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FORMULATION AND EVALUATION OF EZETIMIBE LOADED CHEWABLE TABLETS IN THE TREATMENT OF HYPERLIPIDEMIA

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ABSTRACT

The study aimed to develop and evaluate chewable tablets of Ezetimibe to improve its solubility and patient compliance. A β-Cyclodextrin (β-CD) inclusion complex was prepared in three different molar ratios to enhance the drug's aqueous solubility, with the 1:1 ratio showing the highest solubility improvement. This was confirmed by DSC and pXRD analyses, which indicated reduced crystallinity, while FTIR confirmed no significant drug–excipient interactions. Tablets were formulated using direct compression, incorporating the optimized inclusion complex. A 3^2 full factorial design was employed to optimize the formulation, using HPMC K100 as a binder (X1) and Croscarmellose Sodium as a superdisintegrant (X2), with tablet hardness (Y1) and cumulative drug release (%CDR) (Y2) as dependent variables. The tablets were evaluated for both pre- and post-compression parameters. Among all batches, Batch F6 exhibited the best results, with a hardness of 6.2 kg/cm² and 99.48% drug release, complying with pharmacopeial standards. Stability testing under ICH guidelines confirmed the formulation's physical and chemical stability. Overall, the study successfully developed a stable and effective chewable tablet formulation of Ezetimibe.

KEYWORDS: Ezetimibe, β-Cyclodextrin, 3^2factorial design, solubility enhancement, inclusion complex, FTIR, DSC, 3^2 Full factorial design, CDI.

INTRODUCTION

Hyperlipidemia, commonly referred to as high cholesterol, is characterized by elevated levels of lipids primarily cholesterol and triglycerides in the blood. This condition significantly increases the risk of atherosclerosis, cardiovascular disease, stroke, and myocardial infarction. It is often asymptomatic, earning it the label of a "silent killer." Cholesterol is transported in the bloodstream as lipoproteins HDL (good cholesterol) and LDL (bad cholesterol). While HDL facilitates the removal of cholesterol from arteries, LDL contributes to plaque formation and arterial narrowing. Factors contributing to hyperlipidemia include diet high in saturated fats, physical inactivity, genetic disorders (e.g., familial hypercholesterolemia), and conditions such as hypothyroidism, diabetes, and kidney disease.[1]

Pharmacological treatment options include statins (e.g., atorvastatin), fibrates, cholesterol absorption inhibitors like ezetimibe, and bile acid sequestrants. Among these, ezetimibe offers a unique mechanism by inhibiting intestinal cholesterol absorption, making it a suitable candidate for formulations that improve solubility and enhance compliance.[2]

Chewable tablets represent a novel and patient-friendly oral dosage form designed to disintegrate smoothly in the oral cavity, providing both local and systemic effects. Unlike conventional tablets, they offer ease of administration without the need for water, significantly improving medication adherence among pediatric, geriatric, and dysphagic patients. Their palatable taste and rapid onset of action make them particularly suitable for populations requiring frequent or on-the-go dosing.[3] The mechanism of chewable tablets centers around rapid water absorption, the use of superdisintegrants like croscarmellose sodium, and the presence of soluble excipients, which facilitate swift disintegration and dissolution. Mechanical chewing also increases the surface area for dissolution, leading to faster absorption, sometimes even bypassing hepatic first-pass metabolism. This contributes to improved bioavailability, especially for drugs with poor solubility or extensive hepatic metabolism.[4] Key formulation aspects include flavour, mouthfeel, aroma, and effective taste-masking strategies. Organoleptic properties such as texture and aftertaste are

crucial, as these influence patient acceptability. Common taste-masking techniques include wet granulation, microencapsulation, inclusion complexes (e.g., with β-cyclodextrin), and the use of sweeteners like aspartame and glycyrrhizin. The excipient profile of chewable tablets is critical. Bulking agents like mannitol and sorbitol enhance mouthfeel, while superdisintegrants ensure rapid breakdown. Sweeteners and Flavouring agents improve palatability, and colorants aid product identification and patient appeal. Chewable tablets are manufactured using direct compression, wet granulation, or dry granulation, depending on drug properties and formulation goals.[5][6]

Advantages of Chewable Tablet[7]

1. Easy for children and elderly to take medication.
2. Improved bioavailability and faster drug absorption.
3. Increased patient acceptance, especially in paediatrics.
4. No water needed for administration.
5. Quick alternative to liquid dosage forms.
6. Faster onset of medication action.
7. Sweet taste improves patient compliance.
8. Unique form offers marketing advantages.
9. Chewing reduces tablet size for easier swallowing.
10. Overcomes difficulty of swallowing large tablets.

MATERIAL AND METHODS

Materials

Ezetimibe was obtained as a gift sample from **MSN Laboratories Pvt. Ltd**. All excipients used were of analytical grade and procured from reputed suppliers. These included mannitol as diluent (Research Lab FineChem Industries), HPMC K100, PVP, and MCC as binders (Research Lab FineChem Industries), PEG-4000 as solubilizer (Oxford Lab FineChem LLP), croscarmellose sodium, Crospovidone, and sodium starch glycolate as superdisintegrants (Oxford Lab FineChem LLP), aspartame as sweetener (Research Lab FineChem Industries), Menthol as flavouring agent (Oxford Lab FineChem LLP), magnesium stearate and talc as lubricants/glidants (Oxford Lab FineChem LLP).

Characterization and Pre-Formulation Study: Ezetimibe was evaluated for organoleptic properties such as color, odor, taste, and appearance. Melting point was determined using a capillary method. Solubility studies were carried out in various solvents including water, 0.1N HCl, phosphate buffer (pH 6.8), and methanol. The absorption maxima (λmax) of Ezetimibe were determined using UV-Visible spectrophotometry. A standard calibration curve was constructed using serial dilutions in 0.1N HCl at the identified λmax. Compatibility between drug and excipients was assessed by FTIR analysis to detect any possible interactions.[8]

Preparation of Inclusion Complex: Ezetimibe–β-Cyclodextrin inclusion complexes were prepared by kneading method in different molar ratios like 1:0.5, 1:1 and 1:1.5 of Ezetimibe and β-Cyclodextrin respectively. The complex exhibiting highest solubility enhancement was selected for further formulation. Physicochemical characterization was carried out using Differential Scanning Calorimetry (DSC) to confirm the formation of inclusion complex and evaluate crystallinity reduction.[9][10]

Methodology: Pre-compression parameters such as angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio were measured to evaluate flow properties of the powder blend. Chewable tablets were then prepared by direct compression method[11] using the optimized inclusion complex, binders, diluents, superdisintegrants, and lubricants. Post- compression parameters including tablet weight, thickness, hardness, friability, drug content, disintegration time, and in vitro dissolution were evaluated as per pharmacopeial standards.

Preliminary Trials for Formulation: Initial batches were formulated to screen suitable polymers for use as binder and superdisintegrant. Based on tablet characteristics, optimal excipient ranges were selected to proceed with factorial design.

Optimization of Formulation by Design of Experiment (DoE): 3^2 full factorial design was employed for formulation optimization, where HPMC K100 (X_1) and Croscarmellose Sodium (X_2) were taken as independent variables. Tablet hardness and % cumulative drug release were considered as responses. Factorial batches were prepared, evaluated, and analysed statistically. The model was validated using ANOVA, and a graphical evaluation including contour and response surface plots was used to interpret the data. A checkpoint batch was formulated to confirm model predictions.

Comparison of Optimized Batch with Marketed Formulation: The optimized formulation was compared with a marketed Ezetimibe tablet to evaluate improvement in drug release and patient-friendly characteristics. The chewable formulation showed superior dissolution and taste-masking profile.

Stability Study: The optimized batch was subjected to short-term stability studies as per ICH guidelines (40°C ± 2°C / 75% ± 5% RH) for one month. Evaluation parameters such as hardness, disintegration, drug content, and dissolution were assessed at regular intervals. No significant variations were observed, indicating stability of the formulation.

Table 1: Preliminary Trial Batches for Selection of Polymer.

Ingredients	T1 (mg)	T2 (mg)	T3 (mg)	T4 (mg)	T5 (mg)	T6 (mg)	T7 (mg)	T8 (mg)	T9 (mg)
IC2 (~10 mg EZT)	37.7	37.7	37.7	**37.7**	37.7	37.7	37.7	37.7	37.7
Mannitol	137.3	137.3	137.3	**137.3**	137.3	137.3	137.3	137.3	137.3
PVP	20	20	20	**-**	-	-	-	-	-
HPMC K100	-	-	-	**20**	20	20	-	-	-
MCC	-	-	-	**-**	-	-	20	20	20
PEG-4000	35	35	35	**35**	35	35	35	35	35
Crosscarmellose Sodium	10	-	-	**10**	-	-	10	-	-
Crospovidone	-	10	-	**-**	10	-	-	10	-
Sodium Starch Glycolate	-	-	10	**-**	-	10	-	-	10
Aspartame	3	3	3	**3**	3	3	3	3	3
Menthol	3	3	3	**3**	3	3	3	3	3
Mg. Stearate	2.5	2.5	2.5	**2.5**	2.5	2.5	2.5	2.5	2.5
Talc	1.5	1.5	1.5	**1.5**	1.5	1.5	1.5	1.5	1.5
Total Weight	250	250	250	**250**	250	250	250	250	250

Table 2: Selection of Binder Polymer Range.

Ingredients	B1 (mg)	B2 (mg)	B3 (mg)	B4 (mg)	B5 (mg)	B6 (mg)
IC2 (~10 mg EZT)	37.7	37.7	37.7	37.7	37.7	37.7
Mannitol	145.3	143.3	141.3	133.3	131.3	129.3
HPMC K100	12	14	16	24	26	28
PEG-4000	35	35	35	35	35	35
Crosscarmellose Sodium	10	10	10	10	10	10
Aspartame	3	3	3	3	3	3
Menthol	3	3	3	3	3	3
Magnesium Stearate	2.5	2.5	2.5	2.5	2.5	2.5
Talc	1.5	1.5	1.5	1.5	1.5	1.5
Total Weight	250	250	250	250	250	250

Table 3: Composition with coded and actual value.

Independent Variable		Dependant Variable	
X1	X2	Y1	Y2
HPMC (mg)	Crosscarmellose Sodium (mg)	Hardness (kg/cm²)	% CDR (%)
Levels	Coded Value	Independent Variable	
		X1 (mg)	X2 (mg)
Low	-1	15	8
Intermediate	0	20	10
High	1	25	12

Table 4: Factorial Design Layout.

Batches	Coded Values		Real Values	
	X1	X2	HPMC (mg)	Crosscarmellose Sodium (mg)
F1	-1	-1	15	8
F2	-1	0	15	10
F3	-1	1	15	12
F4	0	-1	20	8
F5	0	0	20	10
F6	0	1	20	12
F7	1	-1	25	8
F8	1	0	25	10
F9	1	1	25	12

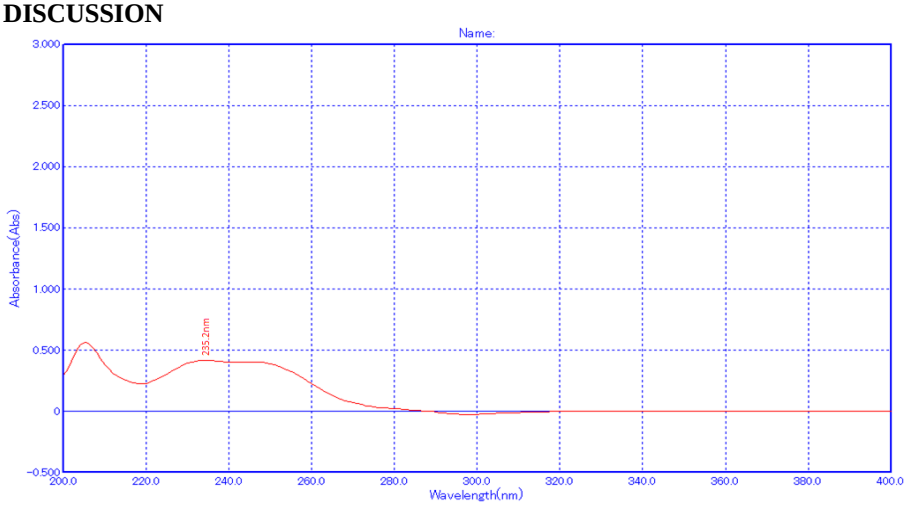
Table 5: Formulation Table for Factorial Batches.

Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)
IC2 (~10 mg EZT)	37.7	37.7	37.7	37.7	37.7	37.7	37.7	37.7	37.7
Mannitol	144.3	142.3	140.3	139.3	137.3	135.3	134.3	132.3	130.3
HPMC K100	15	15	15	20	20	20	25	25	25
PEG-4000	35	35	35	35	35	35	35	35	35
Crosscarmellose Sodium	8	10	12	8	10	12	8	10	12
Aspartame	3	3	3	3	3	3	3	3	3
Menthol	3	3	3	3	3	3	3	3	3
Magnesium Stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total Weight	250	250	250	250	250	250	250	250	250

Evaluation Parameters[12]

- **Angle of Repose:** The angle of repose was measured using the fixed funnel method to assess flow properties of the powder blend. The height of the funnel was adjusted to touch the apex of the heap formed on a flat surface.
- **Bulk Density and Tapped Density:** Bulk density was determined by pouring a known mass of powder into a graduated cylinder and noting the initial volume. Tapped density was measured by tapping the cylinder 100 times and noting the final volume. These values were used to assess powder compressibility and flow.
- **Hausner's Ratio:** Hausner's Ratio was calculated as the ratio of tapped density to bulk density. A lower ratio (1.00–1.11) indicates excellent flow properties, while a ratio above 1.60 indicates very poor flow.
- **Carr's Compressibility Index**: It provides an indirect measure of powder flowability. Values below 15% indicate good flow, whereas values above 25% suggest poor flow characteristics.
- **Weight Variation**: Twenty tablets from each batch were weighed individually and compared to the average weight. The test ensures uniform dosage. According to pharmacopeial standards, weight deviation should not exceed ±5% for tablets weighing more than 250 mg.
- **Tablet Thickness**: Thickness was measured using a vernier calliper. Uniformity in tablet thickness is essential for dose consistency and proper packaging.
- **Hardness**: Tablet hardness, also known as crushing strength, was assessed using a Pfizer hardness tester. Adequate hardness is necessary for tablets to withstand handling during manufacturing, transport, and use, while still ensuring disintegration.
- **Friability**: Friability testing was carried out using a Roche friabilator. Tablets were rotated at 25 rpm for 4 minutes, then weighed before and after the test. A weight loss of less than 1% was considered acceptable, indicating good mechanical strength.
- **Drug Content Uniformity**: Ten tablets were randomly selected, crushed, and analysed spectrophotometrically at 235 nm after dissolution in 0.1N HCl. The assay ensures that each tablet contains the intended amount of active drug within acceptable limits (typically 90–110%).
- **In Vitro Dissolution**: Dissolution studies were conducted using USP Type II apparatus (paddle method) in 900 mL of 0.1N HCl at 37 ± 0.5°C and 50 rpm for Crushed and Intact tablets both. Samples were withdrawn at 5, 10, 15, 20, 25, and 30 minutes, filtered, and analysed using UV spectrophotometry at 235 nm. Results were plotted as cumulative % drug release vs. time.[13]
- **In Vitro Disintegration**: Disintegration testing was carried out in simulated saliva fluid (pH 6.8) using a USP disintegration apparatus without disks. Tablets were observed for softening and breakdown into granules. This test is critical even for chewable tablets, as some patients may swallow them whole.[14][15]
- **Chewing Difficulty Index (CDI)**: CDI was calculated using the formula: [CDI=F×H] where *F* is the force required to break the tablet and *H* is the thickness. A higher CDI value indicates greater chewing effort. This parameter was introduced to assess ease of chewing, especially for paediatric and geriatric patients. CDI for commercial chewable tablets typically ranged between 0.09–1.25 Nm.[16][17]

RESULTS AND DISCUSSION



Absorption Maxima of Ezetimibe (λmax): λmax of Ezetimibe in 0.1N HCl was found to be on 235.2nm in 6 µg/ml solution. Absorption maxima of Ezetimibe shown in fig 1;

Figure 1: Absorption Maxima of Ezetimibe (λmax) in 0.1N HCl Solution.

Drug-Excipients Compatibility (FTIR Study) Results

Fig. 2 presents the FTIR spectrum of EZT and excipients, while the interpreted data is summarized in Table 6. The presence of major peaks in the spectrum confirms the existence of distinctive functional groups in the molecule. Thus, the Ezetimibe sample was identified and the selected excipients were compatible with the drug sample.

Table 6: FTIR Data Interpretation.

Functional group	Reference Wavenumber (cm-1)[18]	Pure Ezetimibe Wavenumber (cm -1)	Ezetimibe + all excipients Wavenumber (cm -1)
C-F Stretching Aromatic, C-H in ring structure	823.42	831.32	840.96
C=O Stretching	1110.56	1103.28	1095.57
C-N Stretching	1396	1354.03	1354.03
C-H Bending	1517.31	1508.33	1510.26
Aromatic C=O Stretching	1750	1716.65	1718.58
C-H Stretching	3133	2912.51	2916.37

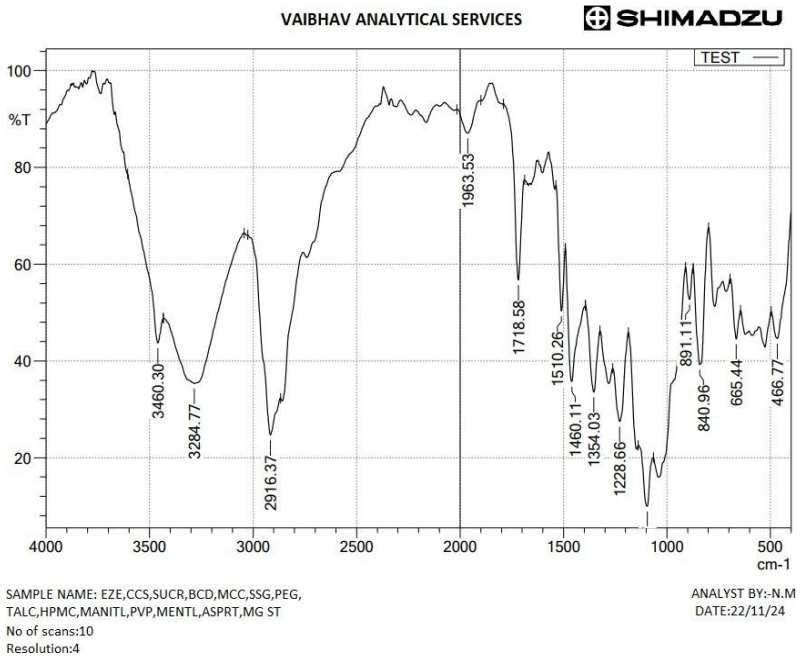


Figure 2: FTIR spectra of pure drug and drug with excipient.

Solubility Results of Inclusion Complex: Among the three inclusion complexes, IC2 (1:1 molar ratio) exhibited the highest solubility (81.54 µg/mL), making it the most suitable for formulation. For a 10 mg dose of Ezetimibe (molecular weight: 409.4 g/mol), the corresponding moles are 0.02443. An equimolar amount of β-Cyclodextrin (molecular weight: 1134.9 g/mol) is required, equating to 27.7 mg. Thus, the optimized inclusion complex (IC2) consists of 10 mg of Ezetimibe and 27.7 mg of β-CD, total 37.7 mg, ensuring improved solubility and drug delivery.

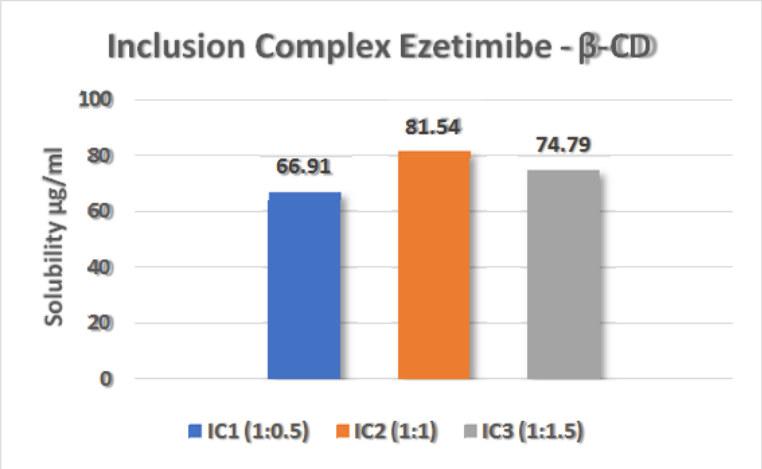


Figure 3: Bar Graph for Solubility of Inclusion Complexes.

The DSC thermogram as shown in Fig. 4 of pure Ezetimibe shows a sharp endothermic peak at 163.65°C, indicating its crystalline nature and poor solubility. In contrast, the Ezetimibe-β- Cyclodextrin inclusion complex displays a broader, less intense peak at 166.13°C, with reduced crystallinity. This shift suggests successful inclusion and molecular interaction between the drug and β-CD, resulting in an amorphous or partially amorphous state.

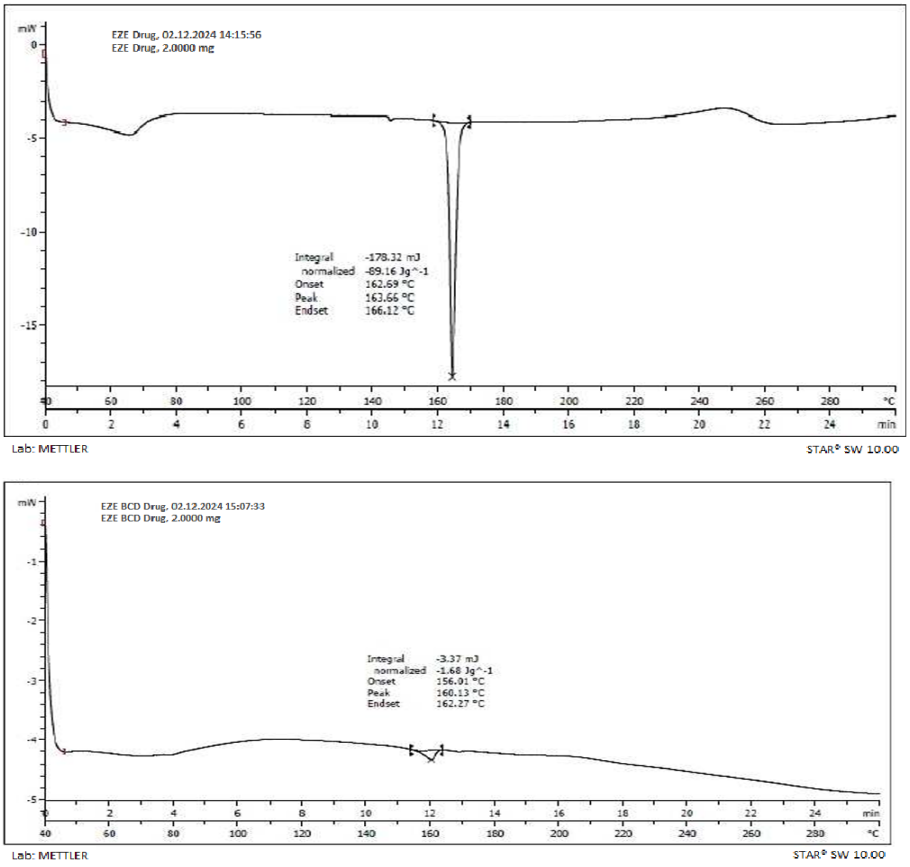


Figure 4: DSC Thermogram of Ezetimibe + β-CD Inclusion Complex.

Preliminary Trial Batches Result

Table 7: Pre-Compression Results for T1-T9 batches.

Batch	Angle of Repose (°) (n=3)	Bulk Density (gm/ml) (n=3)	Tapped Density (gm/ml) (n=3)	Hausner's Ratio	Carr's Index (%)
T1	32.55 ± 0.03	0.609 ± 0.02	0.72 ± 0.01	1.18	15.42
T2	31.86 ± 0.01	0.599 ± 0.01	0.735 ± 0.02	1.22	18.5
T3	32.88 ± 0.1	0.618 ± 0.02	0.728 ± 0.02	1.17	15.11
T4	**31.25 ± 0.021**	**0.626 ± 0.01**	**0.776 ± 0.02**	**1.23**	**19.33**
T5	36.47 ± 0.02	0.631 ± 0.03	0.769 ± 0.01	1.21	17.95
T6	28.54 ± 0.01	0.655 ± 0.05	0.802 ± 0.01	1.22	18.33
T7	30.75 ± 0.19	0.641 ± 0.02	0.788 ± 0.05	1.23	18.65
T8	31.33 ± 0.01	0.595 ± 0.01	0.705 ± 0.02	1.18	15.6
T9	33.57 ± 0.01	0.601 ± 0.02	0.841 ± 0.02	1.39	28.54

Table 8: Post-Compression Results for T1-T9 batches.

Batch	Weight Variation (mg) (n=20)	Hardness (kg/cm²) (n=3)	Thickness (mm) (n=3)	Friability (%) (n=10)	Disintegrating Time (sec) (n=6)	Drug Content (%) n=3
T1	237.5 ± 1.15	5.9 ± 0.4	4.1 ± 0.2	0.46	115 ± 1.89	97.2 ± 1.5
T2	250.2 ± 1.25	6.3 ± 0.5	4.3 ± 0.3	0.52	120 ± 3.78	95.3 ± 2.0
T3	258.7 ± 1.05	6.8 ± 0.4	4.2 ± 0.2	0.49	145 ± 2.22	96.5 ± 1.9
T4	**245.9 ± 0.95**	**6.6 ± 0.6**	**4.8 ± 0.3**	**0.53**	**110 ± 4.2**	**98.5 ± 1.3**
T5	242.1 ± 1.12	6.2 ± 0.5	4.5 ± 0.3	0.47	103 ± 4.1	93.4 ± 1.8
T6	253.4 ± 1.35	8.3 ± 0.6	4.7 ± 0.3	0.54	129 ± 2.69	88.9 ± 2.1
T7	249.8 ± 1.02	6.6 ± 0.6	5.0 ± 0.2	0.51	105 ± 4.5	90.8 ± 1.7
T8	239.3 ± 1.08	8.1 ± 0.7	5.1 ± 0.3	0.5	108 ± 1.25	85.6 ± 1.9
T9	257.2 ± 0.96	7.7 ± 0.5	4.9 ± 0.2	0.55	135 ± 3.56	92.9 ± 1.6

The % Cumulative Drug Release (CDR) data indicates that formulations containing HPMC K100 and Croscarmellose Sodium exhibited the highest drug release within 30 minutes, suggesting their effectiveness in enhancing dissolution. Comparatively, formulations with PVP, MCC, Sodium Starch Glycolate, and Crospovidone showed lower release rates. The results confirm that HPMC and Croscarmellose Sodium are the most suitable excipients for our formulation.

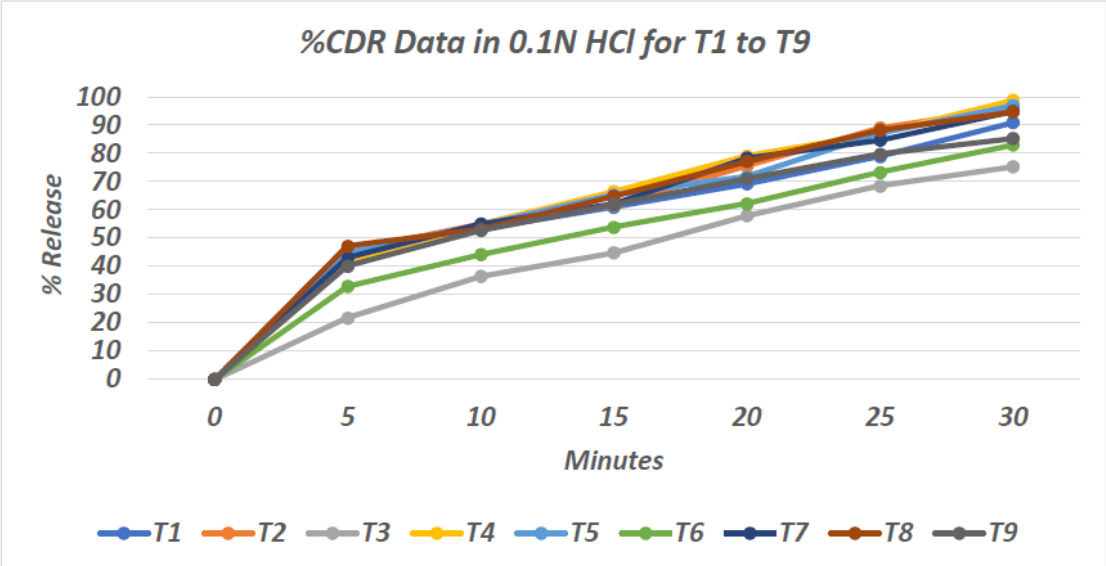


Figure 5: %CDR Data in 0.1N HCl for T1 to T9.

Selection of Polymer Range (B1-B6) Results

Table 9: Pre-Compression Results for B1-B6 batches.

Batch	Angle of Repose (°) (n=3)	Bulk Density (gm/ml) (n=3)	Tapped Density (gm/ml) (n=3)	Hausner's Ratio	Carr's Index (%)
B1	32.47 ± 0.02	0.612 ± 0.02	0.723 ± 0.01	1.18	15.34
B2	31.92 ± 0.01	0.604 ± 0.01	0.740 ± 0.02	1.22	18.38
B3	31.86 ± 0.01	0.599 ± 0.01	0.735 ± 0.02	1.22	18.5
B4	32.10 ± 0.02	0.615 ± 0.02	0.740 ± 0.02	1.2	16.89
B5	32.81 ± 0.09	0.621 ± 0.02	0.731 ± 0.02	1.18	15.04
B6	31.32 ± 0.020	0.630 ± 0.01	0.781 ± 0.02	1.24	19.33

Table 10: Post-Compression Results for B1-B6 batches.

Batch	Weight Variation (mg) (n=20)	Hardness (kg/cm²) (n=3)	Thickness (mm) (n=3)	Friability (%) (n=10)	Disintegrating Time (sec) (n=6)	Drug Content (%) n=3
B1	238.2 ± 1.12	5.3 ± 0.3	3.9 ± 0.2	0.45	139 ± 1.92	92.5 ± 1.4
B2	249.8 ± 1.30	6.2 ± 0.4	4.2 ± 0.3	0.51	107 ± 3.65	95.5 ± 1.9
B3	254.5 ± 1.10	6.4 ± 0.5	4.5 ± 0.2	0.5	126 ± 2.15	96.8 ± 1.8
B4	249.5 ± 1.21	6.0 ± 0.6	4.8 ± 0.4	0.45	108 ± 3.65	97.3 ± 1.1
B5	252.5 ± 1.12	6.1 ± 0.7	4.7 ± 0.3	0.51	127 ± 2.15	95.4 ± 1.9
B6	246.4 ± 0.98	7.05 ± 0.5	4.7 ± 0.3	0.54	145 ± 4.19	93.8 ± 1.2

The cumulative drug release data confirms that formulations containing HPMC K100 in the range of 15–25 mg demonstrated optimal drug release. However, when HPMC was used below 15 mg or above 25 mg the formulations did not exhibit desirable release kinetics. This was evident in B1 and B6, where drug release and disintegration time were not within the expected limits. These findings emphasize the importance of maintaining the optimal concentration range of HPMC K100 to achieve consistent and effective drug release.

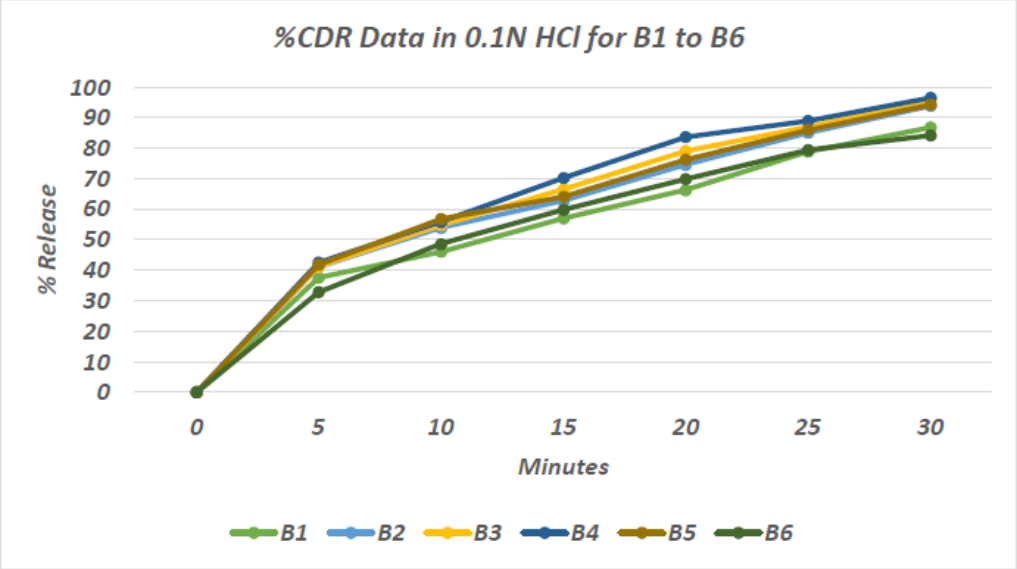


Figure 6: %CDR Data in 0.1N HCl for B1 to B6.

Results of Factorial Batches

Table 11: Pre-Compression Results for F1-F9 batches.

Batch	Angle of Repose (°) (n=3)	Bulk Density (gm/ml) (n=3)	Tapped Density (gm/ml) (n=3)	Hausner's Ratio	Carr's Index (%)
F1	30.98 ± 0.021	0.608 ± 0.012	0.733 ± 0.018	1.2	17.05
F2	32.15 ± 0.023	0.605 ± 0.012	0.730 ± 0.019	1.21	17.12
F3	29.72 ± 0.019	0.620 ± 0.010	0.750 ± 0.015	1.2	18.67
F4	31.62 ± 0.022	0.612 ± 0.010	0.743 ± 0.019	1.21	17.62
F5	31.25 ± 0.021	0.626 ± 0.010	0.776 ± 0.020	1.24	19.33
F6	**30.68 ± 0.018**	**0.614 ± 0.013**	**0.742 ± 0.017**	**1.21**	**17.25**

F7	30.50 ± 0.020	0.630 ± 0.011	0.760 ± 0.013	1.21	17.11
F8	30.78 ± 0.017	0.628 ± 0.011	0.757 ± 0.014	1.2	17.07
F9	31.40 ± 0.022	0.617 ± 0.009	0.748 ± 0.016	1.21	17.49

Table 12: Post-Compression Results for F1-F9 batches.

Batch	Weight Variation (mg) (n=20)	Hardness (kg/cm²) (n=3)	Thickness (mm) (n=3)	Friability (%) (n=10)	Disintegrating Time (sec) (n=6)	Drug Content (%) n=3	C.D.I. (Nm)
F1	243.9 ± 1.25	5.8 ± 0.4	4.4 ± 0.3	0.54	130 ± 4.1	93.9 ± 2.1	0.250
F2	243.8 ± 1.20	6.2 ± 0.5	4.7 ± 0.2	0.47	111 ± 3.6	98.1 ± 1.5	0.285
F3	241.3 ± 1.10	5.7 ± 0.3	4.7 ± 0.2	0.48	112 ± 3.5	97.5 ± 1.8	0.262
F4	249.2 ± 1.18	6.5 ± 0.5	4.8 ± 0.3	0.46	128 ± 3.4	96.4 ± 1.5	0.293
F5	245.9 ± 0.95	6.6 ± 0.6	4.8 ± 0.3	0.53	110 ± 4.2	98.5 ± 1.3	0.310
F6	**248.5 ± 1.15**	**6.2 ± 0.4**	**4.8 ± 0.2**	**0.5**	**108 ± 3.9**	**98.9 ± 1.7**	**0.291**
F7	246.7 ± 1.05	5.7 ± 0.3	4.5 ± 0.2	0.5	108 ± 3.8	96.8 ± 1.6	0.251
F8	244.9 ± 1.08	6.1 ± 0.4	4.6 ± 0.2	0.5	110 ± 3.7	97.6 ± 1.8	0.275
F9	255.2 ± 1.30	5.7 ± 0.5	4.8 ± 0.3	0.42	145 ± 3.0	97.9 ± 1.8	0.268

In vitro dissolution studies of factorial batches F1 to F9 in 0.1N HCl using USP Type II apparatus revealed that crushed tablets consistently showed faster drug release than intact ones. Crushed forms of F6 and F7 achieved nearly 98% release within 15 minutes, while their intact counterparts reached around 99% at 30 minutes. Similar trends were observed in F1 to F5, where crushed tablets released over 95% of the drug by 15 minutes, while intact forms took up to 30 minutes. This enhanced release in crushed tablets is due to increased surface area and improved medium contact.

F6 demonstrated the most favourable release behaviour, with 97.78% drug release in 15 minutes (crushed) and 99.48% in 30 minutes (intact). Batches F7 and F8 also showed efficient release, highlighting the impact of optimized concentrations of HPMC K100 and Croscarmellose Sodium. These results emphasize that the formulation's balance of binder and superdisintegrant is critical for consistent drug release in both chewed and unchewed forms, confirming the robustness of the chewable tablet design across all tested batches.

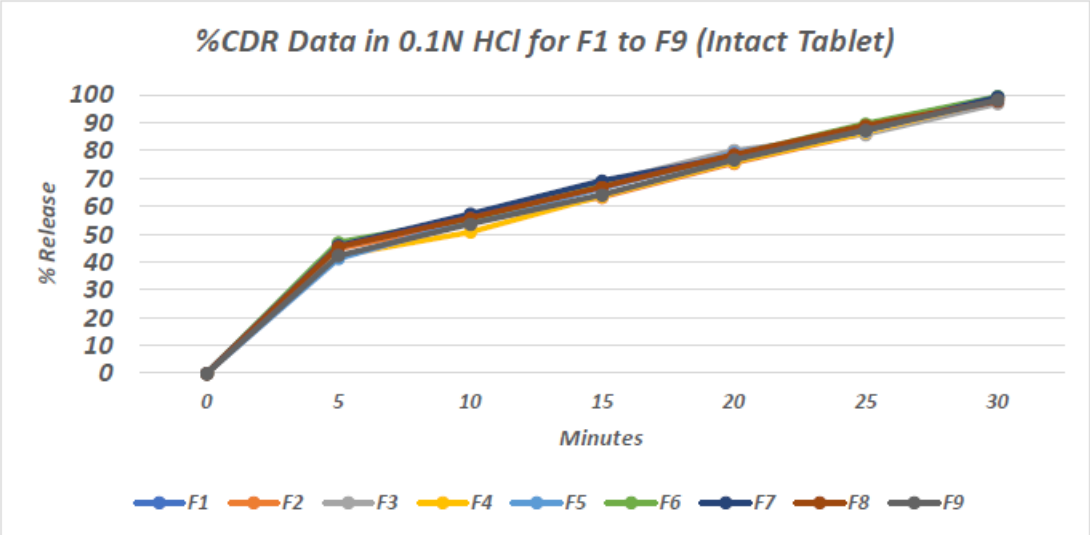


Figure 7: %CDR Data in 0.1N HCl for F1 to F9 (Intact tablet).

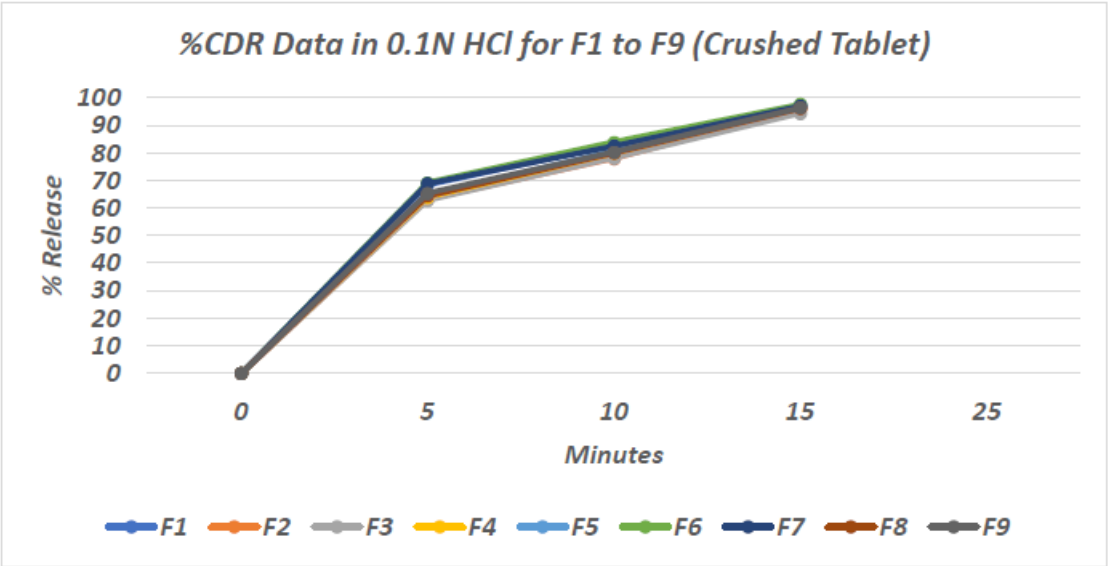


Figure 8: %CDR Data in 0.1N HCl for F1 to F9 (Crushed Tablet).

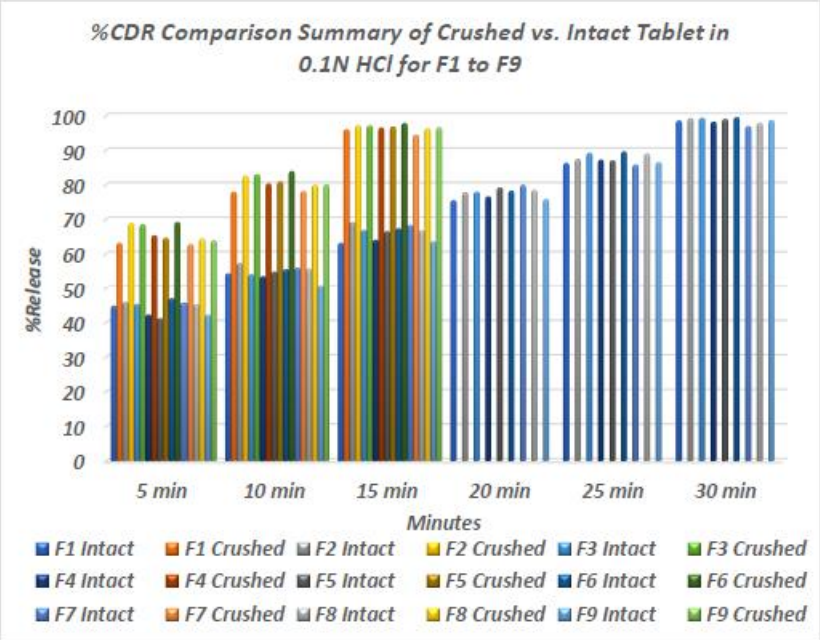


Figure 9: %CDR Data Comparison of Crushed vs. Intact Tablet.

Experimental Design Results: The statistical validation of the 3^2 factorial design was conducted using Design Expert software to analyse the influence of HPMC K100 (X_1) and Croscarmellose Sodium (X_2) on tablet hardness (Y_1) and percent cumulative drug release (%CDR, Y_2). For hardness (Y_1), a quadratic model proved statistically significant with an F- value of 26.12 and a p-value of 0.0112, confirming model reliability. The terms A^2 (HPMC^2) and B^2 (Croscarmellose Sodium^2) were significant contributors to the response. The model displayed strong fit statistics: $R^2 = 0.9775$, adjusted $R^2 = 0.9401$, and predicted $R^2 = 0.7376$, with Adequate Precision of 15.1434, indicating a good signal-to-noise ratio and suitability for navigating the design space.

For %CDR (Y_2), the quadratic model was highly significant with an F-value of 158.04 and a p-value of 0.0008. Significant factors included A (HPMC), B (Croscarmellose Sodium), their interaction (AB), and the quadratic term A^2. The model showed excellent robustness with $R^2 = 0.9962$, adjusted $R^2 = 0.9899$, and predicted $R^2 = 0.9547$, along with a high Adequate Precision value of 38.8634, ensuring strong predictability. Based on statistical and graphical analysis, Batch F6 was identified as the optimized formulation with a desirability score of 0.998, showing a tablet hardness of 6.2 kg/cm^2 and %CDR of 99.48.

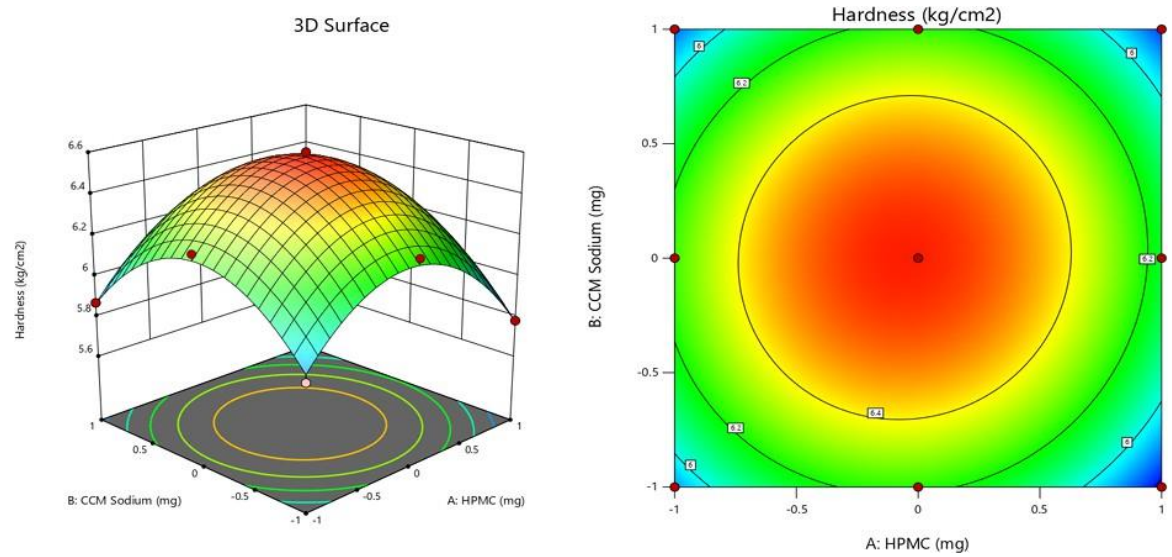


Figure 10: 3D Surface and Contour Plot for Y1-Hardness.

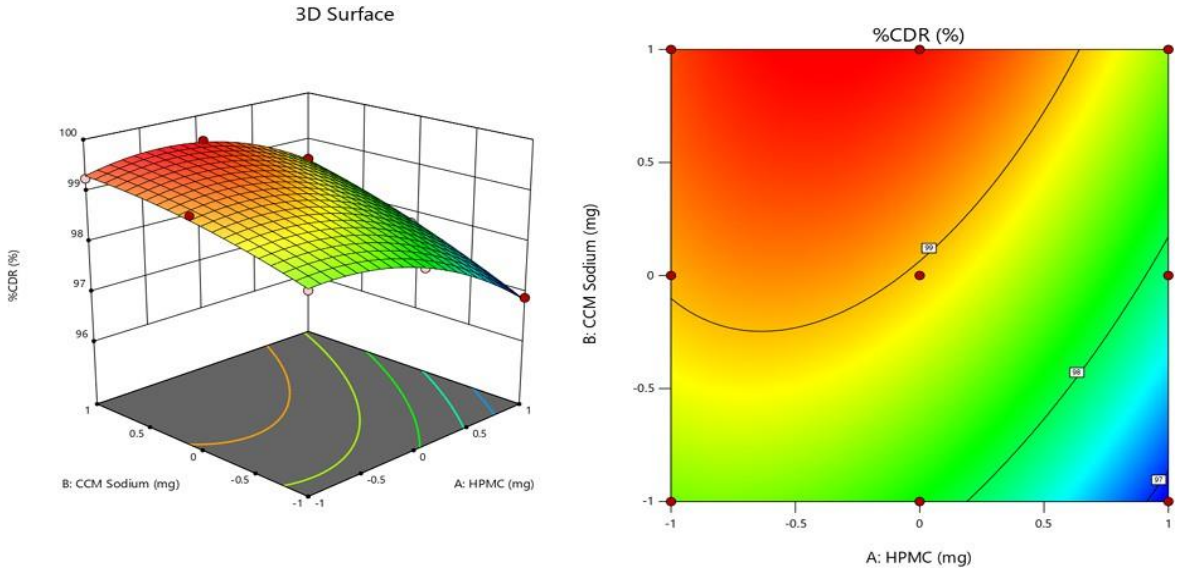


Figure 11: 3D Surface and Contour Plot for Y2-%CDR.

Y1 Hardness: 6.57556 - 0.0416667 * A + 0.00333333 * B + 0.025 * AB - 0.378333 * A2 - 0.353333 * B2.

Y2 %CDR: 98.96 - 0.593333 * A + 0.636667 * B + 0.225 * AB - 0.51 * A2 - 0.15 * B2

Checkpoint batch analysis and optimization based on desirability: The checkpoint batch was formulated at coded values of 0.15 (20.75 mg HPMC) and 1.14 (12.28 mg Croscarmellose Sodium), and its experimental evaluation showed excellent agreement with predicted values recording a hardness of 6.1 ± 0.3 kg/cm² and a %CDR of 99.50 ± 0.21%. This minimal deviation confirms the accuracy and reliability of the model predictions. The application of desirability function and overlay plots not only validated the statistical optimization process but also ensured the robustness of the formulation within the design space.

Batch F6 was selected as the optimized formulation with a high desirability of 0.998, showing ideal tablet hardness (6.2 kg/cm²) and %CDR (99.48%). The overlay plot confirmed the optimized design space, guiding the formulation of the checkpoint batch within defined response limits.

Table 13: Check Point Batch Results.

Independent Variable		Dependant Variable	
X1	X2	Y1	Y2
HPMC (mg)	Crosscarmellose Sodium (mg)	Hardness (kg/cm²)	% CDR (%)
Coded Value: 0.15	Coded Value: 1.14	Predicted Value: 6.08	Predicted Value: 99.51
Actual Value: 20.75	Actual Value: 12.28	Observed Data: 6.1 ± 0.3	Observed Data: 99.50 ± 0.21

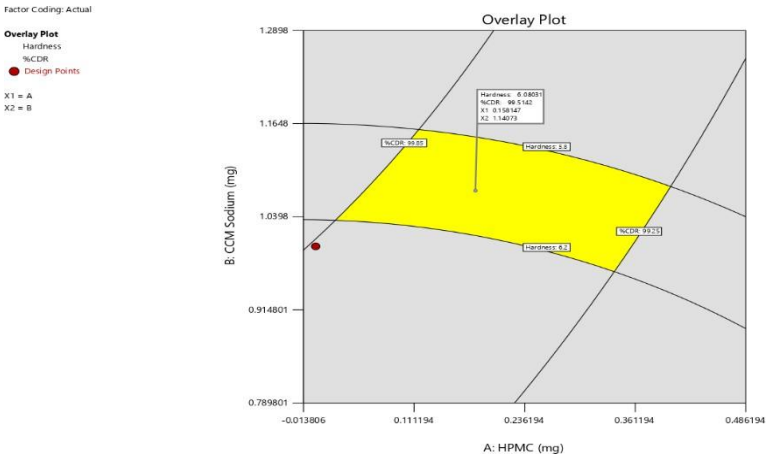


Figure 12: Check Point Batch.

Comparison with Marketed Product: The optimized formulation (Batch F6) was compared with the marketed Ezetimibe product, Ezentia® (Sun Pharma), to evaluate differences in performance characteristics. Significant differences were observed in dissolution profiles, where both crushed and intact forms of F6 exhibited notably faster drug release compared to Ezentia®. Crushed F6 tablets achieved ~98% drug release within 15 minutes, and intact F6 reached nearly 100% within 30 minutes, while the marketed product required 60 minutes for similar release. The f1 (difference factor) and f2 (similarity factor) values further confirmed dissimilarity: f1 was 222.49 (crushed) and 60.94 (intact), while f2 was negative in both cases (−88.06 and −72.24), indicating that F6's dissolution profile was significantly superior in terms of speed and efficiency.

Table 14: Release Comparison with Marketed Product.

% Cumulative Drug Release in 900ml of 0.1N HCl, at 50rpm, 37.0°C in USP Type II (Paddle) Apparatus, (n=4)			
Time (Min)	**Crushed Form (F6)**	**Intact Form (F6)**	**Marketed Ezentia®**
0	0	0	0
5	69.14 ± 0.390	46.91 ± 0.223	12.51 ± 0.242
10	83.88 ± 0.239	55.48 ± 0.275	25.48 ± 0.268
15	97.78 ± 0.385	67.35 ± 0.317	39.78 ± 0.145
20	-	78.19 ± 0.352	52.32 ± 0.312
25	-	89.56 ± 0.393	64.85 ± 0.123
30	-	99.48 ± 0.460	76.57 ± 0.134
40	-	-	89.23 ± 0.197
50	-	-	97.87 ± 0.254
60	-	-	99.89 ± 0.374

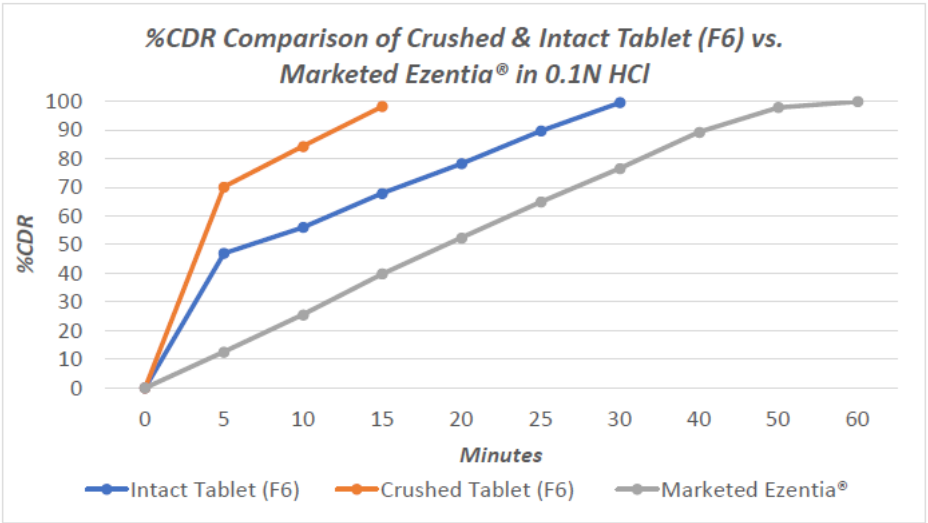


Figure 13: Release Comparison with Marketed Product.

Stability Study: Stability testing of the optimized chewable tablets was conducted under accelerated ICH conditions (40°C ± 2°C / 75% ± 5% RH) over a period of one month. Evaluation parameters including appearance, hardness, disintegration time, friability, and %CDR remained consistent, showing no significant deviations from initial values. For example, hardness remained stable (6.2 ± 0.4 to 6.1 ± 0.2 kg/cm²), disintegration time was within acceptable limits (108 ± 3.9 to 110 ± 1.5 seconds), and %CDR at 30 minutes was virtually unchanged (99.48% to 99.45%). These results confirmed that the optimized formulation maintains both its physical integrity and drug release performance under stress conditions, validating its shelf stability and robustness for commercial viability.

Table 15: Stability Study.

Conditions	40°C ± 2°C / 75 ± 5% RH	
Evaluation Parameters	Initial Observation	After 1 month
Appearance	Uniform Appearance	Uniform Appearance
Hardness (kg/cm2) (n=3)	6.2 ± 0.4	6.1 ± 0.2
Disintegration Time (Sec) (n=3)	108 ± 3.9	110 ± 1.5
Friability (n=10)	0.5	0.5
at 30 minutes (n=3)	99.48 ± 0.460	99.45± 0.312

Figure 14: Prepared Chewable Tablets.

CONCLUSION

In conclusion, the present study successfully developed and optimized a chewable tablet of Ezetimibe aimed at enhancing solubility and patient compliance. Drug-excipient compatibility was confirmed via FTIR, and solubility was significantly improved through a β-Cyclodextrin inclusion complex, with the 1:1 molar ratio showing the best results. The formulation, prepared by direct compression using HPMC K100 and Croscarmellose Sodium, was optimized using a 3^2 factorial design. Batch F6 emerged as the ideal formulation, demonstrating excellent mechanical strength and drug release. Stability studies confirmed the robustness of the optimized batch, validating the formulation strategy and confirming its potential as a patient-friendly and effective oral dosage form.

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