



Formulation And Evaluation Of Optimized Natural Detoxifying Agents' Effervescent Granules Into Gastroretantive Tablet

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Abstract

When a chemical reaction produces gas bubbles in a liquid, this phenomenon is known as effervescence. The research found that the quicker disintegration and faster drug release properties for CGZ may be achieved by the production of effervescent tablets using a mix of sodium bicarbonate, tartaric acid, and fumaric acid. The optimized batch B4 was more drugs were dispensing more quickly than in previous batches. It follows that effervescent pills are easier to create when acids and sodium bicarbonate are used together. To create an effervescent formulation with desirable qualities like rapid disintegration and medication release with little effort in the shortest amount of time, an experimental design may be useful.

Keywords: Effervescent Granules, Gastroretantive Tablet, Curcumin, Garlic, Ginger

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1. Introduction:

The development of innovative drug delivery systems is crucial for improving the bioavailability and therapeutic efficacy of drugs (1). Gastroretentive tablets, also known as gastric retention tablets or floating tablets, have emerged as a promising oral drug delivery system that can prolong the residence time of a tablet in the stomach (2). These tablets are specifically formulated to remain in the stomach for an extended period, allowing for better drug absorption and sustained drug action (3). The primary objective of gastroretentive tablets is to overcome the limitations posed by drugs with a narrow absorption window in the gastrointestinal tract. By keeping the tablet in the stomach, these tablets enhance the bioavailability of such drugs (4). They achieve this by incorporating various mechanisms to achieve gastroretention. One common approach involves the use of high-density materials or gas-generating agents within the tablet formulation, creating buoyancy that keeps the tablet floating on the gastric contents. Other strategies include the use of bioadhesive polymers, swellable polymers, and geometric modifications to the tablet shape to prevent rapid emptying from the stomach. Gastroretentive tablets offer several advantages over conventional drug delivery systems(5). They improve drug solubility, reduce dosing frequency, enhance drug stability, and provide controlled release of the active ingredient. These tablets are particularly useful for drugs that require local action in the stomach or have absorption limitations in the upper gastrointestinal tract (6). However, the development and formulation of gastroretentive tablets require careful consideration of the physicochemical properties of the drug, patient needs, and desired therapeutic outcomes (7). Effervescent formulation is another approach that has gained attention in the development of drug delivery systems. Effervescent tablets are characterized by a chemical reaction that produces gas bubbles when the tablet dissolves in a liquid (8). These tablets typically contain an acid source, an alkaline source, and the active pharmaceutical ingredient(9). When the tablet comes into

contact with water, the acid and alkaline sources react, releasing carbon dioxide gas, which provides effervescence. Effervescent tablets offer advantages such as quicker response time, improved portability, enhanced flavor, and dosing precision (10,11). However, they also have limitations related to manufacturing costs, packaging requirements, and taste preferences. This study focuses on the formulation and evaluation of optimized natural detoxifying agents' effervescent granules into gastroretentive tablets. The combination of gastroretentive and effervescent technologies aims to enhance drug delivery and improve patient adherence(12,13). The incorporation of natural detoxifying agents adds an additional therapeutic dimension to the formulation, potentially providing detoxification benefits in the gastrointestinal tract. The study aims to investigate the properties of gastroretentive tablets and effervescent formulations, their advantages, limitations, and the general manufacturing processes involved. The development of effervescent granules using wet granulation, dry granulation, and direct compression methods will be explored. The formulation and evaluation of gastroretentive tablets with optimized natural detoxifying agents' effervescent granules will be the main focus, aiming to achieve controlled drug release, prolonged gastric residence time, and improved therapeutic outcomes. Overall, this study contributes to the growing field of innovative drug delivery systems by combining gastroretentive and effervescent technologies with natural detoxifying agents. The findings of this study have the potential to advance drug delivery strategies, enhance patient adherence, and provide new therapeutic options for detoxification in the gastrointestinal tract.

2. Materials

The materials used in the study were provided by Svgro Pvt Ltd., Ahmedabad. Curcumin, Garlic Extract, and Zinger Officinal (CGZ) were obtained from Svgro Pvt Ltd. Other materials used, including succrose, sodium bicarbonate, lactose, sodium benzoate, tartaric acid, and polyvinyl pyrrolidone (PVP), were purchased from Merck India Ltd.

and Sigma Aldrich in India. High-quality, analytical-grade substances and compounds were used in the research.

3. Methods

3.1 Maximal UV Absorption

A UV spectrophotometer (Shimadzu UV 1800) was used to acquire a UV spectrum. A 10mcg/ml solution of Curcumin, Garlic Extract, and Zinger Officinal (CGZ) dissolved in 0.01M hydrochloric acid was prepared. The highest absorbance observed at 264 nm was used for estimation in this study. To establish a standard calibration curve, 100 milligrams of CGZ were dissolved in 100 milliliters of 0.01M hydrochloric acid. From the resulting stock solution,

1 milliliter was combined with 1 milliliter of solvent, resulting in a 2 solution with a concentration of 100 micrograms per milliliter ($\mu\text{g/ml}$). Further dilutions were made to obtain CGZ solutions with concentrations of 2, 4, 6, 8, 10, 12, and 14 micrograms per milliliter (mcg/ml) using 0.01M hydrochloric acid. The maximum absorbance of each CGZ solution was determined using a UV-VIS spectrophotometer(14).

3.2 FT-IR Analysis

The FT-IR spectrophotometer (Perkin Elmer spectrum GX FT-IR) was used to collect infrared data. A pellet consisting of the drug and dry potassium bromide was compressed under a pressure of 7-10 tonnes using a hydraulic pellet press. The FT-IR spectrum of the drug was recorded in the range of 400 to 4000 cm^{-1} . The obtained FT-IR spectrum was compared to a reference spectrum to verify the purity of the drug.

3.3 Making Fizzy Tablets

Tartaric acid, fumaric acid, sodium bicarbonate, lactose, and sucrose underwent a sieving process using a 40-pound sieve for 15 minutes. A double cone mixer (Minipress-II, Karnavati Engineering Ltd.) was used for the sieving process. The resulting powdered mixture was compressed into tablets with a consistent diameter of 10 mm using a tablet compression device (RIMEK Mini Press II, Karnavati Engineering). The tablets were subjected to various quality assessment procedures as per the Indian Pharmacopoeia

(IP) to determine their rating and adherence to specified standards.

3.4 Optimization of Effervescent Tablet Using 32 Full Factorial Design

A 3^2 full factorial design was used to prepare effervescent tablets. The design included two independent factors, concentration of xanthan gum (X1) and concentration of HPMC (X2), each with three levels. The effects of these factors on hardness, disintegration time, and drug release (dependent variables) were analyzed. The variables and their levels were chosen based on a literature survey. The compositions of the effervescent tablets were prepared as per the design.

4. Evaluation of Developed Effervescent Tablets of

• Tap Density

Tap density, angle of repose, and Carr's index of powder blends were measured for all batches (F1 to F9). The tap density was measured using a density tester (ETD-1020, Electrolab) by adding 10 g of the powder blend to the cylinder and tapping the sample 100 times.

• Angle of Repose

The angle of repose was determined by pouring a 5-gram powder blend into a glass funnel placed at a specific height above the base. The powder that fell onto graph paper was measured for diameter and height. The angle of repose was calculated using the obtained measurements.

• Post Compression Evaluation of Tablet

Individual tablets were weighed using a digital scale to calculate their mean weights and investigate the range of possible weights. Hardness of the tablets was measured using a hardness tester (DHT-250, Cambell Electronics Machine) to determine the force required to crush the tablet. Diameter and thickness of the tablets were also measured using the same instrument. The degree of brittleness was determined using a Roche friabilator USP(15).

• pH of the Solution

A glass beaker containing 200 ml of distilled

water was used to determine the pH of the solution. The tablet was placed in the beaker and left until the fizzing substance completely dissolved. pH levels were measured using digital pH meters (Mettler Toledo).

• **Disintegration Time Study**

The disintegration time of the tablets was studied by dissolving three tablets in water in a 250ml beaker. The time taken for complete tablet disintegration was observed and recorded. The disintegration time was required to be less than 5 minutes as per pharmacopeial requirements.

• **In Vitro Dissolution Study**

A dissolution test was conducted using a USP apparatus II (TDT08L, Electrolab) in 500 cc of M HCl buffer media at 37 °C ± 2 °C and 50 RPM. Samples were collected at 5, 15, 30, 45, 60, and 90-minute intervals over a total of 120 minutes. Each sample was replaced with an equal volume of fresh dissolving media. The concentration of the medication was measured using a spectrophotometer (Shimadzu UV 1800) at a wavelength of 264 nm. A calibration equation was developed using a standard curve to plot the cumulative percentage of drug release against time(16).

• **Chromatographic Conditions**

The concentration of CGZ in the samples was determined using a Shimadzu LC-20AT HPLC system equipped with an SPD-20A detector. The CGZ was detected at a wavelength of 262 nm using a UV-Visible

detector. A mixture of methanol and phosphate buffer (pH 2.8) in a ratio of 60:40 was used as the mobile phase. The mobile phase was pumped at a rate of 1 ml/min.

• **Stability Studies**

Stability studies were conducted on the formulations that exhibited the desired zero-order drug release profile. The studies were carried out in a stability chamber at 40 degrees Celsius and 75 percent relative humidity for 6 months, following ICH recommendations. Samples were collected at 0, 3, and 6 months to analyze the in-vitro drug release profile, drug content, and time to disintegration. The percentages of medicine release intervals were compared using the similarity factor method.

5. RESULT

5.1. PREFORMULATION STUDIES

• **Drug-Excipient Compatibility Study by FT-IR**

The FT-IR spectrophotometer was utilised to conduct compatibility tests. Figure displays the spectra of the pure medicine and excipients, and table summarizes their interpretation. There is a direct relationship between the drug spectrum's peaks and those seen in the spectra of each formulation. There are no obvious peaks shifting, suggesting no clear interaction between Curcumin, Garlic Extract, Zinger Officinal and the other excipients. This means that the medicine may be combined safely with the other ingredients in the formulation.

Table 1: Curcumin Spectral Interpretation

S. No	Wave Number (cm ⁻¹)	Interpretation
01.	3551 w	OH <i>str.</i>
02.	3183 w	Aromatic C-H <i>str.</i>
03.	2933 w	Aromatic C-H <i>str.</i>
04.	2923 w	Asymmetric CH <i>str.</i> of CH ₃ group
05.	2852 w	Symmetric CH <i>str.</i> of CH ₃ group

The finished bilayer formulation's FTIR peak exhibited no change or removal of the distinctive peaks, indicating no interaction between the two medicines as well as the excipients inside the formulation.

Table 2: Garlic Extract Spectral Interpretation

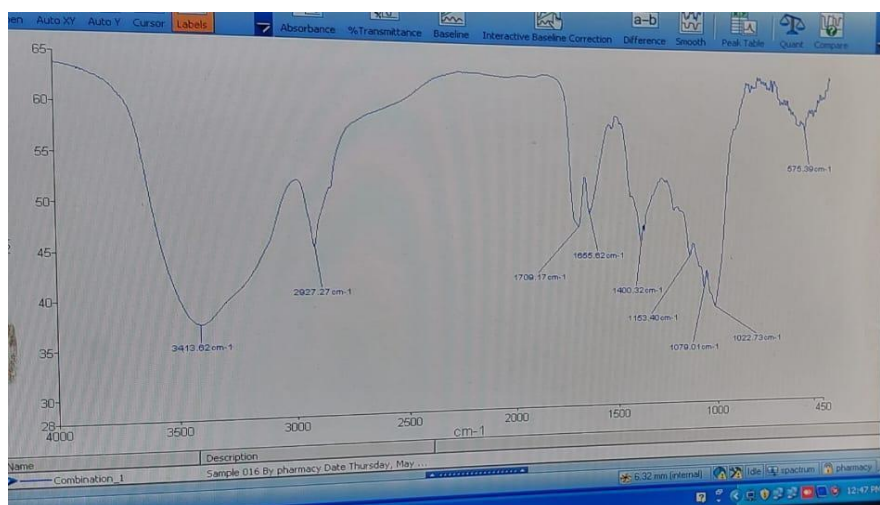
S. No	Wave Number (cm ⁻¹)	Interpretation
01.	3265	Hydroxyl
02.	2926	Aromatic compounds
03.	1619	Carbonyl and carboxylic
04.	1395	Carboxylic
05.	1036	Organosulfur

The finished bilayer formulation's FTIR peak exhibited no change or removal of the distinctive peaks, indicating no interaction between the two medicines as well as the excipients inside the formulation.

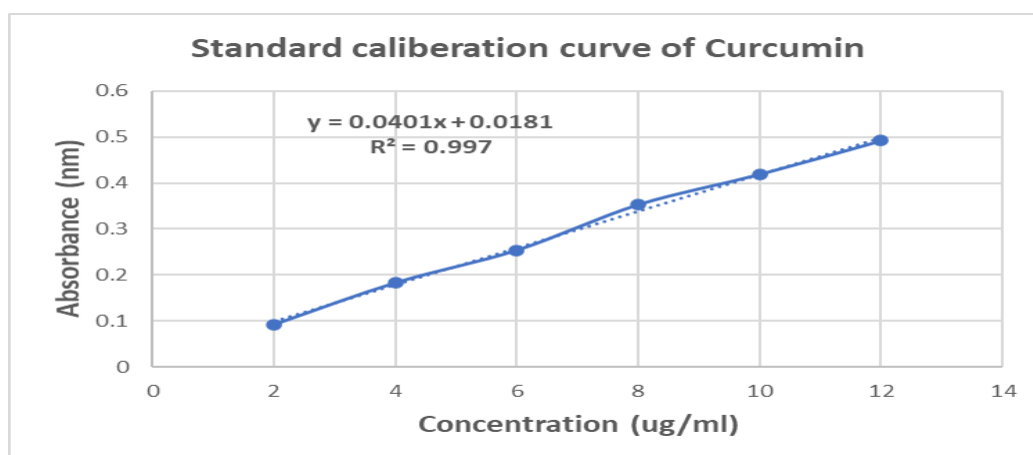
Table 3: Zinger Officinal Spectral Interpretation

S. No	Wave Number (cm ⁻¹)	Interpretation
01.	3350	OH stretching vibration
02.	2900	CH
03.	1650	C = O stretching vibration
04.	1380	CH in plane bending vibration C – O – C stretching vibration
05.	1230	OH deformation bands in alcohol group CH out of plane banding vibration
06.	1120	OH stretching vibration
07.	780	CH

The finished bilayer formulation's FTIR peak exhibited no change or removal of the distinctive peaks, indicating no interaction between the two medicines as well as the excipients inside the formulation.



5.2. Standard Calibration Curve of Curcumin, Garlic Extract, Zinger Officinal in 0.01 M HCl

**Fig no 1 - Calibration Curve for CURCUMIN**

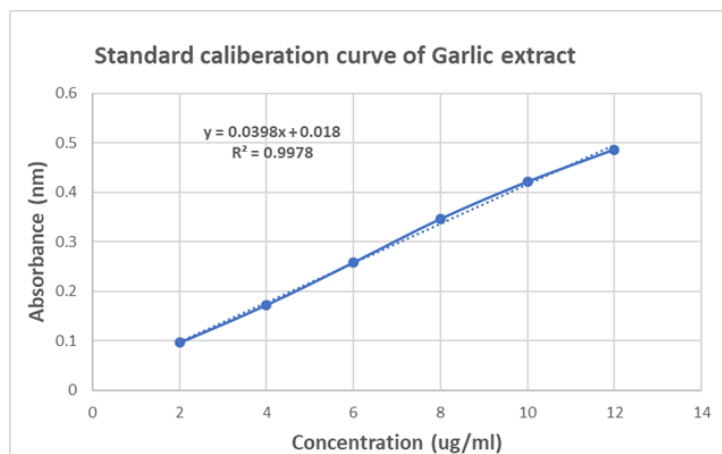


Fig no 2 - Calibration Curve for *GARLIC EXTRACT*

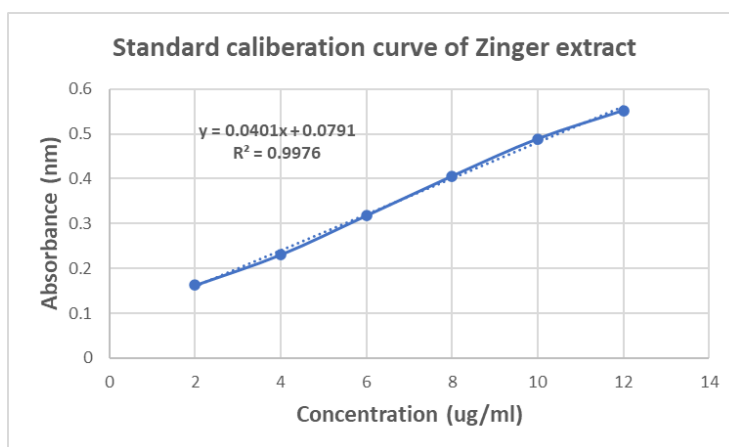


Fig no 3 - Calibration Curve for *ZINGER OFFICINAL*

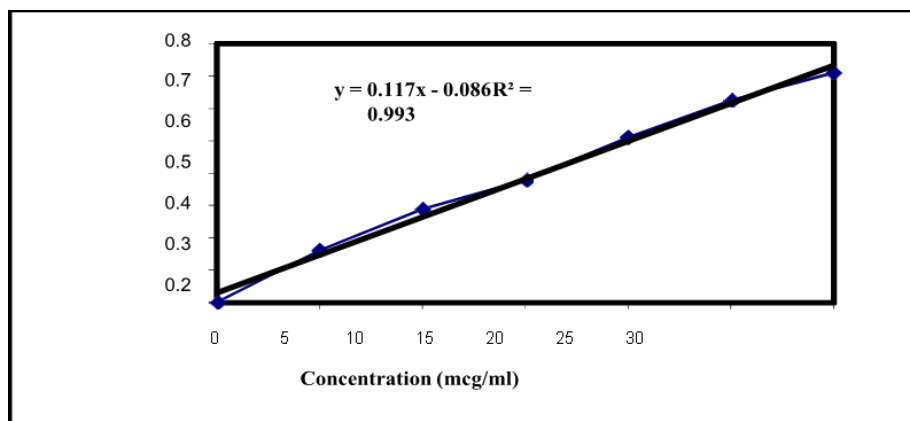


Figure 4: Calibration Curve of CGZ in 0.01 M HCl

The UV spectra of drug shown max 264.5 nm (figure 5.1). Linear graph with regression coefficient value of 0.993 was obtained which indicates that it obeys Beer's Lambert's law.

5.3 In Vitro Drug Release of Preliminary Trial Batches

It was made in many batches, each with its own unique acid and carbonate/bicarbonate content.

Sodium bicarbonate was selected as carbonate sources from the total medication release across all batches. Additionally, various acid sources were mixed with sodium bicarbonate to make the batches. Sodium bicarbonate and citric acid were shown to speed up the release profile of the medication. Both tartaric acid and fumaric acid were shown to increase the rate of medication release.

5.4 Flow Properties of Powder

The research group looked at the CGZ effervescent powder's flow characteristics. Powder was found to have an angle of repose between -23.690.59 and 42.710.23 degrees. Density measurements took from 0.570.05 to 0.970.04 for the powder. It was determined that the powder has a carr's index of 8.560.6 - 17.150.06. The pharmacopoeia stipulated that this powder was of sufficient quality because it had satisfactory flow properties.

5.5 Post Compression Evaluation of Tablets

5.6 Experimental Design

Table. - 4 Formulation of Effervescent Tablet Using 3^2 Full Factorial Design

BatchCode	X1	X2	Y1= Hardness(n/mm ²)	Y2= Disintegration time (secs)	Y3= Drug Release (%)
B1	-1	-1	4	149.98	61.6
B2	0	0	4	157.56	64.4
B3	-1	1	4.6	143.52	75.4
B4	1	1	4.8	158.38	82.2
B5	0	1	4.5	153.38	74.8
B6	1	0	4.4	162.85	73.3
B7	0	-1	4.3	139.39	70.1
B8	-1	0	4.2	155.39	66.7
B9	1	-1	5	128.76	86.2

The results of each experimental design run are shown in Table 4 (B1 to B9).

Hardness, disintegration time, and drug release were all observed to increase with varied concentration of xanthum gum, and HPMC using 3^2 designs. Data from a statistical analysis of design batches generated in Design Expert®.

The fluid dynamics of CGZ effervescent powder were examined by the researchers. Powder was found to have an angle of repose ranging from - 23.690.59 to 42.710.23 degrees. There was a wide variation in the powder's density, from 0.570 to 0.970. In a carr's index analysis, the powder scored between 8.560.6 to 17.150.06. Such a powder's flow characteristics are in accordance with the pharmacopoeia's standards, indicating that it is of sufficient quality.

5.7 Analysis of Variance for Hardness

The p-value for the disintegration time response surface quadratic model is 0.0492 (less than 0.05), as shown in Table..... This indicates the model's validity from a statistical standpoint. If the cumulative P-value of the two factors is less than 0.05, then the two factors are significantly related.

Table. -5 ANOVA of Hardness

Source	Sum of Squares	df	Sum of Square	F value	p-value	
Model	0.8778	5	0.1756	9.12	0.0492	Significant
A- Concentration of Xanthum Gum	0.3267	1	0.3267	16.96	0.0259	
B- Concentration of HPMC	0.0600	1	0.0600	3.12	0.1757	
AB	0.1600	1	0.1600	8.31	0.0634	
A ²	0.1089	1	0.1089	5.65	0.0978	
B ²	0.2222	1	0.2222	11.54	0.0426	
Residual	0.0578	3	0.0193			
Cor Total	0.9356	8				

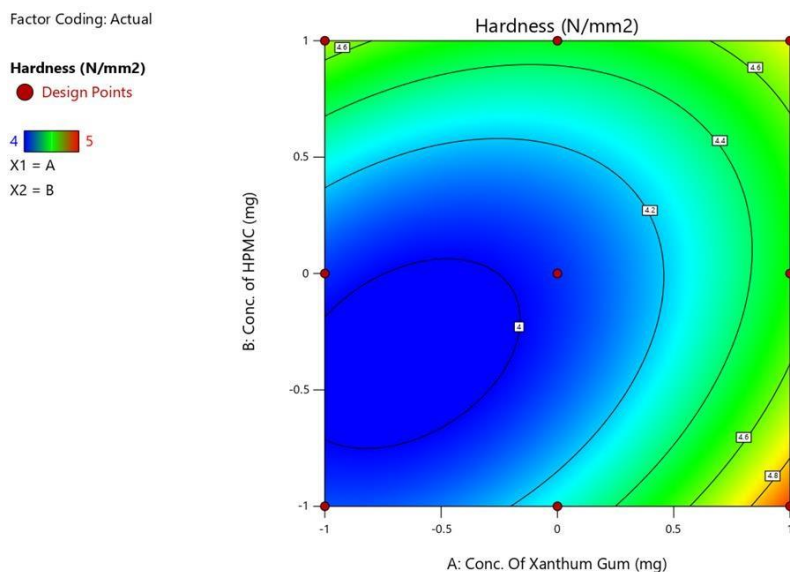


Figure-5 Contour Graph of Hardness

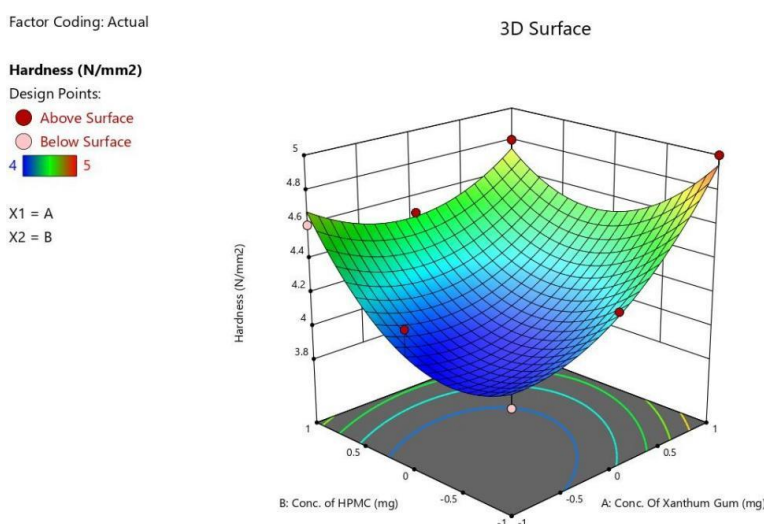


Figure- 6 3D Surface Graph of Hardness

ANOVA (Analysis of Variance) for Disintegration Time

The p-value for the disintegration time response surface quadratic model is 0.0321 (less than 0.05), as shown in Table.....

This indicates the model's validity from a statistical standpoint. If the cumulative P-value of the two factors is less than 0.05, then the two factors are significantly related.

Table. - 6 ANOVA of Disintegration Time

Source	Sum Squares	df	Sum of Square	F value	p-value	
Model	895.49	5	179.10	12.46	0.0321	Significant
A- Concentration of Xanthum Gum	0.2017	1	0.2017	0.0140	0.9132	
B- Concentration of HPMC	230.02	1	230.02	16.00	0.0280	
AB	325.44	1	325.44	22.64	0.0176	
A ²	0.1760	1	0.1760	0.0122	0.9189	
B ²	339.65	1	339.65	23.63	0.0166	
Residual	43.12	3	14.37			
Cor Total	938.61	8				

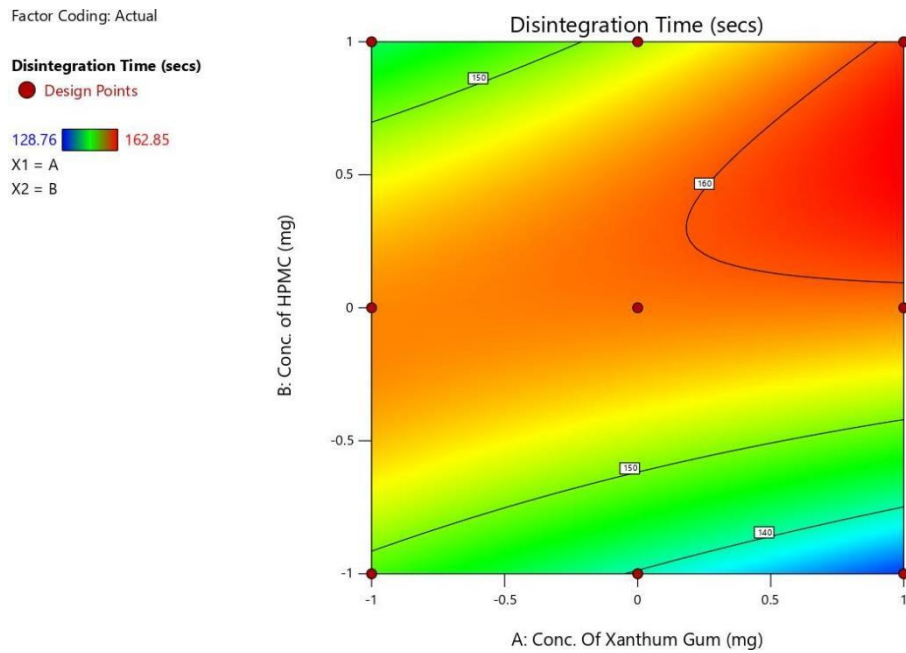


Figure-7 Contour Graph of Disintegration Time

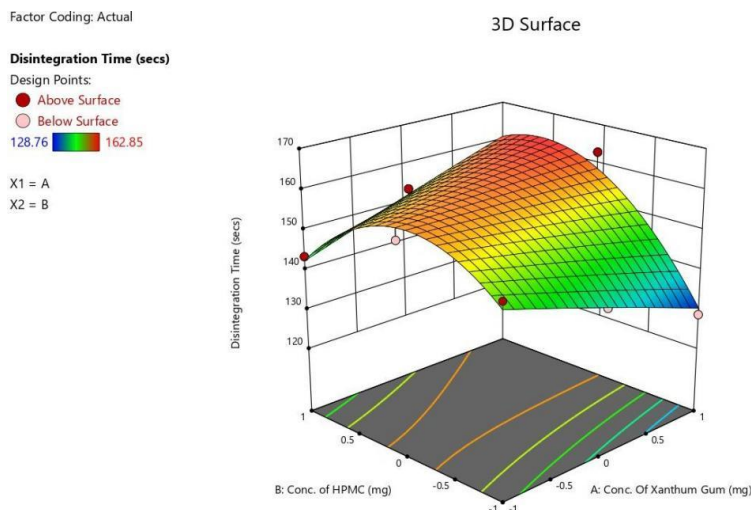


Figure- 8 3D Surface Graph of Disintegration Time

ANOVA (Analysis of Variance) for Drug Release

The p-value for the disintegration time response surface quadratic model is 0.0424 (less than 0.05), as shown in Table This

indicates the model's validity from a statistical standpoint.

If the cumulative P-value of the two factors is less than 0.05, then the two factors are significantly related.

Table- 7 ANOVA of Drug Release

Source	Sum Squares	ofdf	Sum of Square	F value	p-value	
Model	490.50	5	98.10	10.18	0.0424	Significant
A- Concentration of Xanthum Gum	240.67	1	240.67	24.98	0.0154	
B- Concentration of HPMC	35.04	1	35.04	3.64	0.1525	
AB	79.21	1	79.21	8.22	0.0642	
A ²	39.90	1	39.90	4.14	0.1347	
B ²	95.68	1	95.68	9.93	0.0512	
Residual	28.90	3	9.63			
Cor Total	519.40	8				

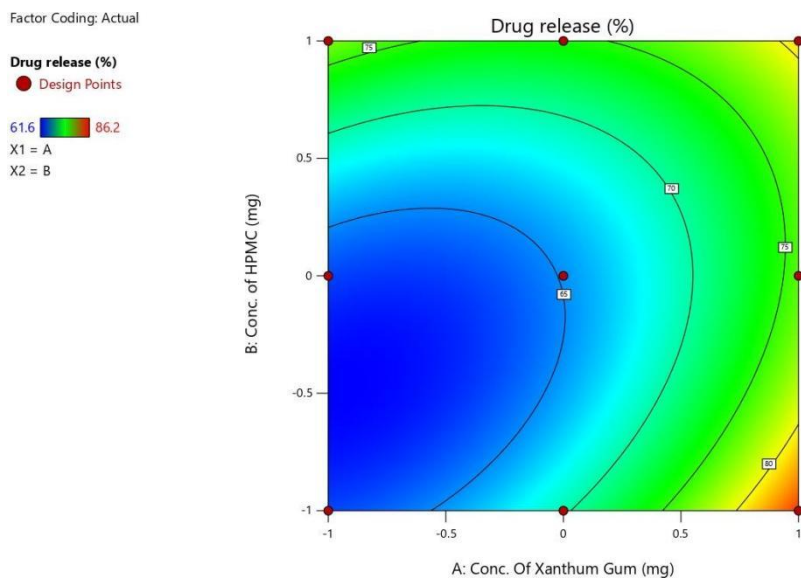


Figure- 9 Contour Graph of Drug Release

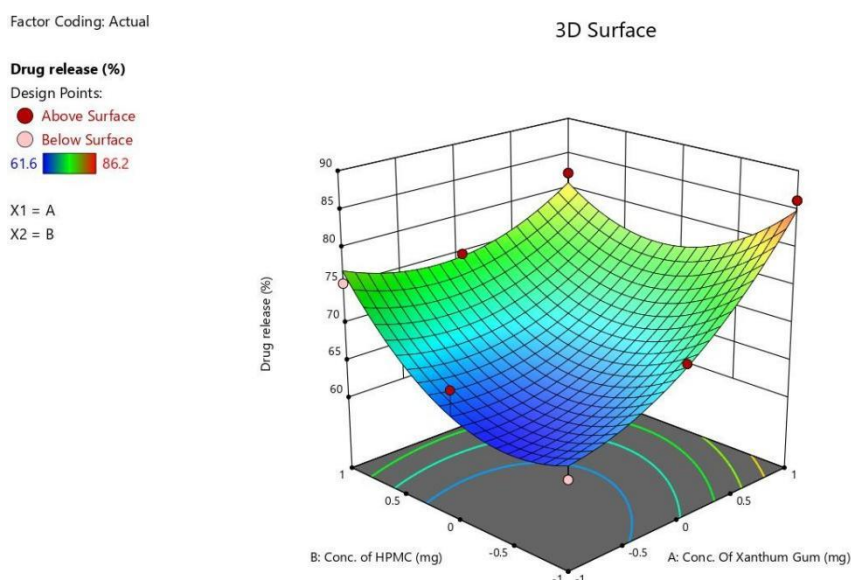


Figure- 10 3d Surface Graph of Drug Release

5.8 Stability Studies

A stability test was run to observe the effects of various environmental conditions on the pills. Tablets were taken out at 0, 3, and 6 months to test in vitro drug release, hardness, friability, and overall quality. Table 4.18 compiles the findings of the tests conducted on the stabilized B4 batch. Figure 4.14 depicts the in vitro drug release profile of the preserved sample, which was determined to be

consistent with the first sample. The similarity analysis yielded b2 values of 79.09 for the baseline and 3-month stability sample and 87.98 for the baseline and 6-month stability sample. If b2 is more than 50, there is a statistically significant relationship between the two release properties. The developed product was stable since no statistically significant changes in any of the attributes were found over the course of the experiment.

Table 8: Stability Study of Optimized Batch (B4) at $40 \pm 2^\circ\text{C}$ & $75 \pm 5\%$ RH

Parameters	0 MONTH	3 MONTHS	6 MONTHS
Drug content (%)	98.4	97.6	98.8
pH	3.69	3.29	3.49
Disintegration time (sec)	158.33	149.79	153.91

6. CONCLUSION

Effervescent tablets of CGZ were made with ingredients like citric acid, tartaric acid, and fumaric acid, as well as sodium carbonate, sodium bicarbonate, and potassium bicarbonate. During the experiment, both the acid and carbonate concentrations were altered. After all the research was done, sodium bicarbonate was chosen as the carbonate. Acid combinations were also tested in an effort to speed up the disintegration process. The breakdown was sped up by the combination of tartaric acid and fumaric acid. The research found that the quicker disintegration and faster drug release properties for CGZ may be achieved by the production of effervescent tablets using a mix of sodium bicarbonate, tartaric acid, and fumaric acid. The optimized batch B4 was more drugs were dispensing more quickly than in previous batches. It follows that effervescent pills are easier to create when acids and sodium bicarbonate are used together. To create an effervescent formulation with desirable qualities like rapid disintegration and medication release with little effort in the shortest amount of time, an experimental design may be useful. It was thus determined that the optimal formulation did not have an unpleasant aftertaste.

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