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Optimization, Formulation And Evaluation Of Tablet-In-Capsule: Sodium Bicarbonate Buffer With Pantoprazole Sodium Mini-Tablet

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ABSTRACT

Objective: This study aimed to formulate and optimize a Tablet-in-Capsule containing sodium bicarbonate and pantoprazole sodium using response surface methodology to optimize pantoprazole sodium mini-tablets.

Methods: Mini-tablets were prepared via the direct compression method, utilizing Croscarmellose sodium as a disintegrating agent, Microcrystalline cellulose as a binder, Mannitol & Dicalcium Phosphate as fillers. Magnesium stearate was used as a glidant and talc as a lubricant.

Results: The sodium bicarbonate dose was determined via Digital pH meter measurements for one hour. Mini-tablet formulation aimed for a disintegration time of 5.5 minutes. Subsequently, a desirability plot yielded a D value of 0.995. The optimized formulation was evaluated for thickness (3.65±0.10mm), weight variation (195.71±4.8 mg), hardness (6.9±0.70 kg/cm2), friability (0.51±0.02%), disintegration (5.5±0.15 min), and dissolution(99.11±0.15%).

Conclusion: A formulation containing sodium bicarbonate (400mg) and pantoprazole sodium mini-tablets with concentrations of pantoprazole sodium (40mg) Croscarmellose sodium (8mg), Dicalcium Phosphate (25mg), Microcrystalline cellulose (23mg) ,Mannitol (98mg) talc (2mg) magnesium stearate (4mg) with a total tablet weight of 200 mg, met the prerequisites of optimum formulation. This combination yielded a disintegration time of 5.5 minutes and 99.11% drug release in 50 minutes, aligning with the optimized result.

KEYWORDS: Pantoprazole sodium, Sodium bicarbonate, tablet-in-capsule, optimization, design expert, formulation.

Introduction

The oral route of drug administration plays a crucial role in healthcare delivery as it is the most common and natural form of drug delivery offering numerous benefits including convenience, patient-centered care, and cost-effectiveness, making it a preferred choice for a diverse array of therapeutic interventions.(1) Oral drug delivery stands out as the most favored and preferred approach for administering therapeutic agents to achieve systemic effects. Tablets and capsules are solid dosage forms commonly used for drug delivery. They offer convenience, precise dosing, and easy administration. Tablets are compressed powders or granules, while capsules consist of gelatin shells enclosing drug formulations. Both tablets and capsules are available in various sizes, shapes, and formulations to accommodate diverse therapeutic needs.(2) Tablet-in-Capsule, a novel approach that combines the advantages of both tablet and capsule dosage forms. This amalgamation offers precise dosing, ease of administration, and improved drug stability. Gastrointestinal (GIT) diseases encompass a range of conditions affecting the digestive tract.(3)

Common gastrointestinal conditions encompass GERD (Gastroesophageal Reflux Disease), peptic ulcer disease, IBD (Inflammatory Bowel Disease), IBS (irritable bowel syndrome), gastroenteritis, and more.

Proton pump inhibitors (PPIs) are commonly used to treat such gastric conditions by inhibiting the proton pump enzyme in the stomach lining, which is responsible for producing acid.(4) By reducing acid production, PPIs help to relieve symptoms and promote healing of gastric conditions. But the acidic environment in stomach, leads to degradation of the drug molecules of PPI's. To mitigate the degradation of PPIs and ensure their efficacy, tablet-in-capsule technology is employed.(5) So, the current frontier in PPI therapy is immediate-release mini-tablet of Pantoprazole sodium combined with Sodium bicarbonate acting as buffering agent which prevents the degradation of drug by neutralizing the pH of stomach before absorption and protect the drug from low pH. (6)

Computer-aided modelling:

The mathematical relationship, expressed as a polynomial equation and visualized using the Box-Behnken design, was plotted to represent the measured responses. This was achieved using the statistical package of Design Expert V.13. (7)

Box-Behnken Experimental Design

For the optimization of mini tablet, three independent variables representing different concentrations of excipients were utilized. Design Expert 13, specifically employing the Box-Behnken design, facilitated this optimization process. Each numeric factor was set to three levels, allowing for a comprehensive exploration of the design space. The Box-Behnken design was duplicated for every combination of the categorical factor levels, ensuring thorough coverage of the parameter space.(8,9)

MATERIALS AND METHOD

Materials

Pantoprazole sodium was obtained as sample from IPCA Labs, Pithampur, Indore. Croscarmellose sodium and micro crystalline cellulose was obtained from Sisco Research Laboratories pvt. ltd., Mumbai, India.

Sodium bicarbonate, Potassium dihydrogen phosphate, disodium hydrogen phosphate, sodium bicarbonate, talc, magnesium stearate was obtained from LOBA Chemie pvt. Ltd.

Estimation of Alkalizing Power of Sodium Bicarbonate

The study determined the acid-neutralizing capacity of sodium bicarbonate within a dosage range of 300-800mg, alkalizing capacity within this range was investigated using a digital pH meter for one hour and the investigation was conducted in two media: HCl buffer and artificial gastric juice.(10)

Formulation Development of Pantoprazole Sodium Mini-Tablets

The mini-tablets were fabricated using the direct compression method using Croscarmellose sodium used as a Disintegrating agent, Microcrystalline cellulose used as binder, Mannitol & Dicalcium Phosphate used as a filler. Magnesium stearate used as a glidant and talc used as a lubricant.

An ideal mixture was directly punched into tablets weighing about 200 mg containing 40 mg of pantoprazole sodium sesquihydrate, using rotary tablet compression machine using 5.6 mm diameter concave punches. The different batches of pantoprazole tablets were collected and stored in air tight containers.

Optimization of Mini Tablet:

Three formulation factors, namely CROSS (Croscarmellose sodium), MCC (Microcrystalline cellulose), and DCP (Dicalcium Phosphate), exerted significant influence on powder flowability, compressibility, and consequently, the characteristics of compressed tablets via direct compression. Table 1 outlines the levels for each variable determined in preliminary studies. Disintegration time (DT), cited in Table 2, served as the selected response variable.

A five-level three-factor BB experimental design assessed the impact of chosen independent variables on enhancing flowability, compressibility, characterizing drug release, and optimizing procedures.

This design enables exploration of quadratic response surfaces and construction of second-order polynomial models, facilitating process optimization with minimal experimental runs. In the three-level three-factor BB experimental design, 17 experimental runs were conducted, as indicated in Table 2. Tablets were assessed for physiochemical properties, with disintegration time (DT) measured as the response variable. Polynomial regression equations were derived and tested for significance. Subsequently, the process was optimized to determine levels of A, B, and C that yield optimal Y values under constrained conditions.

To confirm these values, a new formulation was created following the anticipated levels of A, B, and C. Subsequently, tablets were manufactured based on the optimized values and compared with the predicted values, as illustrated in Table 3. (11)

Table 1: Composition of Tablet:

Factor	Name	Units	Type	SubType	Minimum	Maximum	Coded Low	Coded High	Mean	Std. Dev.
A	CROSS	Mg	Numeric	Continuous	2.00	10.00	-1 ↔ 2.00	+1 ↔ 10.00	6.00	2.83
B	MCC	Mg	Numeric	Continuous	23.00	80.00	-1 ↔ 23.00	+1 ↔ 80.00	51.50	20.15
C	DCP	Mg	Numeric	Continuous	25.00	85.00	-1 ↔ 25.00	+1 ↔ 85.00	55.00	21.21

Table: 2 Experimental run Project:

Std	Run	Factor 1 A:CROSS mg	Factor 2 B:MCC mg	Factor 3 C:DCP mg	Response 1 Disintegration min
17	1	6	51.5	55	8.12
15	2	6	51.5	55	8.12
1	3	2	23	55	11
9	4	6	23	25	7.38
6	5	10	51.5	25	4.63
14	6	6	51.5	55	7.12
16	7	6	51.5	55	7.12
5	8	2	51.5	25	12.46
7	9	2	51.5	85	14.7
2	10	10	23	55	3.4
12	11	6	80	85	12
11	12	6	23	85	9.23
10	13	6	80	25	9.98
4	14	10	80	55	5.62
8	15	10	51.5	85	5.95
3	16	2	80	55	15.54
13	17	6	51.5	55	8.12

Table 3: Fit Statistics:

Std. Dev.	0.4727		**R^2**	0.9915
Mean	8.85		**Adjusted R^2**	0.9806
C.V. %	5.34		**Predicted R^2**	0.9582
			Adeq Precision	31.8803

Quadratic Coded Equation:

15.0969 + -1.05725 * A + -0.00666205 * B + -0.111199 * C + -0.00508772 * AB + -0.00191667 * AC + 4.97076e-05 * BC + 0.0299219 * A^2 + 0.000851031 * B^2 + 0.00137361 * C^2

Where, A=CROSS, B= MCC, C=DCP

Evaluation

Pre-Compression Parameters

The flow characteristics of powders play a crucial role and are vital for optimizing tabletting efficiency. Efficient tabletting relies on good powder flow for effective mixing and uniform tablet weight. Common flow property measurements, such as Bulk Density, Tapped Density, Compressibility Index, Hausner's Ratio, and Angle of Repose, inform the selection of compression techniques by assessing material flow characteristics. The flow property measurements of drug and blend, guides the selection of Compression method based on the flow characteristics of materials.(12)

Bulk Density

Bulk density is crucial in tablet manufacturing as it influences blend homogeneity, tablet weight uniformity, compression behaviour, tablet hardness, disintegration, dissolution, and manufacturing efficiency.

Tapped Density

Tapped density in tablet manufacturing ensures optimal powder compaction, uniform tablet weight, and consistent tablet hardness.

Angle of Repose

Angle of repose in tablet manufacturing determines powder flow properties and influences manufacturing processes such as blending, filling, and compaction.

Carr's Index

Carr's index in tablet manufacturing assesses powder compressibility, aiding in formulation optimization and ensuring consistent tablet quality.

Hausner's Ratio

Hausner's ratio in tablet manufacturing evaluates powder flowability, indicating potential processing challenges and affecting tablet compression efficiency.

POST-COMPRESSION PARAMETERS

Post-compression parameters such as hardness, thickness, weight variation, friability, disintegration time, and dissolution rate are vital for ensuring the quality, efficacy, and safety of pharmaceutical tablets. These parameters directly influence the tablet's strength, uniformity, durability, and drug release properties, crucial for its performance in treating patients. Hence, meticulous control and monitoring of these parameters are essential to uphold product quality and comply with regulatory standards.(13)

Hardness Test

The tablets prepared underwent hardness testing, carried out using a monsanto hardness tester and results were expressed in kg/cm2.

Thickness Test

Thickness is measured by the tablet diameter using micrometres or vernier calliper.Twenty tablets

from the batch are sampled, and their average thickness is calculated. Acceptable thickness falls within ±5% variation of the standard value.(14)

Friability Test

The friability test, conducted with a friabilator, presents results as a percentage (%). Twenty tablets from each batch are weighed individually (Wt. Initial) and subjected to 100 revolutions at 25 rpm in the friabilator. Subsequently, the tablets are reweighed (Wt. Final), and the percentage friability (F) is calculated using a specified formula.

Weight Variation Test

The weight variation test selects twenty tablets from the lot, weighs each to find the average weight, and calculates the percent deviation from this average. Acceptable weight ranges, as per pharmacopeial standards, determine maximum and minimum allowable weights for the tablets. The batch passes if no more than 2 tablets exceed the specified limit.

Drug Content Uniformity

Drug Content Uniformity ensures that each unit dose of a drug product contains the correct amount of active pharmaceutical ingredient (API) within acceptable limits. Randomly select 30 tablets from the batch for testing. Out of which 10 tablets were assayed individually.

The batch is considered to pass the test if 9 out of 10 tablets contain not less than 85% and not more than 115% of the labelled drug content, and the 10th tablet must also contain not less than 75% and not more than 125% of the labelled drug content. Should these conditions not be met, the remaining 20 tablets are assayed individually, and none may fall outside of the 85%-115% range.

Disintegration Test

Disintegration test was carried out using disintegration test apparatus. It assesses the time taken for a dosage form to break down into smaller particles or disintegrate into its individual components when exposed to a specified medium under standard conditions.

Randomly 6 tablets were selected from the batch for testing in water as disintegration medium at 37 ± 0.5 ºC and recorded the time taken for each unit to completely disintegrate. Compare the observed disintegration times of the dosage units to the pharmacopeial standards. If all units meet the specified disintegration time, the batch passes the test.

In-vitro drug release studies

In vitro drug release studies of the formulation were conducted in 900 ml of 6.8 phosphate buffer as the dissolution media using a USP type 1 dissolution apparatus. The apparatus was maintained at 50 rpm and 37 ± 0.5 ℃ for 1 hour. During the dissolution test, samples were withdrawn at appropriate time interval and replaced with equivalent volume of fresh medium to maintain sink condition. The samples were filtered, diluted appropriately and then analysed spectrophotometrically for Pantoprazole sodium at 285nm.(15)

Results and Discussion

Estimation of Acid Neutralizing Capacity of Sodium Bicarbonate

Sodium bicarbonate was taken at doses spanning 300mg to 800mg in HCl buffer and artificial gastric juice. The objective was to assess its ability to neutralize acidity within the stomach, potentially safeguarding pantoprazole sodium mini-tablets from degradation by altering pH levels from acidic to alkaline conditions. The optimum dose i.e., 400mg was selected on the basis of ANC and its ability to maintain the pH at or above 5.5 for 1 hour. figure 1 While selecting the optimum dose it

was assured that pH should not shift too much alkaline that it impacts the digestion process.

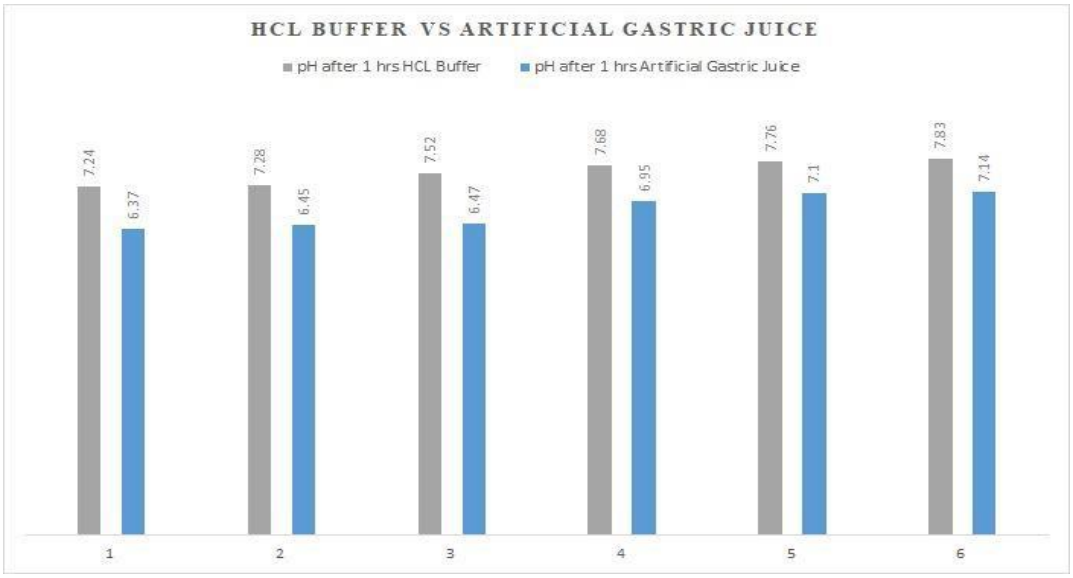


Figure 01: pH profile of the formulation.

Optimization data analysis and validation of Optimization model:

Box-Behnken design was used to study the optimal levels of independent variables. As shown in Table 1, a total of 17 anticipated runs were observed. The sequential model sum of squares [Type III] confirms the highest fit Statistics. The **Predicted R²** of 0.9582 is in reasonable agreement with the **Adjusted R²** of 0.9806; i.e. the difference is less than 0.2.

The sequential p value for the Quadratic model was found to be 0.0018, which is below the level of significance (< 0.001). The Predicted R² of 0.9582 is in reasonable agreement with the Adjusted R² of 0.9806; i.e. the difference is less than 0.2. Fig. 02.

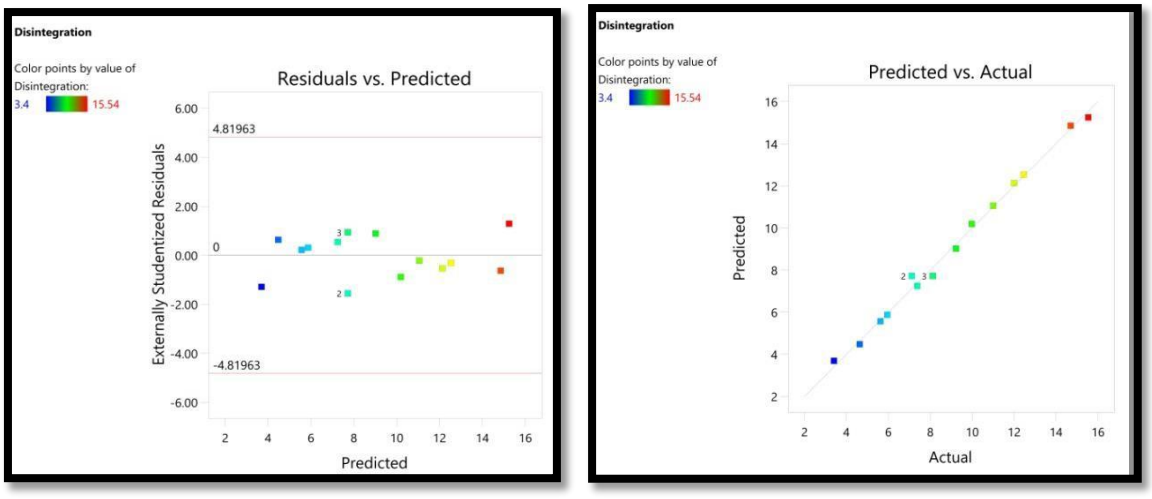


Figure 02: Drug release profiles of Mini tablet formulations

Adequate precision, as assessed by the signal-to-noise ratio, is essential for ensuring model reliability. A ratio exceeding 4 is considered desirable, and our ratio of 31.880 indicates a robust signal, underscoring the model's efficacy for navigating the design space (refer to Table 2). The quadratic model, characterized by a precision ratio of 31.8578, signifies satisfactory signal strength for exploration within the design space. This is further bolstered by a relatively low coefficient of variation (CV) of 2.42%. Although studentized results displayed slight deviation from the

straight line, they affirm the accuracy of the quadratic modelling.

ANOVA results (Table 4) reinforce the model's reliability, with a significant Model F-value of 215.13 and a non-significant Lack of Fit value, indicating the model's adequacy in representing the data. Polynomial equations, derived from multiple regression analysis, enable the estimation of variable effects on selected responses, with significant factors determined by p-values less than 0.0500. (16)

In particular, Response I is significantly influenced by both the antagonistic effect of factors A and B ($p < 0.001$) and the synergistic effect of the interaction term AB and the polynomial term of A (with p-values of 0.0007 and 0.0012, respectively). Notably, factor B exhibits the highest magnitude of impact on Response I among all significant factors. **Table 4: Disintegration**

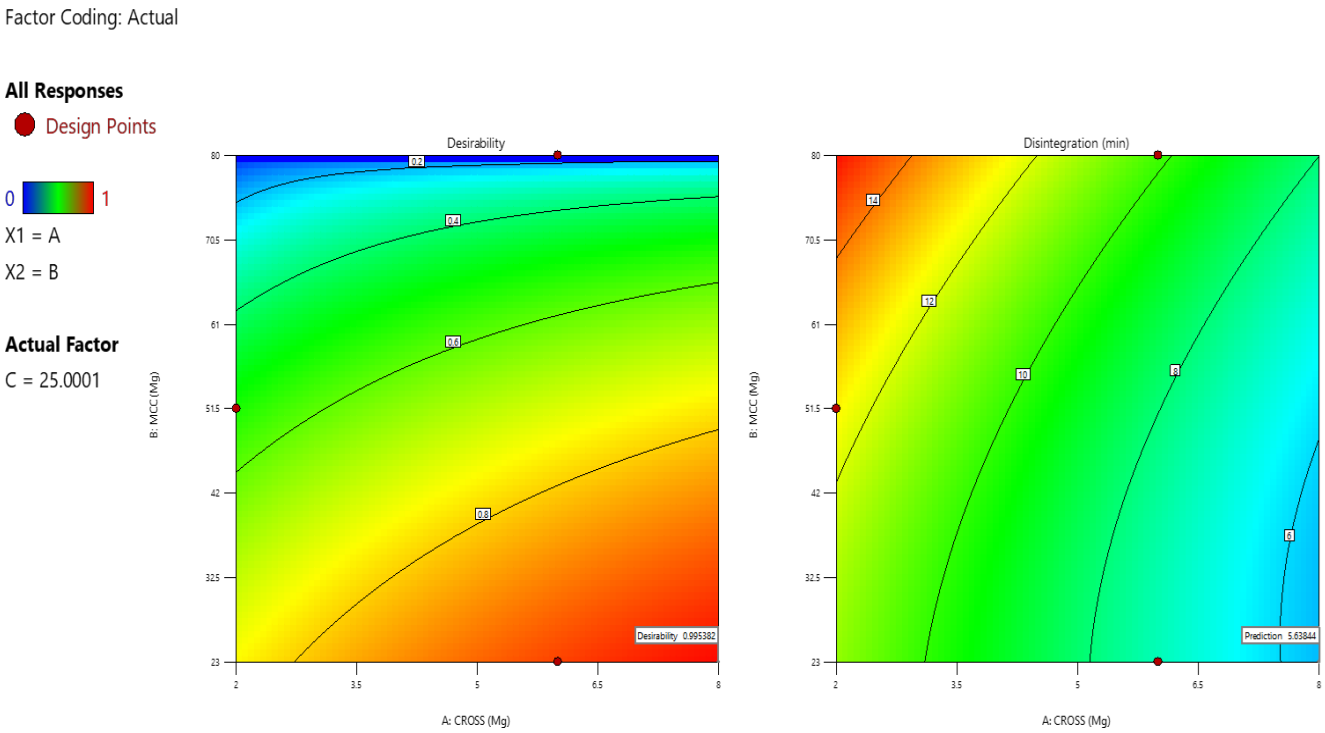
Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	182.51	9	20.28	90.76	< 0.0001	significant
A-CROSS	145.35	1	145.35	650.56	< 0.0001	
B-MCC	18.39	1	18.39	82.32	< 0.0001	
C-DCP	6.90	1	6.90	30.89	0.0009	
AB	1.35	1	1.35	6.02	0.0438	
AC	0.2116	1	0.2116	0.9471	0.3629	
BC	0.0072	1	0.0072	0.0323	0.8624	
A^2	0.9651	1	0.9651	4.32	0.0763	
B^2	2.01	1	2.01	9.00	0.0199	
C^2	6.44	1	6.44	28.80	0.0010	
Residual	1.56	7	0.2234			
Lack of Fit	0.3640	3	0.1213	0.4044	0.7585	not significant
Pure Error	1.20	4	0.3000			
Cor Total	184.08	16				

Factor coding is **Coded**.
Sum of squares is **Type III - Partial**
The Model F-value of 90.76 suggests that the model is highly significant. The probability of such a large F-value occurring due to noise is only 0.01%.(17)
P-values less than 0.0500 indicate that model terms are significant, implying their influence on the response. In this case, factors A, B, C, AB, B^2, and C^2 are all found to be significant model terms. Conversely, values greater than 0.1000 suggest that the model terms lack significance. Additionally, a polynomial equation can be employed to predict the response at any given level of the factor. Utilizing response surface methodology enables the elucidation and analysis of the effects of factors on selected responses. Visual representations such as contour plots and 3-dimensional (3-D) response surface graphs (RSG) provide a clear illustration of calculated responses.
Final Equations in Terms of Coded Factors
15.0969 + -1.05725 * A + -0.00666205 * B + -0.111199 * C + -0.00508772 * AB + -0.00191667 * AC + 4.97076e-05 * BC + 0.0299219 * A^2 + 0.000851031 * B^2 + 0.00137361 * C^2

GLOBAL DESIRABILITY FUNCTION

Optimization of the process can be done by setting the goal for every response then the Global desirability function (D) was applied simultaneously. Response I was targeted to 5.5 min. On basis of these criteria, the desirability plot was generated with a D value of 0.995 (Fig. 3). In

conclusion, formulation with Croscarmellose concentration of 8mg, MCC concentration of 23 mg and DCP concentration of 25mg and total tablet weight of 200 mg, can accomplish the prerequisites of optimum formulation and the use of such combination will achieve CDH at 5.5 min which matches with the optimized result.



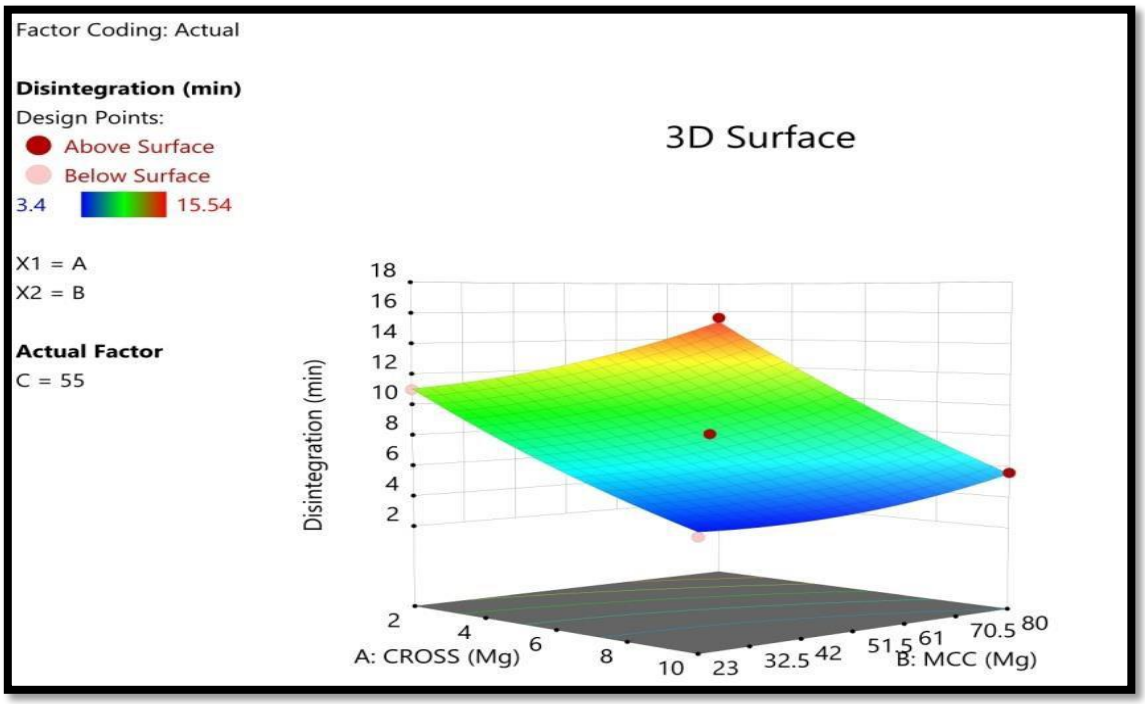


Figure 03: Normal probability plots of the residuals and model residuals

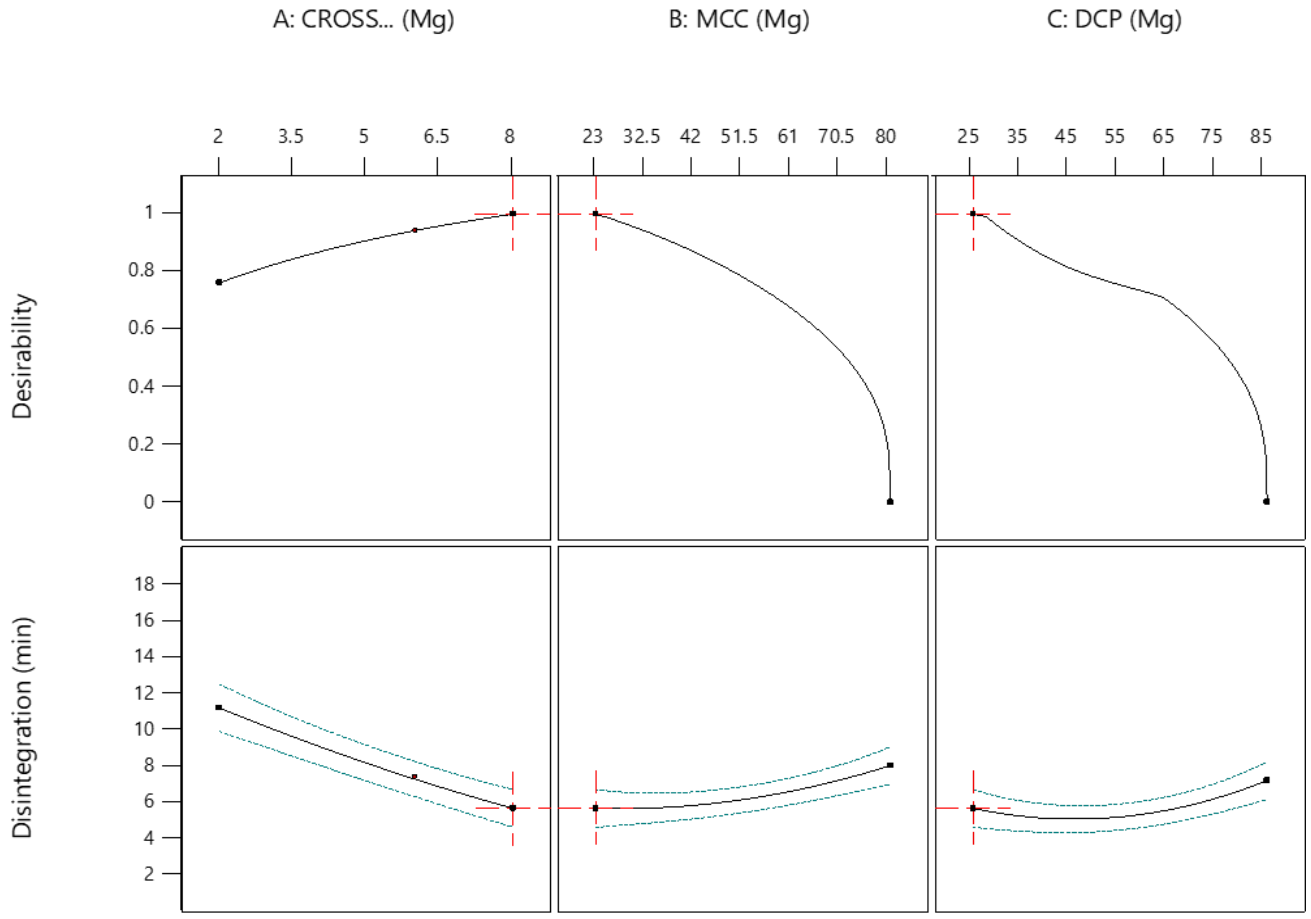


Figure 04: All factor interaction for desirability

Preparation of Pantoprazole sodium tablets

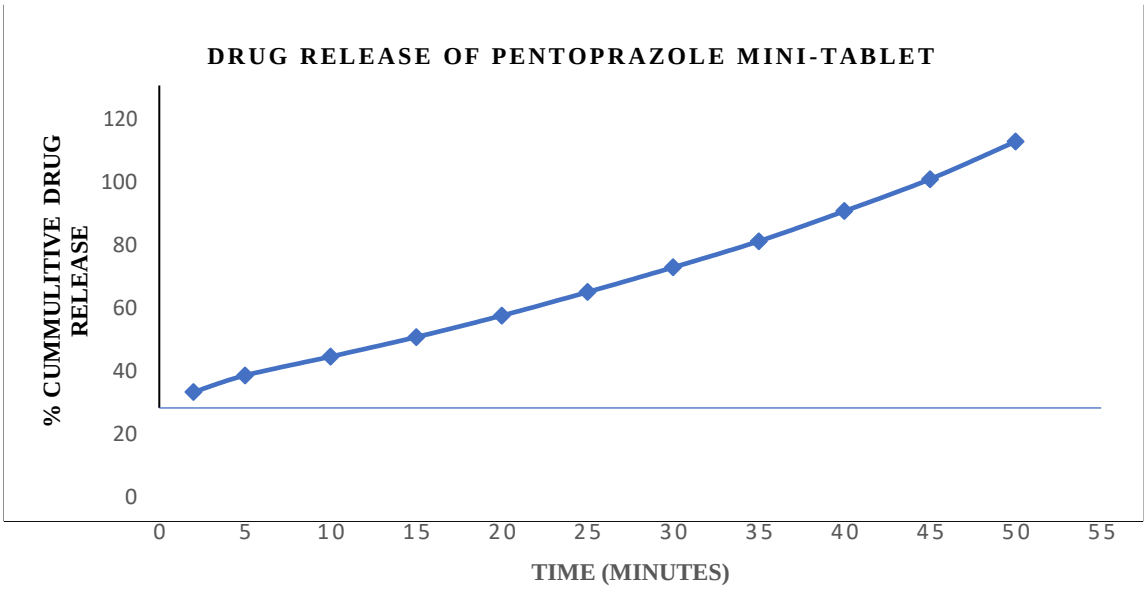
Pre-compression and post-compression parameters: Powder blend of mini-tablet is evaluated for pre-compression parameters. Obtained results were compared with standard values to confirm the flow characteristics. Formulation blend of tablet shows the Hausner's ratio of 1.25 and Carr's index as 20%. The maximum angle of repose was found to be 32.8ɵ. All these results confirm the good to fair flow property. Prepared mini-tablet formulations were found to be flat, oval with thickness in the range of 3.65 mm. Hardness and thickness for mini-tablet was maintained as 6.9 kg/cm^2 and 3.65mm. Weight variation for mini-tablet was found to be within the acceptable range i.e., 195.71mg. Percentage friability for mini-tablet is 0.51% which shows good mechanical strength. Desired formulation was selected on the basis of disintegration profile and according to global desirability function. Drug release profile of the optimized formulation was found to be 99.11%.

PARAMETER	RESULTS	FLOW CHARACTERISTICS
Bulk density	0.36±0.021	-
Tapped density	0.45±0.2	-

Angle of repose	32.8	Good
Carr's index	20±2	Fair
Hausner's ratio	1.25±0.25	Fair

PARAMETER	**RESULTS**
Thickness	3.65±0.10 mm
Hardness	6.9±0.70 kg/cm^2
Weight variation	195.71±4.8 mg
friability	0.51±0.02%
Disintegration	5.5±0.15 min
In-vitro drug release	99.11±0.15 %

Dissolution Profile



The kinetic parameters revealed that release data of optimized formula showed r^2 value of 0.989 which is close to 1, indicating that release of drug follows **zero** order **kinetics** and the release are independent of concentration.

Conclusion

In conclusion, this study successfully formulated and optimized a Tablet-in-Capsule containing sodium bicarbonate and pantoprazole sodium using response surface methodology, specifically the Box-Behnken Design, to enhance the performance of pantoprazole sodium mini-tablets. The precise determination of the sodium bicarbonate dose via Digital pH meter measurements ensured accurate control over the alkalizing capacity of the formulation. Utilizing a desirability plot, a highly desirable D value of 0.995 confirmed the effectiveness of the optimized formulation. Evaluation of the formulation revealed excellent characteristics, including appropriate thickness, minimal weight variation, satisfactory hardness, and minimal friability, crucial for tablet integrity and patient compliance. Moreover, the formulation achieved a disintegration time of 5.5 minutes and 99.11% drug release within 50 minutes, indicating robust performance in drug delivery. This comprehensive approach highlights the potential of Tablet-in-Capsule technology to improve the therapeutic outcomes of pantoprazole sodium, offering promising avenues for enhanced patient treatment and compliance in managing gastroesophageal reflux disease.

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CONFLICT OF INTEREST

No conflict of interests.

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