varied at two different levels (high and low) [27-29].

The purpose of this study was to analyze how independent variables affect the release of drugs after 6 hours, as well as the percentage and hardness of the tablets. These parameters were considered important for optimization. The used of a 2^3FD to create different trial formulations of PCM matrix tablets using the direct compression method [30]. These ingredients used are listed in **Table. 02.** The results of the experiments and the corresponding responses are summarized in **Table. 03.** The ANOVA results confirmed the significance of these models for all response parameters, as shown in **Table. 04.**

Table. 04: The list of statistics of ANOVA generated response for R6h and Hardness

Derivation	Composition of R^2	d.f.[x]	Mean R^2	*F* value	*P* value prob.> *F*
R_{6h} (%)[y]					
Models	594.66	6	99.95	2516.98	0.0249 (K)
X	99.85	1	97.85	2422.75	0.0124 (K)
Y	334.08	1	324.08	8764.86	0.0069 (K)
Z	155.19	1	156.19	4214.12	0.0094 (K)
XY	2.95	1	1.93	54.25	0.0763 (NK)
XZ	6.59	1	5.49	152.09	0.0416 (NK)
YZ	6.16	1	6.24	187.02	0.0452 (K)
Hardness (kg/cm^2)					
Models	0.87	6	0.16	455.16	0.0451 (K)
X	0.12	1	0.12	403.77	0.0466 (K)
Y	0.15	1	0.14	394.05	0.0425 (K)
Z	0.59	1	0.69	1950.05	0.0159 (K)

XY	2.82×10^{-3}	1	2.82×10^{-3}	8.00	0.3149 (NS)
XZ	0.06	1	0.07	170.03	0.0588 (S)
YZ	1.04×10^{-3}	1	1.04×10^{-3}	4.25	0.4429 (NS)

The Design-Expert 8.0.6.1 software used the data to create polynomial model equations that included main factors and interaction factors. The equation showing the relationship between R and 6h% can be rewritten in the following ways:

$$R\ 6h\ (\%) = 85.36 - 0.66G - 0.85H - 0.79J + 6.6 \times 10^{-3}GH + 1.3 \times 10^{-2}GJ + 9.4 \times 10^{-3}\,HJ,$$

$$R^2 = 0.9999;\ F\ value = 2815.99;\ P < 0.05$$ **Equation [3]**

The model equation, which describes the connection between the response variable hardness, has now taken a different form as followings:

$$Hardness\ kg/cm^2 = 3.86 + 0.03G + 8.86 \times 10^{-3}\,H + 0.06J + 2.49 \times 10^{-4}\,GH - 1.09\times 10^{-3}\,GJ - 1.16 \times 10^{-4}\,HJ$$

$$R^2 = 0.9997;\ F\ value = 456.19;\ P < 0.05$$ **Equation [4]**

A simplified model was produced by eliminating non-significant components ($P > 0.05$) from multiple regression analysis-derived model equations during the model simplification phase [29-31].

$$R6h.\ (\%) = 85.39 - 0.69G - 0.89H - 0.78J + 9.5 \times 10^{-3}\,HJ,$$ **Equation [5]**

$$Hardness\ kg/cm^2 = 2.89 + 0.04G + 7.89 \times 10^{-3}H + 0.08\,J - 1.09 \times 10^{-3}\,GJ$$

The **Fig. 03**and **Fig. 04** present Pareto charts that were used to analyze the statistical significance of each response coefficient (R6h% and Hardness) respectively.

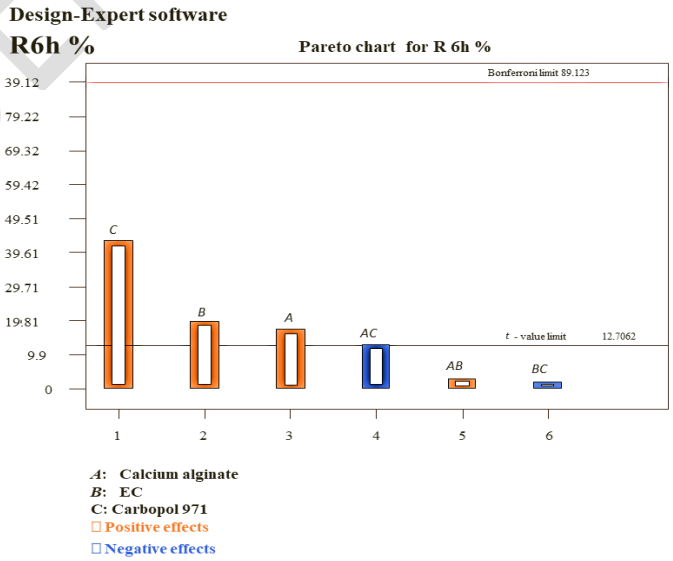


Figure. 03: The schematic representation of design expert software for R6h. %

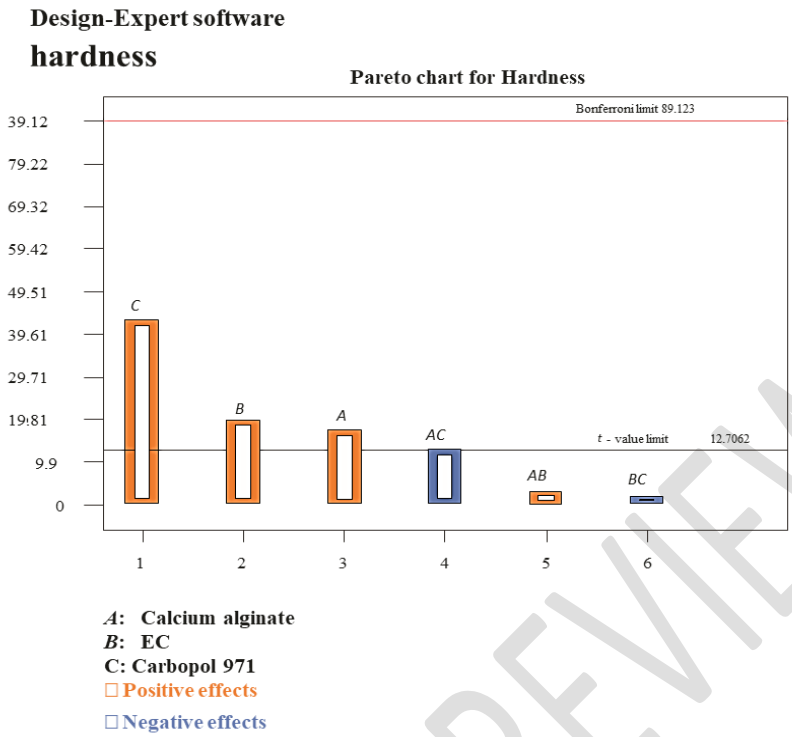


Figure. 04: The schematic representation of design expert software forhardness

These charts show the importance of each coefficient visually. Coefficients with t values above the Bonferroni line are considered important, while coefficients with t values between the Bonferroni line and the t limit line are likely to be important. However, coefficients with t values below the t limit line are not statistically significant. These Pareto charts also help confirm the ANOVA resulting by identifying and removing terms that are not significant (P > 0.05) in the model equations [32].

RSM is a very successful method that is applied to the creation and improvement of drug delivery systems. The 3D RSP and the accompanyingCP are shown in **Fig. 05, 06, 07, 08, 09,** and **10,** and they aid in estimating the impacts of independent variables on each response under investigation.

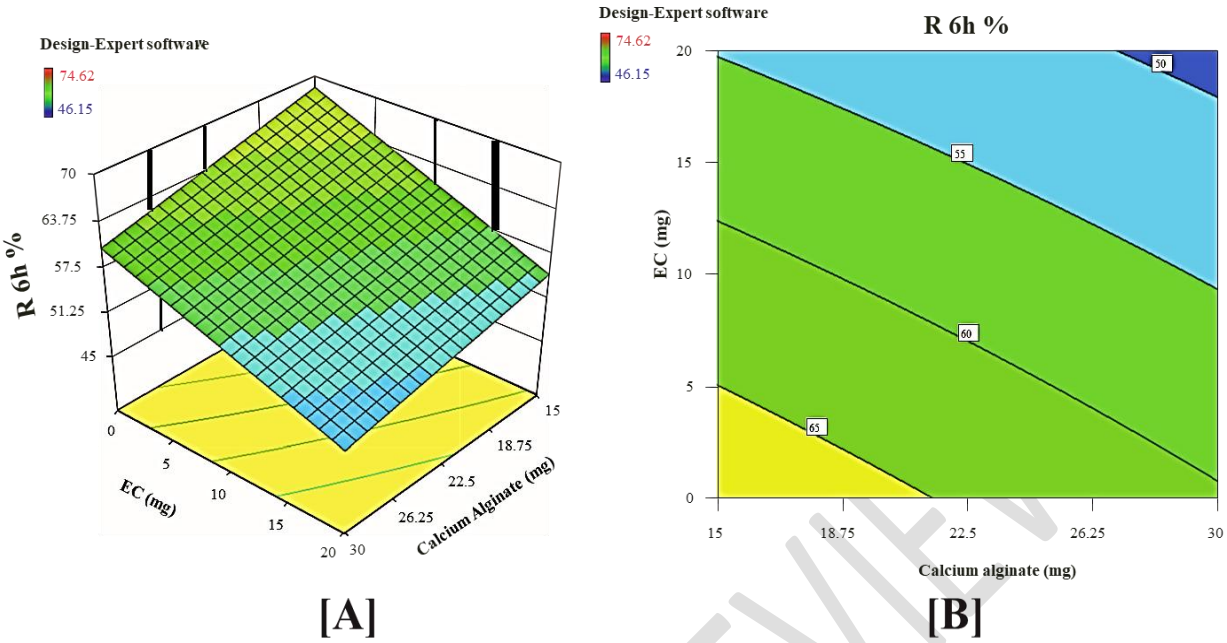


Figure. 05: The RSP [A] and CP [B] illustrate the impact of varying quantities of calcium alginate and EC on the R6h (%) outcome

These plots are valuable tools for understanding the main and interaction effects of the variables. Additionally, the 2DCP provides a visual representation of the response values. In the case of hardness, as shown in **Fig.03**, the Pareto chart reveals both positive and negative effects [30-31].

More calcium alginate, EC, and carbopol 971 in PCM matrix tablets results in lower R6h % values and higher hardness values, as seen by the 3D RSP and CP for R6h and hardness. To created optimised PCM matrix tablets using the direct compression approach in order to evaluate the optimisation capabilities of the models created based on a 2^3FD [32]. One of the carefully chosen ideal process variable configurations suggested by the experimental design was employed.

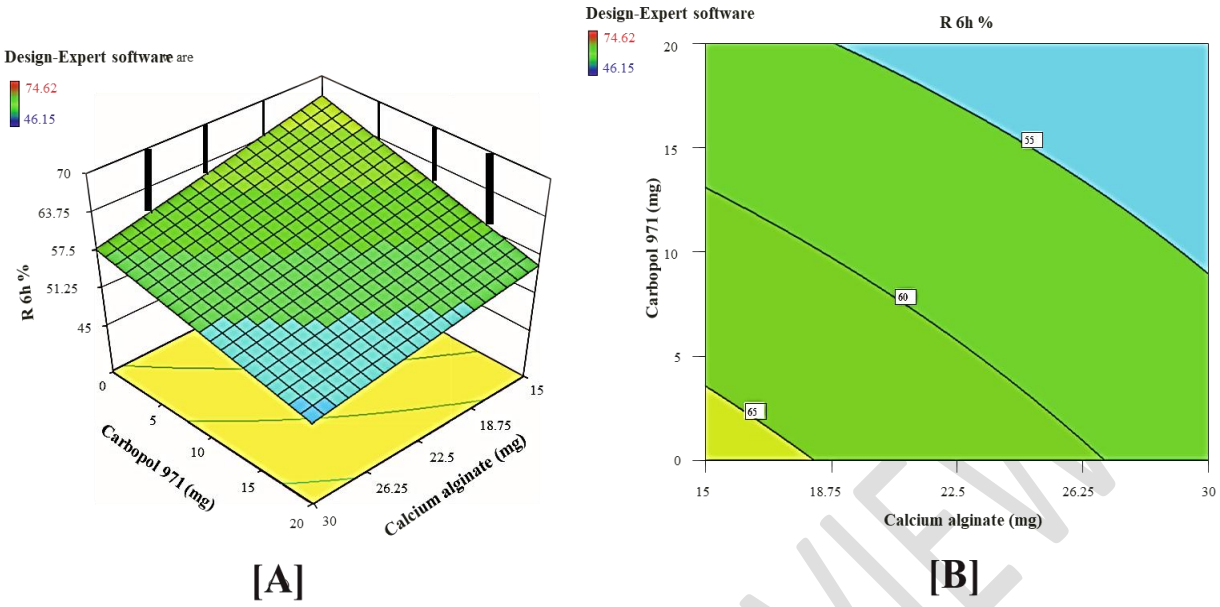


Figure. 06: The RSP [A] and CP [B] illustrate the impact of varying quantities of calcium alginate and Carbopol 971 on R6h (%).

The optimized formulation ofPCM matrix tablets involved using M = 16.29 mg, N = 34.11 mg, and R = 30.32 mg as selected optimal process variable settings. To determine the optimal values of responses based on the desirability criterion, we conducted numerical analysis with the assistance of Design expert 8.0.6.1 software [33]. This analysis led to the development of optimized PCM matrix tablet.

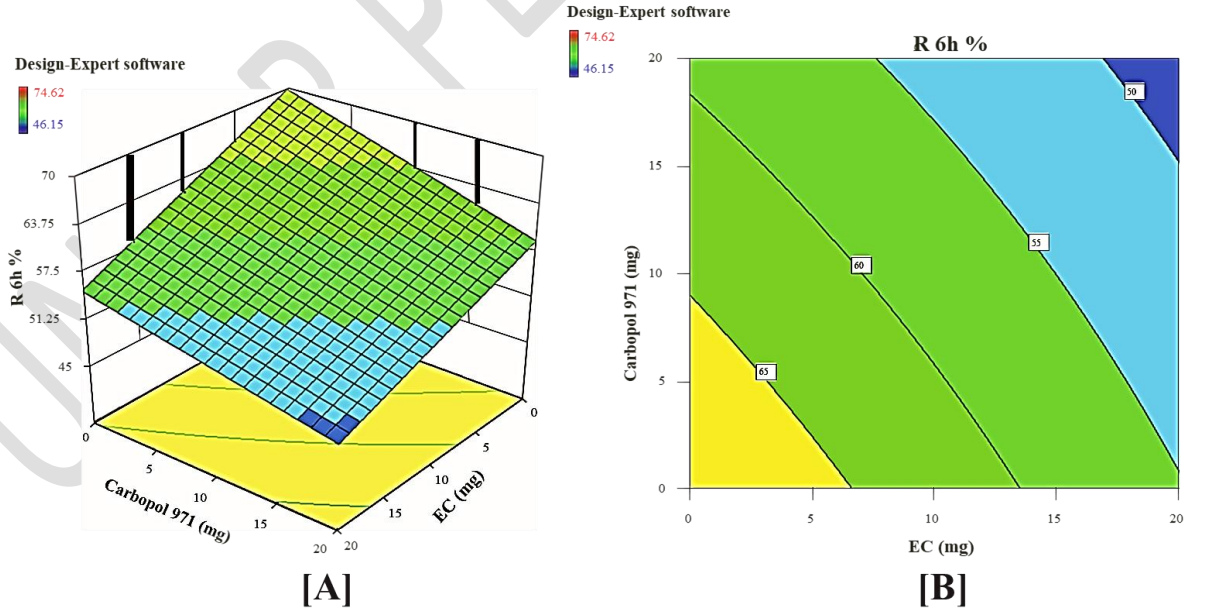


Figure. 07: The RSP [A] and CP [B] illustrate the impact of varying quantities of EC and Carbopol 971 on R6h (%)

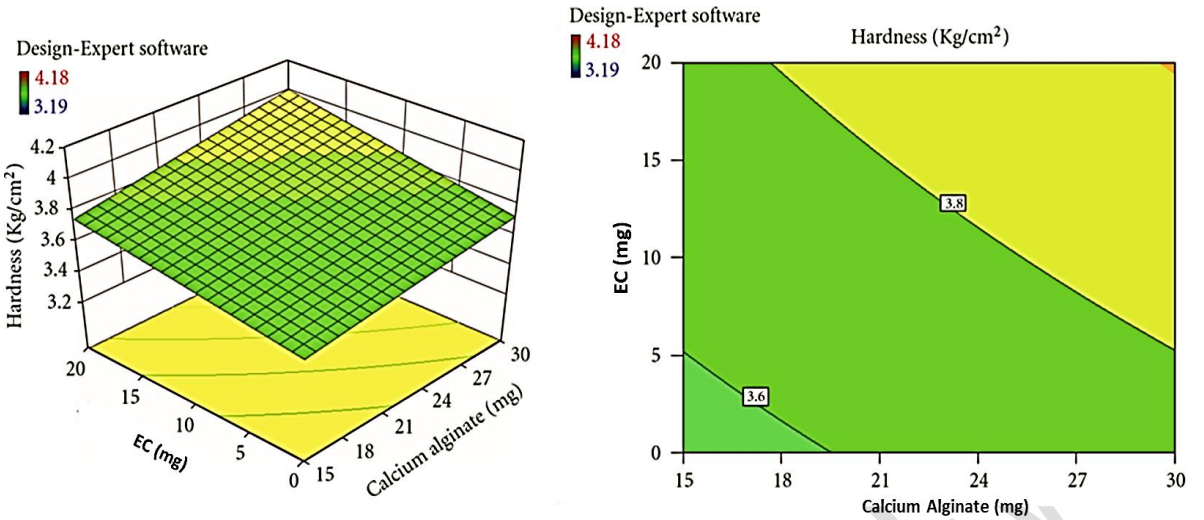
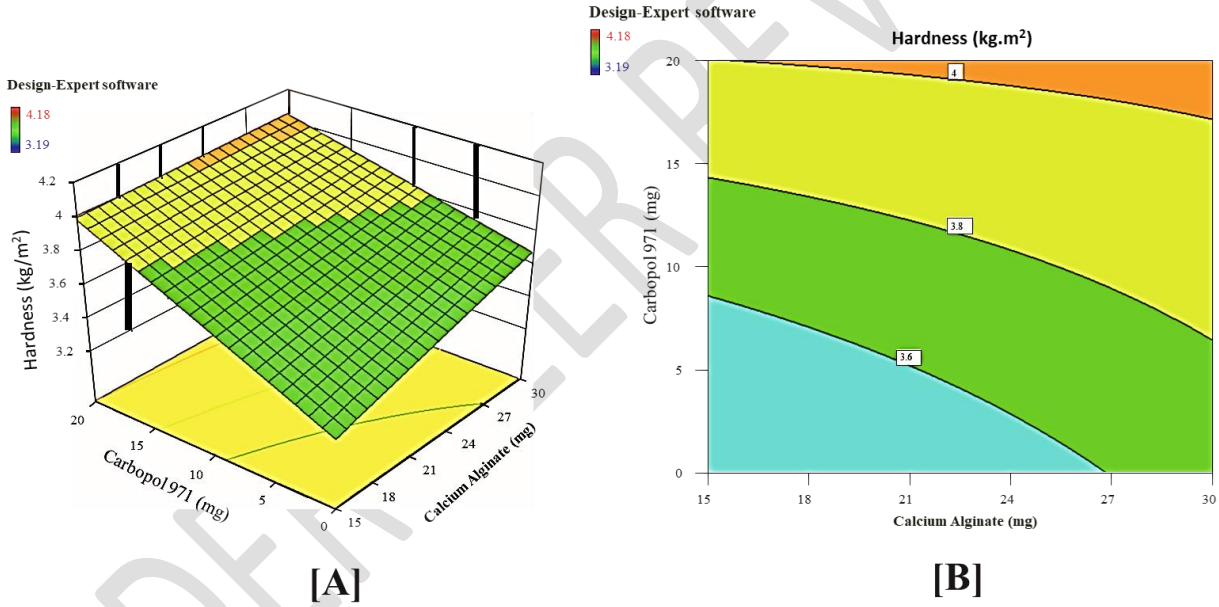


Figure. 08: The RSP [A] and CP [B] illustrate the impact of varying amounts of calcium alginate and EC on the hardness (kg/cm^2).



[A] **[B]**

Figure. 09: The RSP [A] and CP [B] show how different concentrations of Carbopol 971 and calcium alginate affect hardness (kg/cm^2)

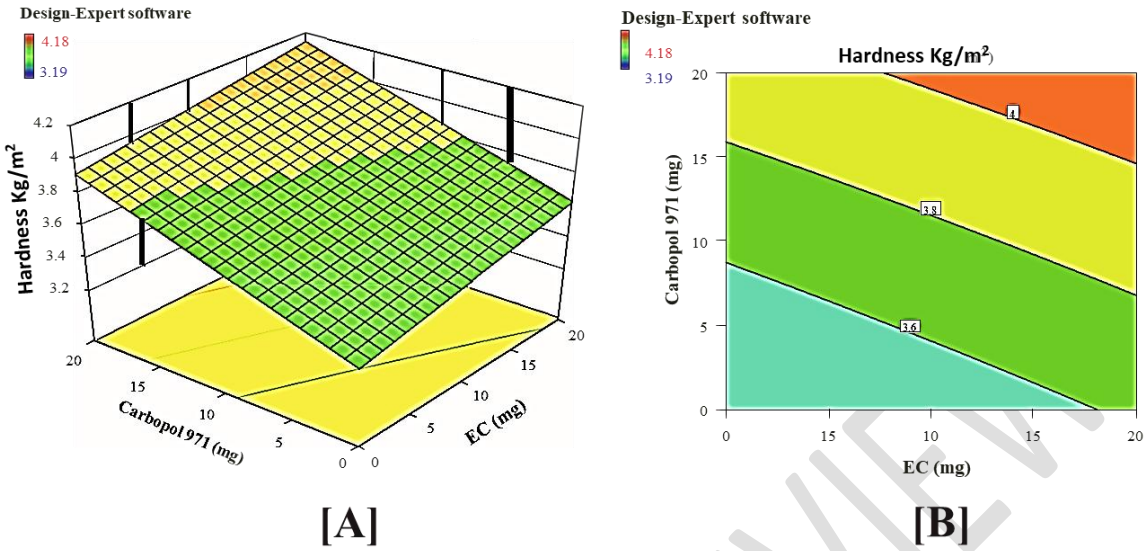


Figure. 10: The RSP [A] and contour plot (CP) [B] illustrate the impact of varying quantities of EC and Carbopol 971 on the hardness (kg/cm^2)

The actual values observed during the practical experiments are presented in **Table. 05** along with the projected values derived from the mathematical model [33-34].

Table. 05: The Observations obtained from experiments to confirm optimization aptitude

Formulation Code	Calcium alginate (mg) [M]	EC (mg) [N]	Carbopol 971 (mg) [R]	Observations	
				R_{6h} (%)^x	Hardness (kg/cm^2)
RO	16.29	33.16	31.34	Actual values^y	
				42.62± 1.89	4.76± 0.08
				Predicted values	
				39.985.59	
		% Error		4.04	2.43

aR6h (%): DR accumulated after 6 hours; b mean ± S.D. of actual values, n = 3; c% error = (actual value − predicted value)/predicted value × 100; A, B, and C denote the primary factors.

The PCM matrix tablets that were optimized showed an R6h of 42.64 ± 1.96% and a hardness of 4.67 ± 0.08 kg/cm^2. The error values were small, less than 5, which suggests that the mathematical models derived from the 2^3 FD were a good fit [35].

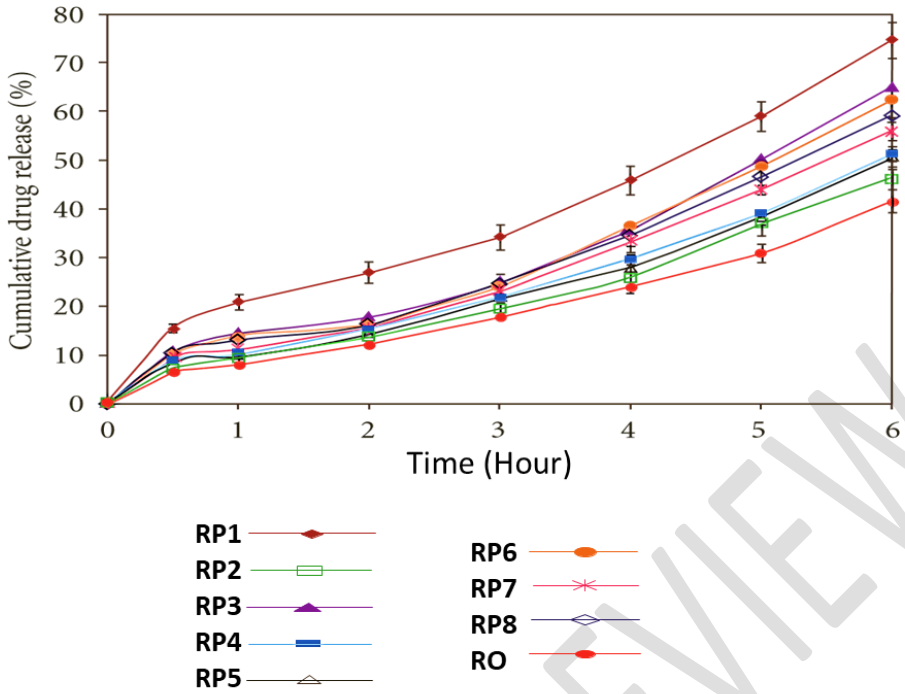


Figure. 11: The drug release from different PCM matrix tablets (RP1 to RO) was evaluated in-vitro. The values are expressed as the mean ± standard deviation (SD), with a sample size

Table. 06: The Drug content and weight variation of PCM matrix tablets

Formulation codes	Drug content (%) [x]	Weight variation (%)[y]
RP1	98.04± 0.61	2.14± 0.19
RP2	97.43± 0.71	3.36± 0.32
RP3	98.25± 0.66	2.15± 0.31
RP4	99.98± 0.84	3.06± 0.32
RP5	99.22± 1.24	3.42± 0.16
RP6	97.64± 0.54	2.89± 0.16
RP7	97.81± 0.77	2.04± 0.15
RP8	99.63± 0.56	3.84± 0.15
RO	97.84±0.73	1.69±0.09

Where; xMean ± S.D., n = 20; y: coefficient of weight variation (%) [The weight variation coefficient (%) can be calculated by dividing the standard deviation by the mean weight and then multiplying the result by 100]

Table. 07: The outcomes of curve fitting for the release data of *In-vitro* PCM from various PCM matrix tablets

Formulation Batches	Correlation coefficient (R^2)				
	Zero Order	First Order	Higuchi	Korsmeyer-Peppas	Release exponent (n)
RP1	0.9645	0.9807	0.8278	0.9510	0.61
RP2	0.9798	0.9930	0.7069	0.9416	0.74
RP3	0.9577	0.9952	0.6844	0.8988	0.70
RP4	0.9810	0.9949	0.7288	0.9418	0.71
RP5	0.9733	0.9942	0.7062	0.9084	0.71
RP6	0.9677	0.9908	0.6925	0.9048	0.72
RP7	0.9774	0.9954	0.7059	0.9093	0.72
RP8	0.9670	0.9944	0.7214	0.9098	0.69
RO	0.9744	0.9920	0.7211	0.9470	0.75

4.2.Optimization of Drug Content and Weight Variation:

All matrix tablets containing PCM were analyzed and found to contain PCM within the range of 97.99 ± 0.85 to 99.03 ± 0.59 (**Table. 06**). This confirms that the drug content is present in the appropriate amount in all the matrix tablets. The weight variation of the tablets also indicates adherence to GMPs by the manufacturers and the amount of APIs in the formulation. This PCM loaded matrix tablets meet the weight uniformity specifications outlined in the USP. The tablets exhibited a weight variation ranging from 2.79 ± 0.07 to 4.08 ± 0.29%, with none of them deviating by more than 5% from their average weight (**Table. 06**) [34-35]. The uniform mixing of CPM with other ingredients is evident from the consistent drug content and weight of the formulated PCM matrix tablets.

4.3.Hardness:

The purpose of conducting the hardness test on PCM matrix tablets was to evaluate their ability to endure handling without breaking or chipping. It has been determined that a minimum force of approximately 4 kg/cm^2 is necessary for the tablets to possess satisfactory hardness. The results obtained from the hardness evaluation indicated that the hardness of the matrix tablets was found to be within the acceptable range of 3.20 ± 0.26 and 5.67 ± 0.08 kg/cm^2 (**Table. 03** and **04**) [35-36]. These findings confirm that the tablets possess the desired level of hardness.

4.4.In-Vitro Drug Release (DR):

All PCM matrix tablets exhibited drug release in 0.1 N HCl (pH 1.2) for the initial 2 hours, followed by release in phosphate buffer (pH 7.4) for 4 hours. These matrix tablets consistently demonstrated prolonged and sustained drug release for a total of 6 hours (**Fig. 11**). The cumulative DR from these tablets after 6 hours of dissolution (R6h, %) ranged from 41.61 ± 1.97 to 74.62 ± 2.36%. Analysis of the response surface revealed that the R6h % values decreased as the three independent variables (amount of calcium alginate, EC, and Carbopol 971) increased**Table. 07.**The presence of larger quantities of hydrophilic polymers, such as calcium alginate, EC, and Carbopol 971, leads to an elevated viscosity [35]. This increased viscosity can promote the creation of extremely thick gels when exposed to the aqueous fluids in the dissolution medium. Consequently, this process would decelerate the rate at which drugs are released from the PCM matrix tablets.The release exponent (n) value, obtained from in-vitro PCM release data of different matrix tablet, varied between 0.49 and 0.76. This range suggests the presence of an anomalous diffusion mechanism for drug release. The anomalous diffusion mechanism indicates a combination of diffusion-controlled and swelling-controlled DR from PCM matrix tablets [36-38].

5. CONCLUSION:

The SR application of PCM matrix tablets was successfully achieved through the use of RSM based on a 2^3 FD. The analysis and optimization of the properties of the matrix tablet, including drug release and hardness, were conducted in a comprehensive manner, focusing on the effects of calcium alginate, EC, and Carbopol 971. Through the examination of RSP and CP, it was observed that higher quantities of calcium alginate, EC, and Carbopol 971 led to reduced drug release (R6h %) values and increased hardness values.The PCM matrix tablets (RO) that were optimized displayed a drug release rate of 44.72 ± 1.89% within a span of 6 hours, along with a hardness value 4.86 ± 0.08 kg/cm^2. This final optimized tablet showcased an extended sustained release of PCM for a period of 12 hours, which has the potential to enhance patient adherence by decreasing the frequency of dosing when compared to traditional tablets.

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