

Improving Patient Compliance in Hypertension Treatment: Development of Hydrochlorothiazide ODTs with Enhanced Solubility

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Abstract

The development of oral disintegrating tablets (ODTs) for antihypertensive drugs represents a promising approach to improve patient adherence, especially for those with difficulty swallowing traditional tablets. This study focuses on the formulation and optimization of hydrochlorothiazide (HCTZ) ODT using Box-Behnken design (BBD) for process optimization. The research employs excipients such as fenugreek seed powder, Cross-povidone and Locust bean gum as a super disintegrant, Banana powder as binders, corn starch as a glidant, magnesium stearate as a lubricant, microcrystalline cellulose (MCC) as a filler, and aspartame as a sweetener. Additionally, polyethylene glycol 4000 (PEG-4000) is used as a solubility enhancer through solid dispersion techniques. The BBD method investigates the effect of concentrations of fenugreek seeds mucilage, Locust bean gum and PEG-4000 on tablet properties such as disintegration time, dissolution rate, hardness, friability etc. The optimized formulation exhibits rapid disintegration (within 30 seconds), improved dissolution profile and enhanced bioavailability of hydrochlorothiazide due to the solubility-enhancing properties of PEG-4000. The results indicate that the combination of excipients and solid-phase dispersion methods can significantly improve the efficacy of ODT, providing a potential solution to improve therapeutic outcomes in the treatment of Hypertension.

Keywords: hypertension; oral disintegrating tablets (ODTs); hydrochlorothiazide; box-behnken design (BBD); super disintegrants; solid dispersion; solubility enhancement

Introduction

Hypertension is a significant contributor to illness and death globally. It ranks among the top causes of cardiovascular problems, such as ischemic heart disease, stroke, and heart failure, as well as chronic kidney disease and overall mortality rates. The number of individuals affected by hypertension is anticipated to rise as the population ages. About 10% to 15% of patients receiving treatment for hypertension experience resistant hypertension. Without confirmatory tests, resistant hypertension is characterized by blood pressure readings that remain above the target, despite the patient using three or more antihypertensive medications, usually including a diuretic, or needing four or more medications to manage blood pressure effectively [1-4].

Enhancing therapies for managing resistant hypertension is essential since various studies indicate that individuals with this condition face a heightened risk of adverse outcomes. In large retrospective studies involving 200,000 to 400,000 patients, those suffering from resistant hypertension were nearly twice as likely to experience cardiovascular events—such as heart attacks, ischemic heart disease, heart failure—as well as

strokes, chronic kidney disease (CKD) or end-stage renal disease, and mortality compared to their counterparts without resistant hypertension. Furthermore, resistant hypertension is linked to poorer outcomes in patients with certain comorbidities, including CKD, ischemic heart disease, obesity, diabetes, and obstructive sleep apnea. As a result, resistant hypertension imposes significant medical and financial challenges due to treatment expenses, disability, and early death. Thus, it is vital to explore more effective approaches for managing patients with resistant hypertension to enhance their overall prognosis [5-6].

Diuretics are a diverse group of medications primarily designed to promote increased urine production. They generally work by altering the movement of ions at various points in the nephron, thus encouraging the kidneys to eliminate water and electrolytes, mainly sodium and chloride. These drugs are classified based on their method of action and location of effect into categories such as carbonic anhydrase inhibitors, osmotic diuretics, thiazides, loop (or high-ceiling) diuretics, and potassium-sparing diuretics. Thiazide diuretics are the most frequently prescribed

antihypertensives and are sometimes used in combination with potassium-sparing diuretics. Loop diuretics, on the other hand, are reserved for specific situations [7].

Hydrochlorothiazide

Hydrochlorothiazide (HCTZ) is a thiazide diuretic that has been in clinical use for over fifty years. It functions by blocking the sodium-chloride cotransporter system located in the distal convoluted tubules of the kidneys, leading to its diuretic effect as water follows the increased potassium and sodium within the nephron. HCTZ is widely prescribed and is recognized as a primary treatment option for high blood pressure. Its popularity stems from its affordability, efficacy, and its ability to address additional conditions like heart failure and fluid

retention. Despite its common prescription, HCTZ can lead to several typical side effects, including imbalances in electrolytes, elevated blood sugar levels, increased lipid levels, and higher uric acid levels. Nevertheless, health authorities continue to recommend it as the main option for managing hypertension. HCTZ can also result in low potassium levels, low sodium levels, high calcium levels, and low magnesium levels, along with potential kidney issues in patients with compromised renal function [3]. Recommended dosages for HCTZ suggest an intake of 25 mg to 100 mg daily for edema, while 25 mg to 50 mg is advised for those dealing with high blood pressure [8]. Hydrochlorothiazide has the ability to activate calcium-dependent potassium channels, leading to hyperpolarization of vascular smooth muscle cells.

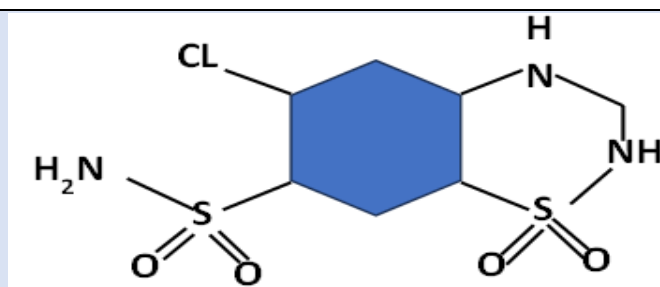


Figure 1: Hydrochlorothiazide

This process results in the closure of calcium channels, ultimately reducing calcium influx and preventing vasoconstriction. Additionally, hydrochlorothiazide inhibits carbonic anhydrase in blood vessels, which may alter the pH within smooth muscle cells and support the mechanism mentioned above. While these effects have been extensively studied in laboratory settings, their specific contribution to the antihypertensive action of thiazides remains uncertain. It is clear, however, that the primary effect targets the sodium-chloride cotransporter, as thiazides exhibit a diminished antihypertensive response in patients with kidney dysfunction. Furthermore, individuals with functional mutations in the SLC12A3 gene tend to have lower blood pressure compared to those without such mutations [9-10].

Oral Disintegrating tablets (ODTs)

These fast-dissolving tablets provide an effective solution for patients who struggle with taking medications orally, including children, individuals

receiving medical therapies, or those dealing with mental health issues. Created from a soft molded matrix that has low porosity and compressive strength, these tablets quickly dissolve in saliva, negating the need for water and offering an easy method of delivery for those facing oral intake challenges. They greatly improve the overall experience for patients who have trouble swallowing, ultimately enhancing treatment results while remaining easy to use [11-12].

Orodispersible tablets (ODTs) are solid medication forms that dissolve in the mouth within seconds, without needing to be chewed or swallowed. They offer a potential way to enhance patient adherence and make medication administration easier for elderly individuals, children, and those with upper gastrointestinal tract issues. A variety of ODTs are already on the market, including options like pain relievers, blood pressure medications, and antidepressants. Recently, there has been increased interest in creating ODTs with active ingredients such as naloxone, hydramine, metformin, and probiotics.



Figure 2: Oral disintegrating tablet

ODTs must meet high standards, particularly regarding their disintegration speed. The European Pharmacopoeia stipulates that ODTs should disintegrate in no more than 3 minutes. In contrast, the requirements set by the USP and FDA are more stringent, allowing a maximum disintegration time of just 30 seconds. Consequently, these tablets need to have adequate porosity or incorporate an efficient super disintegrant [13-14].

Box-Behnken Experimental Design

Response Surface Methodology (RSM) investigates the connection between control and response variables. It is crucial to optimize the test design to lower costs, necessitating careful thought regarding the mix and levels involved. Techniques like full factorial, Box-Behnken Design (BBD), and central composite designs play a vital role in this optimization. The Box-Behnken Design, utilizing Design Expert® software (version 7.0, Stat-Ease Inc.), allows for three levels and ensures reliability across 15 runs with five repetitions. A second-order polynomial model was created to represent the measured variables. This approach speeds up the development of pharmaceutical data and enhances research efficiency by delivering powerful, straightforward, and optimized research solutions [15-16].

Materials and Methods

Hydrochlorothiazide is given as gift sample by (Unichem Laboratories Ltd, District Kolhapur Maharashtra-416 236), microcrystalline cellulose (Maple Biotech Pvt Ltd., Pune, India), Superdisintegrants (G. M. Herbal medicine store in Indore). Talc and magnesium stearate were purchased from S. D. Fine Chem Ltd., Mumbai, India. All other solvents and reagents were purchased from the market.

Extraction

Locust Bean Gum: Carob pods are crushed to separate the seeds from the pulp. The steps involved in processing carob seeds include dehusking (using acid or thermo-mechanical methods), splitting, milling, sifting, clarification, and drying. This processing can be quite challenging due to the hard and tough outer layer of the seeds. To remove the outer shell of carob kernels, one can either treat them with dilute sulfuric acid or use thermo-mechanical techniques known as acid peeling and thermal peeling, respectively. In the acid peeling method, carob seeds are exposed to sulfuric acid at high temperatures to break down the seed coat. The remnants of the seed coat are then washed away from the endosperm through an effective washing and brushing process. The cleaned kernels are dried and cracked, causing the brittle germ to be crushed. These germ pieces are separated from the unbroken halves of the endosperm, referred to as splits.



Figure 3: Locust bean gum

The carob bean gum produced from these splits is light in color and has a higher viscosity. In the thermo-mechanical peeling method, carob kernels are roasted in a rotating furnace, causing the seed coat to pop off

from the inner parts. After mechanical processing, the endosperm halves or carob splits are collected from the roasted outer layer or husk and the crushed germ.

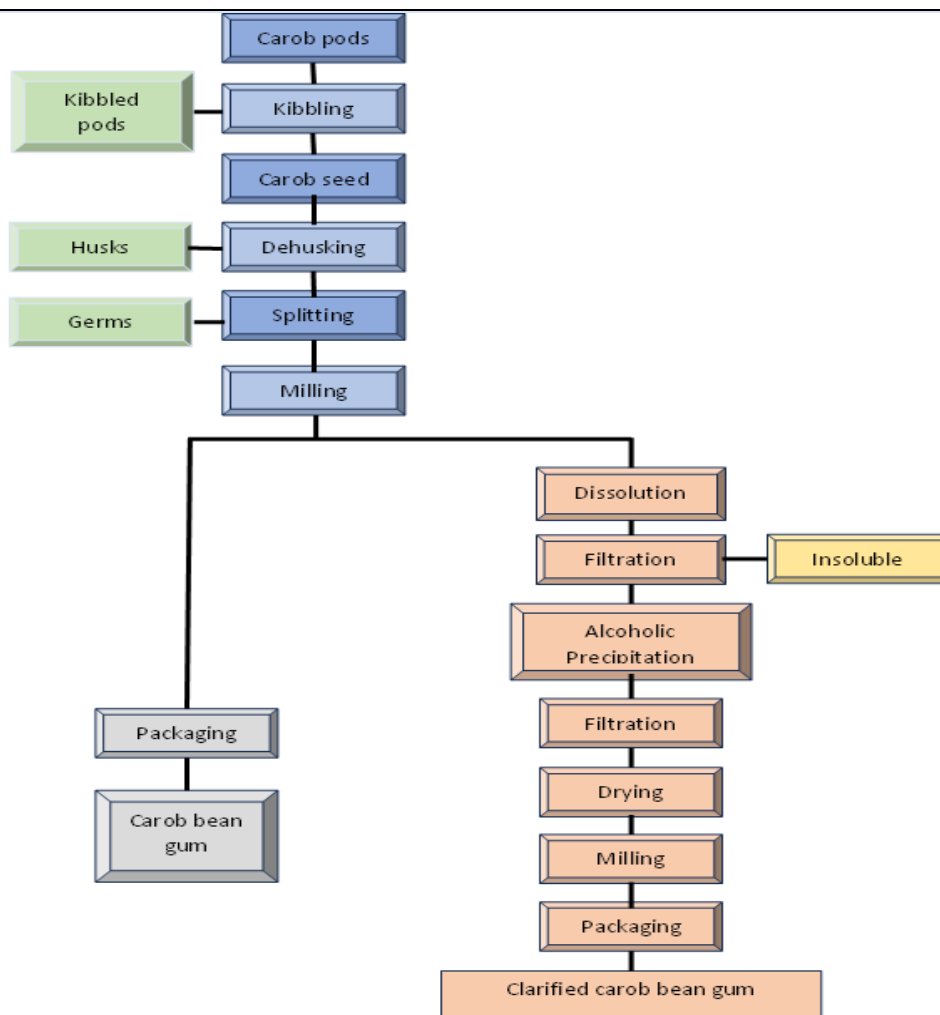


Figure 4: Flow diagram for manufacturing of locust bean gum

These isolated endosperm halves are then milled and screened to create a fine powdered form of native carob bean gum or locust bean gum (Figure 4). The resulting product tends to be darker due to the heating or roasting process. This thermo-mechanical

method produces no waste since it does not use sulfuric acid during processing. To clarify the native locust bean gum, it can be dispersed in water and dissolved through heating. This solution is then filtered to remove any insoluble materials, resulting in

a clear liquid. Locust bean gum is recovered by using isopropanol or ethanol for precipitation, followed by filtering, drying, and milling to create a fine powder of clarified or purified carob bean gum [17-19].

Fenugreek seed mucilage: FSM was extracted from fenugreek seeds following established procedures

found in the literature. Two hundred grams of fenugreek seeds were immersed in 1.5 liters of distilled water at room temperature for 12 hours. The mixture was then heated in a water bath until a slurry was formed. Once it cooled, the slurry was placed in the refrigerator overnight to allow undissolved particles to settle.



Figure 5: Fenugreek seed mucilage

The clear liquid on top was decanted and concentrated in a water bath at 60 °C to one-third of its original volume. After cooling to room temperature, this solution was mixed with three times its volume of acetone while stirring continuously. The resulting precipitate was washed several times with acetone and allowed to dry at room temperature for 24 hours. The isolated substance was then passed

through an 80-mesh sieve and stored in desiccators for future use [20].

Banana powder: The ripe banana fruits peeled off, sliced transversely (2mm thickness), incubated in 0.5% (w/v) sodium metabisulphite solution for 5 minutes and dried in oven at 60°C for 18 hrs the dried slices were grinded in mill and passed through sieve (mesh size 60) to obtain CBP [21].



Figure 6: Ripe banana and powder

Solid Dispersion Technique: A solid dispersion method called solvent evaporation is used to improve the solubility, rate of dissolution, and bioavailability of medications that are not very soluble in water, such as hydrochlorothiazide. By dispersing the medication within a hydrophilic polymer, it improves wettability, decreases particle size, and inhibits recrystallization. This approach is perfect for fast-release formulations since it is affordable, scalable, and appropriate for medications that are heat-sensitive. HCTZ was made into a solid dispersion by employing the fusion-solvent process. Accurate weights of PEG-4000 and

HCTZ were obtained. PEG-4000 was melted in a water bath, and HCTZ was dissolved in methanol. The molten PEG-4000 was vigorously stirred while the medication solution was gradually added. Prior to being granulated through a mesh no. 20, the residue was dried in a desiccator for 24 hours after the solvent was evaporated over a water bath.

Box-Behnken Experimental Design: Using Design Expert® software (version 7.0, Stat-Ease Inc.), the Box-Behnken Experimental Design was utilized to create hydrochlorothiazide tablets that were optimized for quick drug release. The study examined

the effects of three factors at three distinct levels, ranging from low to high: locust bean gum, fenugreek seed mucilage, and Crospovidone. This comprehensive approach allowed for the identification of the optimal combination of ingredients to achieve fast-dissolving tablets with optimal efficacy. 15 experimental runs were carried out using the three-factor and three-level design concepts, with three central points to evaluate

experimental error and design accuracy. As shown in Table 1, mean tablet hardness, in vitro dissolving time, and in vitro disintegration time were the main responses or dependent variables evaluated.

Selected Independent variables and Dependent variables

The selected independent variables are displayed in Table 1.

Table 1: Independent variables with levels

Factor	Name	Unit	Minimum	Maximum
A	Locust bean gum	%	0	10
B	Fenugreek seed mucilage	%	0	4
C	Crospovidone	%	0	5

The selected Dependent variables are displayed in Table 2.

Table 2: Dependent variables

Response	Variables	Unit
1.	Hardness	kg/cm ²
2.	Disintegration time	Seconds
3.	In vitro drug release	%

Table 3: Composition of experimental batches of tablets

Std	Runs	Independent Variables			Dependent Variables		
		Locust bean gum %	Fenugreek seed mucilage %	Crospovidone %	Hardness (Kg/cm ²)	Disintegration time (Second)	In vitro drug release %
10	1	5	4	0	2.76	15.7	96.21
4	2	10	4	2.5	2.57	13.2	94.2
15	3	5	2	2.5	2.43	20.5	95.64
12	4	5	4	5	2.51	14.6	94.74
6	5	10	2	0	2.89	16.5	96.34
9	6	5	0	0	2.67	26.3	93.78
8	7	10	2	5	2.41	12.2	98.67
1	8	0	0	2.5	2.56	24.3	94.89
14	9	5	2	2.5	2.46	18.5	97.45
13	10	5	2	2.5	2.49	19.2	95.23
5	11	0	2	0	2.6	31.2	93.98
11	12	5	0	5	2.56	14.5	98.56
2	13	10	0	2.5	2.72	12.3	98.78
3	14	0	4	2.5	2.59	15.6	97.45
7	15	0	2	5	2.5	15.3	97.34

Formulation of Oral Disintegrating tablets by using Direct Compression Method

Preparation of Powder Blend: The solid dispersion of Hydrochlorothiazide (HCTZ) and PEG-4000 is thoroughly mixed with microcrystalline cellulose (MCC), mannitol, corn starch, aspartame, and banana powder until a uniform mixture is obtained.

At this stage, the lubricant is not added to prevent interference with the blending process.

Addition of Polymers and Super disintegrants: The locust bean gum and fenugreek seed mucilage are directly incorporated into the powder mixture before further mixing to ensure even distribution. Crospovidone, a super disintegrant, is then added, and the mixture is blended until a homogeneous

Quality Control and Evaluation: Quality control tests are crucial for ensuring that formulated tablets adhere to pharmaceutical standards. The hardness test gauges the mechanical strength, ensuring that tablets can endure handling without breaking. The

friability test checks for brittleness and overall durability, assessing resistance to wear and tear. The disintegration test measures how quickly a tablet dissolves in oral conditions, allowing for swift drug release and absorption. Uniformity tests ensure consistent weight and size across production batches, avoiding variations that might affect effectiveness. The assay test confirms the exact drug content in each tablet, ensuring the correct dosage is delivered for effective treatment. Other important tests include dissolution studies, which evaluate the drug's release characteristics in simulated biological environments, and moisture analysis, which examines stability and shelf life. These thorough assessments are essential for maintaining quality, safety, and effectiveness, guaranteeing that each tablet functions as designed. Compliance with regulatory standards ensures that patients receive dependable and effective medication with each dose [22-24].

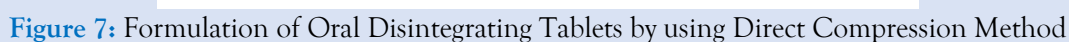


Table 4: Formulation Batches

Formulation Code	S.D. of HCTZ (mg)	Locust Bean Gum (mg)	Fenugreek Seed Mucilage (mg)	Crospovidone (mg)	Banana Powder (mg)	Corn Starch (mg)	Mg Stearate (mg)	Aspartame (mg)	MCC (mg)
ODT 1	50	5	4	0	4	2	1	2	32
ODT 2	50	10	4	2.5	4	2	1	2	24.5
ODT 3	50	5	2	2.5	4	2	1	2	22.5
ODT 4	50	5	4	5	4	2	1	2	27
ODT 5	50	10	2	0	4	2	1	2	29
ODT 6	50	5	0	0	4	2	1	2	35
ODT 7	50	10	2	5	4	2	1	2	24
ODT 8	50	0	0	2.5	4	2	1	2	28.5
ODT 9	50	5	2	2.5	4	2	1	2	21.5
ODT 10	50	5	2	2.5	4	2	1	2	32.5
ODT 11	50	0	2	0	4	2	1	2	39
ODT 12	50	5	0	5	4	2	1	2	29
ODT 13	50	10	0	2.5	4	2	1	2	28.5
ODT 14	50	0	4	2.5	4	2	1	2	34.5
ODT 15	50	0	2	5	4	2	1	2	34

Precompression Studies

Angle of repose: The maximum angle at which a buildup of loose powder remains stable without collapsing is known as the angle of repose. It acts as a gauge of the cohesiveness and flow properties of the powder. Better flow is indicated by lower angles, and greater angles indicate worse flow. A mound of powder is progressively built up on a level surface until it starts to slump in order to be measured.

$$\text{Angle of repose (tan}\theta\text{)} = \frac{\text{Height of pile (h)}}{\text{Radius of the base pile (r)}}$$

Bulk Density: The mass of a powder divided by its whole volume, which includes the empty spaces between particles, is known as its bulk density. It is commonly given in quantities such as g/cm³ or kg/L and indicates how well the powder packs together. Using tools like a graduated cylinder, a known volume of the powder—including its vacant spaces—must be weighed in order to make a determination.

$$\text{Bulk density} = \frac{\text{Mass of bulk powder}}{\text{Volume of bulk powder}}$$

Tapped Density: The maximum bulk density attained when a powder is tapped or vibrated to remove interparticle gaps is known as "tapped density." The powder is tapped repeatedly in a container until no more volume loss takes place, indicating the powder's packing capabilities under compaction.

$$\text{Tapped density} = \frac{\text{Mass of bulk powder}}{\text{Final volume of tapped powder}}$$

Hausner's Ratio: Hausner's ratio is the ratio of tapped density to bulk density, calculated using the formula:

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

It offers information about the packing efficiency and flow behaviour of the powder. Good flowability is indicated by a ratio near 1, and poor flowability is indicated by values greater than 1.

Carr's Index: Carr's index, or compressibility index, quantifies the powder's compressibility and is calculated as follows:

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100\%$$

It shows the extent of volume reduction brought about by compression or tapping. Superior flowability is indicated by lower Carr's index values, whereas reduced flow or enhanced cohesion are implied by higher values.

Partition Coefficient: A partition coefficient study was carried out using 10 mg of hydrochlorothiazide dissolved in 50 ml of n-octanol, which had previously been saturated with water. The solution was mixed thoroughly and shaken vigorously before adding 50 ml of distilled water that had been saturated with n-octanol. This mixture was then subjected to mechanical shaking for 24 hours to enable the drug to distribute between the two immiscible phases. Once equilibrium was achieved, the phases were carefully separated, and the concentrations of hydrochlorothiazide in each phase were measured using UV absorbance readings. The partition coefficient ($P_{o/w}$) was calculated using the formula:

$$\text{Partition Coefficient}_{o/w} = \frac{\text{Concentration}_{\text{oil}}}{\text{Concentration}_{\text{water}}}$$

Hydrochlorothiazide identification studies:

Hydrochlorothiazide 100 mg was accurately weighed and dissolved in 100 ml distilled water and subsequent dilution was made to get the required concentrations (1000µg/ml). The wave length of maximum absorbance (λ_{max}) of this clear solution was determined from 200- 400nm and water was used as blank.

Preparation of stock solution: Hydrochlorothiazide 100 mg was dissolved in water 100 ml (1000µg/ml) Stock solution I. From this solution 10 ml was pipetted and diluted with water up to 100ml (100µg/ml) Stock solution II was prepared.

Preparation of sample solution: From Stock solution II 1 ml was pipetted and diluted with water up to 10ml (10µg/ml). From Stock solution II was carried out taking 0.5, 1.0, 1.5, 2.0, 2.5, 3.0 ml and made up to 10 ml to obtain the concentration of 5, 10, 15, 20, 25 and 30 µg/ml respectively. The absorbance was measured at 273nm against the respective blank solution using UV visible spectrophotometer 1800. The standard curves were plotted by putting the known concentration on X- axis and the obtained absorbance on Y-axis.

Melting point of Hydrochlorothiazide: Melting point of Hydrochlorothiazide was determined using electric melting point apparatus. One end sealed capillary tube was filled with drug sample and put in the designated slot of the apparatus. Apparatus was switched on and the tube was observed from the magnifying glass of the apparatus. The temperature at which the sample began to melt was noted from the thermometer as the melting point of the sample and

average of three consecutive readings was stated as the final reading.

Post-compression Studies

Organoleptic characters: Each batch of tablets is evaluated for sensory properties, including appearance, colour, odor and shape, through direct observation and analysis.

Thickness and diameter: Measure tablet thickness and diameter length using vernier caliper. Five tablets were selected from each batch and their measurements averaged to give a representative value expressed in millimeters.

Hardness: The hardness of the tablets was assessed with a Monsanto hardness tester to evaluate their mechanical strength and capacity to endure physical stress. Three tablets from each batch were randomly chosen, and their hardness was gauged by applying force until the tablet broke. The average hardness value was recorded to confirm consistency within the batch. These measurements were represented in kilograms per square centimeter (kg/cm²) to provide a standardized metric. Testing hardness is a vital aspect of quality control in pharmaceuticals since it helps identify the tablet's resistance to chipping, breaking, and crumbling during handling, packaging, transportation, and storage. While ensuring sufficient mechanical strength, the tablets must also disintegrate correctly in the gastrointestinal tract to facilitate effective drug release. A tablet that is excessively hard may not break down as intended, resulting in delayed drug absorption, while one that is too soft may fracture too easily.

By upholding an optimal range of hardness, this test ensures that the tablets satisfy pharmaceutical standards, offering both physical stability and effective drug delivery to patients. This quality control practice is essential for guaranteeing the safety, efficacy, and consistency of the final product.

Friability: Friability testing for the tablets was performed with a Roche friability tester, adhering to the Indian Pharmacopoeia (IP) standards to evaluate mechanical strength. To begin, the initial weight (W_i) of 20 tablets was recorded. The friability tester was programmed to run at a speed of 25 revolutions per minute (rpm) for 4 minutes, applying controlled mechanical pressure to the tablets. Once the testing was finished, the tablets were gathered, dusted off, and weighed again to find the final weight (W_f). The percentage of friability (%F) was calculated using the following formula:

$$F = \frac{W_i - W_f}{W_i} \times 100$$

A friability value below 1% is considered acceptable, ensuring that the tablets possess adequate mechanical strength to withstand handling, transportation, and packaging without significant weight loss. This test plays a crucial role in evaluating tablet durability while maintaining their ability to disintegrate efficiently, ensuring optimal drug release, product stability, and patient compliance in pharmaceutical formulations.

Weight variation: Twenty tablets were selected from each batch before weighing, individual weight was measured and averaged. The weight was measured as per the specifications mentioned in the Indian Pharmacopoeia (I.P.). According to the I.P standard the average difference in weight should not exceed 5% and two tablets and no tablet should exceed two times the percentage.

$$\% \text{ Deviation} = \frac{\text{Wt. of each tablet} - \text{average Wt of tablet}}{\text{average Wt of tablet}} \times 100$$

In-vitro disintegration time: Tablet disintegration time was evaluated using a USP disintegration tester with water kept at 37 ± 2 °C, following established protocols. Six tablets from each batch were submerged in one liter of distilled water, and the time taken for complete disintegration was noted. Ideally, all tablets should dissolve within 3 minutes to meet the required standard. Should more than one tablet fail to achieve this standard, the test would be conducted again with 12 additional tablets to verify the results. According to regulatory guidelines, a maximum of 2 out of 18 tablets is permitted to not meet the specified disintegration time. This test ensures that tablets break down appropriately in the gastrointestinal tract, leading to quick drug release and absorption. Effective disintegration improves bioavailability, ensuring that the treatment is efficient. This assessment is vital for quality control, confirming that the tablets adhere to pharmaceutical standards for dissolution and overall performance, thereby enhancing patient safety and treatment effectiveness.

In-vitro dissolution studies: The release rate of Hydrochlorothiazide tablets was evaluated using a USP Type II dissolution apparatus in paddle configuration. Place one tablet in 6 dissolution vials, each containing 900 ml of separation medium, pre-equilibrated at 37 ± 0.5 °C and mixed at 50 rpm. At the appointed time, remove 2 ml aliquots of the dissolution medium and replace them with fresh dissolution medium. The sample was then filtered, diluted, and analyzed spectrophotometrically at 273

nm to determine the concentration of the drug relative to the corresponding concentration. This process is done on all batches. The average percentage of Hydrochlorothiazide released at different time points was determined from the sample image and plotted against time.

Calculation of % drug release involves the following steps:

$$\text{Amount of drug release} = \frac{\text{Concentration} \times \text{dilution factor} \times \text{volume of dissolution medium}}{1000}$$

Stability Studies: In this research, all formulations underwent a one-month stability assessment in accordance with the acceler stability testing criteria established by the International Council for Harmonization (ICH). The samples were meticulously wrapped in aluminum foil to shield them from moisture and light, and were stored in sealed glass containers to avert any external contamination. The tablets were subjected to three distinct temperature scenarios, mimicking various environmental factors that could influence their stability. Throughout 10, 20, and 30 days, tablets were methodically taken from storage and examined for physical attributes, disintegration properties, and drug concentration. Evaluations of the physical aspects encompassed alterations in appearance, color, and texture, while disintegration characteristics were scrutinized to guarantee tablet integrity and

Determined concentration of drug released by using formula:

$$Y = mx + c$$

Y is absorbance, m is slope, C is intercept, X is concentration (µg/ml)

consistency. Drug concentration assessments ensured that the active pharmaceutical ingredient (API) remained within acceptable thresholds during the duration of the study.

This stability evaluation is vital for forecasting the shelf life and long-term effectiveness of the formulations, confirming that the tablets retain their potency, safety, and efficiency across varying storage scenarios. Adhering to ICH guidelines ensures that the pharmaceutical product complies with global quality standards, delivering dependable and consistent therapeutic results for patients [25-27].

Result and Discussion

Organoleptic properties: Organoleptic properties of the drug sample were found to be as given in table below.

Table 5: Organoleptic properties of Hydrochlorothiazide

S. No.	Organoleptic Characteristics	Result
1.	Color	White to off-white crystalline compound
2.	Nature	Crystalline powder
3.	Odour	Odorless
4.	Taste	Bitter

Melting point of Hydrochlorothiazide: The final reading was obtained by averaging the results of three independent experiments, resulting in a temperature of 268–270°C.

Partition Coefficients: The partition coefficients of Hydrochlorothiazide found to be -0.07.

pH determination of Hydrochlorothiazide: The pH range of Hydrochlorothiazide is adjusted to 5.5–7.0 during preparation to ensure that it is stable and effective in treating hypertension.

Table 6: Flow properties of powder blend

Formulati on batch	Angle of Repose (θ)	Bulk Density (g/cm³)	Tapped Density (g/cm³)	Hausner's Ratio	Carr's Ratio (%)
ODT 1	29.81 ± 1.29	0.457 ± 0.0131	0.508 ± 0.004	1.2548 ± 0.0217	25.79 ± 1.0134
ODT2	27.96 ± 1.69	0.505 ± 0.0119	0.578 ± 0.018	1.3148 ± 0.0233	21.87 ± 1.1245
ODT3	24.96 ± 1.66	0.464 ± 0.0116	0.490 ± 0.023	1.2768 ± 0.0127	22.32 ± 1.0043
ODT4	28.61 ± 1.17	0.498 ± 0.0114	0.547 ± 0.024	1.2878 ± 0.0323	25.27 ± 1.0021
ODT5	29.61 ± 1.27	0.478 ± 0.0126	0.506 ± 0.019	1.3218 ±0.02317	22.27 ± 1.1425

ODT6	25.40 ± 1.02	0.453 ± 0.0116	0.498 ± 0.026	1.2341 ± 0.0212	27.83 ± 1.2571
ODT7	26.85 ± 1.78	0.449 ± 0.0132	0.501 ± 0.032	1.3412 ± 0.0301	26.89 ± 1.1121
ODT 8	29.17 ± 1.54	0.510 ± 0.0134	0.574 ± 0.012	1.3032 ± 0.0123	27.14 ± 1.2372
ODT 9	27.64 ± 0.66	0.468 ± 0.0129	0.528 ± 0.028	1.2431 ± 0.0732	26.68 ± 0.8414
ODT 10	28.95 ± 0.99	0.479 ± 0.0131	0.521 ± 0.023	1.2842 ± 0.0345	27.12 ± 1.1571
ODT 11	26.45 ± 0.92	0.480 ± 0.0152	0.536 ± 0.055	1.2989 ± 0.0312	27.85 ± 1.1571
ODT 12	29.05 ± 0.45	0.557 ± 0.0194	0.593 ± 0.012	1.2965 ± 0.02987	28.11 ± 1.1522
ODT 13	27.22 ± 0.35	0.447 ± 0.0192	0.483 ± 0.011	1.2714 ± 0.0312	27.71 ± 1.2578
ODT 14	28.35 ± 0.15	0.489 ± 0.0192	0.514 ± 0.015	1.3192 ± 0.0297	27.29 ± 1.2278
ODT 15	30.32 ± 0.41	0.560 ± 0.0219	0.596 ± 0.025	1.2954 ± 0.0231	26.34 ± 1.1578

Post-compression Studies

Organoleptic characters

Table 7: Organoleptic properties of Hydrochlorothiazide Tablets

S. No.	Organoleptic Characteristics	Result
1.	Color	White to off-white
2.	Shape	Circular
3.	Odour	Odorless
4.	Taste	Appreciably sweet

Identification of Hydrochlorothiazide by UV spectrophotometry

Derivation of drug spectrum: The stock solution of Hydrochlorothiazide, prepared with NaOH** and a concentration of 10 µg/ml displayed a peak absorption (**λ_{max} of **273 nm. At this specific, the solution absorbance was recorded at 0.3455. This absorbance reading was utilized for additional analysis and to determine the drug's concentration in the solution. Understanding the absorption properties is essential for quantitative analysis in various analytical methodologies, allowing for precise evaluation of Hydrochlorothiazide levels in formulations and contributing to the creation of trustworthy pharmaceutical tests.

Preparation of calibration curve of Hydrochlorothiazide in NaOH:

The calibration curve for Hydrochlorothiazide dissolved in 0.1M NaOH was plotted using a UV spectrophotometer, with measurements taken at a wavelength of 273 nm. The curve was constructed from six dilutions of the stock solution, each prepared at a concentration of 5 µg/ml. This calibration method is essential for quantitative analysis, providing a relationship between absorbance and concentration of Hydrochlorothiazide. By measuring absorbance at the specified wavelength, this curve can be used to determine the concentration of Hydrochlorothiazide in unknown samples. The results of the calibration curve are summarized in the accompanying table.

Table 8: Calibration curve data of Hydrochlorothiazide in NaOH

S. No.	Concentration (µg/ml)	Absorbance at 273 nm
1.	5	0.1765
2.	10	0.3455
3.	15	0.5223
4.	20	0.6905
5.	25	0.8464
6.	30	0.9967

Calibration curve of Hydrochlorothiazide in 0.1M NaOH at λ_{max} 273nm.

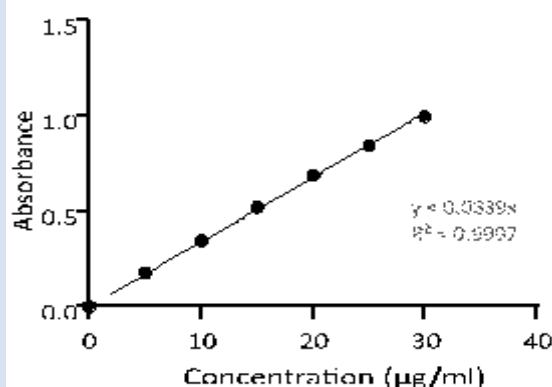


Figure 8: Calibration curve of Hydrochlorothiazide

Table 9: Post-compression parameters of tablets

Formulation Batch	Thickness (mm)	Hardness (Kg/cm ²)	Friability (%)	Disintegration time (Sec)	Weight (mg)
ODT 1	1.85±0.07	2.76	0.53±0.12	15.7	99.23±0.12
ODT2	1.88±0.04	2.57	0.52±0.13	13.2	101.25±0.13
ODT3	1.89±0.02	2.43	0.57±0.12	20.5	98.67±0.12
ODT4	1.86±0.04	2.51	0.53±0.04	14.6	97.54±0.04
ODT5	1.87±0.04	2.89	0.52±0.08	16.5	99.67±0.08
ODT6	1.85±0.08	2.67	0.55±0.50	26.3	97.34±0.50
ODT7	1.87±0.09	2.41	0.51±0.09	12.2	100.67±0.09
ODT 8	1.89±0.01	2.56	0.57±0.07	24.3	98.24±0.07
ODT 9	1.86±0.05	2.46	0.54±0.01	18.5	99.80±0.01
ODT 10	1.87±0.04	2.49	0.51±0.13	19.2	102.65±0.13
ODT 11	1.85±0.09	2.6	0.56±0.50	31.2	99.67±0.50
ODT 12	1.86±0.06	2.56	0.57±0.50	14.5	101.24±0.07
ODT 13	1.89±0.02	2.72	0.52±0.11	12.3	99.80±0.01
ODT 14	1.88±0.04	2.59	0.59±0.08	15.6	104.65±0.13
ODT 15	1.87±0.04	2.5	0.51±0.04	15.3	97.67±0.50

In-vitro dissolution studies

Table 10: Cumulative drug release of Hydrochlorothiazide Tablets formulations (F1-F15)

Formulation code	Cumulative Drug Release (%)				
	Time (Minutes)				
	1	3	5	10	15
ODT 1	20.67±0.23	32.98±0.53	53.47±0.62	74.39±0.57	87.41±1.32
ODT2	21.28±0.40	35.76±0.62	57.22±0.32	78.54±1.12	84.87±0.47
ODT3	22.43±0.43	33.12±0.67	56.63±1.00	72.65±0.62	86.85±0.63
ODT4	19.34±0.54	31.72±0.62	59.65±0.09	75.32±0.43	89.41±1.32
ODT5	26.72±1.23	39.98±0.76	52.50±0.68	78.39±0.57	94.92±0.44
ODT6	23.63±1.12	34.80±0.74	53.47±0.62	75.65±0.71	88.78±0.81
ODT7	22.43±0.43	36.98±0.53	59.12±0.81	79.43±0.95	96.90±1.00
ODT 8	21.67±0.23	33.12±0.67	52.54±0.65	76.78±0.78	91.78±1.15
ODT 9	25.19±0.34	31.78±1.45	59.63±1.00	78.20±1.32	89.20±0.78
ODT 10	26.46±0.87	36.87±1.15	51.40±0.37	73.65±0.62	90.87±0.47
ODT 11	23.23±0.76	35.98±0.43	54.80±1.32	75.54±1.12	96.85±0.63
ODT 12	21.28±0.73	33.32±0.54	58.22±0.32	73.29±0.65	87.65±1.34
ODT 13	25.13±1.00	32.76±0.62	53.98±0.91	72.50±0.47	84.43±1.27
ODT 14	23.28±0.40	34.32±0.67	52.65±1.00	72.22±0.37	94.67±0.78
ODT 15	21.86±0.51	37.19±1.32	51.32±0.78	74.63±0.23	92.20±0.28

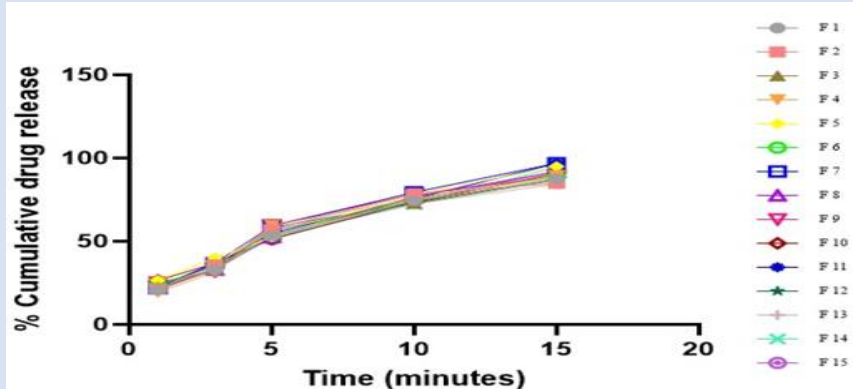


Figure 9: Cumulative drug release of Hydrochlorothiazide Tablets (ODT 1-ODT 15)
Response data for all 15 batches by using Box-Behnken Experimental Design (F1-F15)

Response 1: hardness

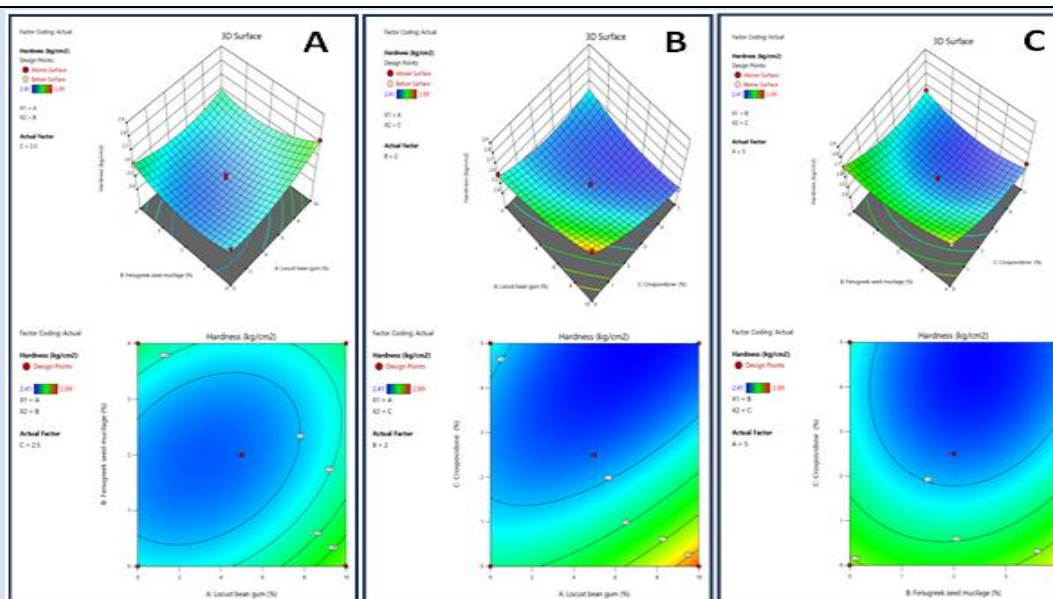


Figure 10: The 2D contour plot and 3D surface graph show that how Hardness is affected by factors X_1 (Hardness), X_2 , (Disintegrating time), X_3 (In vitro release)

ANOVA for Quadratic model Response 1: Hardness

Table 11: R1(Hardness)

Source	Sum of Squares	df	Mean Square	F-value	p-value	df
Model	0.2313	9	0.0257	11.17	0.0081	significant
A-Locust bean gum	0.0145	1	0.0145	6.28	0.0541	
B-Fenugreek seed mucilage	0.0008	1	0.0008	0.3478	0.5810	
C-Crospovidone	0.1104	1	0.1104	48.02	0.0010	
AB	0.0081	1	0.0081	3.52	0.1194	
AC	0.0361	1	0.0361	15.70	0.0107	
BC	0.0049	1	0.0049	2.13	0.2042	
A^2	0.0144	1	0.0144	6.27	0.0542	
B^2	0.0283	1	0.0283	12.29	0.0172	
C^2	0.0222	1	0.0222	9.64	0.0267	
Residual	0.0115	5	0.0023			
Lack of Fit	0.0097	3	0.0032	3.59	0.2253	not significant
Pure Error	0.0018	2	0.0009			
Cor Total	0.2428	14				

Response 2: Disintegrating time

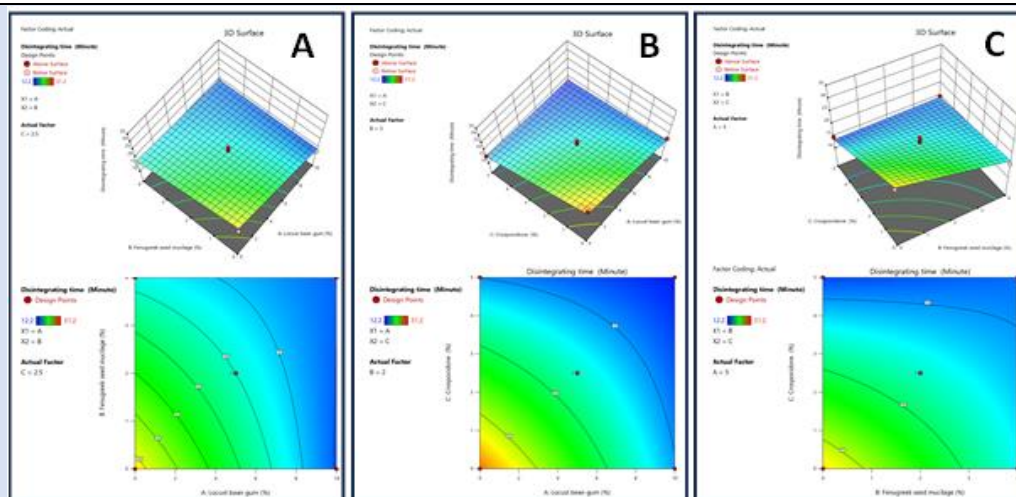


Figure 11: The 2D contour plot and 3D surface graph show that how Disintegrating time is affected by factors X_1 , X_2 , X_3

ANOVA for 2FI model Response 2: Disintegrating time

Table 12: R2 (disintegrating time)

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	393.72	6	65.62	17.15	0.0004	significant
A-Locust bean gum	129.60	1	129.60	33.87	0.0004	
B-Fenugreek seed mucilage	41.86	1	41.86	10.94	0.0107	
C-Croscopolldone	136.95	1	136.95	35.79	0.0003	
AB	23.04	1	23.04	6.02	0.0397	
AC	33.64	1	33.64	8.79	0.0180	
BC	28.62	1	28.62	7.48	0.0256	
Residual	30.61	8	3.83			
Lack of Fit	28.55	6	4.76	4.62	0.1886	not significant
Pure Error	2.06	2	1.03			
Cor Total						

Response 3: In vitro drug release

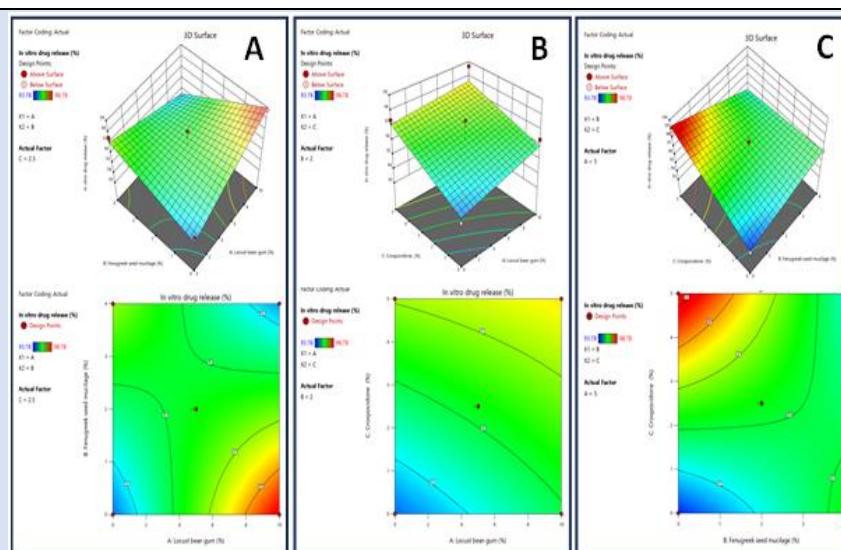


Figure 12: The 2D contour plot and 3D surface graph shows that how In vitro drug release is affected by factors X_1 , X_2 , X_3

ANOVA for 2FI model Response 3: In vitro drug release

Table 13: R3 (In vitro drug release)

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	36.70	6	6.12	8.22	0.0045	significant
A-Locust bean gum	2.34	1	2.34	3.15	0.1139	
B-Fenugreek seed mucilage	1.45	1	1.45	1.95	0.1999	
C-Crospovidone	10.13	1	10.13	13.60	0.0061	
AB	12.74	1	12.74	17.12	0.0033	
AC	0.2652	1	0.2652	0.3563	0.5671	
BC	9.77	1	9.77	13.12	0.0068	
Residual	5.96	8	0.7445			
Lack of Fit	3.16	6	0.5275	0.3780	0.8499	not significant
Pure Error	2.79	2	1.40			
Cor Total	42.65	14				

Table 14: formulation of optimized batch from BBD (ODT 16)

S. No.	Ingredients	Quantities (mg)
1	Solid dispersion of HCTZ and PEG-4000 (mg)	50
2	Locust bean gum (mg)	7.9
3	Fenugreek seed mucilage (mg)	1.6
4	Crospovidone (mg)	2.85
5	Banana powder (mg)	4
6	Corn Starch (mg)	2
7	Mg Stearates (mg)	1
8	Aspartame (mg)	2
9	MCC (mg)	28.35

Table 15: pre compressional data of optimized batch (ODT 16)

S. No.	Pre-compressional evaluation parameter	Results
1	Bulk density	0.501 ± 0.0131
2	Tapped density	0.523 ± 0.0119
3	Hausner's ratio	1.274 ± 0.0217
4	Carss index	23.79 ± 1.0134
5	Angle of repose	26.96 ± 1.069

Table 16: post compressional data of optimized batch (ODT 16)

S. No.	Post-compression evaluation parameter	Results
1	Weight (mg)	102
2	Thickness (mm)	1.86
3	Hardness (kg/cm ²)	2.76
4	Disintegration time (second)	16
5	Friability (%)	0.52

Table 17: In vitro drug release for optimized batch (ODT 16)

Formulation Batch	Cumulative Drug Release (%)				
	Time (Minutes)				
	1	3	5	10	15
ODT 16	21.67±0.23	34.98±0.53	53.47±0.62	74.39±0.57	97.41±1.32

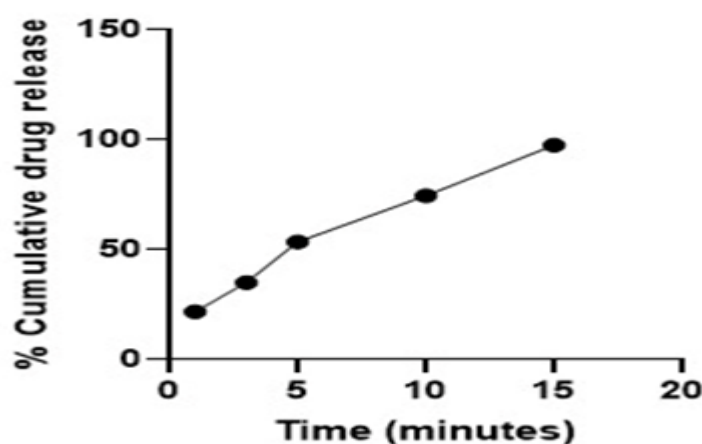


Figure 10: Percent drug release of batch ODT 16 (optimised batch)

The obtained Percent drug release of batch ODT 16 (optimised batch) has 95.981 % of drug release in 15 minutes, and the optimized batch was evaluated for all the pre and post compressional parameters required for quality control of dosage form and the obtained results was found between satisfied range.

Stability Studies: The stability studies of fast-dissolving tablets of Hydrochlorothiazide at a 25mg dose indicated that the best formulation remained stable even after storing at $40\pm 20^{\circ}\text{C}$ / $75\pm 5\%$ RH for 3 months. The tablets were visually examined for any physical changes, evaluated for drug content, and in vitro drug release at monthly intervals. The results showed that the formulation maintained its drug release profile within the specified limits, demonstrating stability over the study period.

Conclusion

In conclusion, this study successfully employed a Box-Behnken design and direct compression to develop fast dissolving Hydrochlorothiazide tablets. Natural (Locust bean gum and Fenugreek seed mucilage) and synthetic (Croscopolvidone) superdisintegrants were evaluated for optimal disintegration and drug release. Pre-formulation studies ensured compatibility. This approach presents a promising patient-centric formulation with improved compliance, especially for Hypertension with swallowing difficulties. To confirm clinical efficacy, further research is needed to assess large-scale production and conduct in-vivo studies. Acknowledgement: I would like to show my sincere gratitude towards IPS Academy College of Pharmacy for providing the necessary requirements and facilities throughout the study. Lastly, I would like to express my appreciation to all my colleagues and peers for their helpful discussions and moral support, which contributed to the success of this work.

Conflict of interest

The authors declare no conflict of interest.

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