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FORMULATION AND EVALUATION OF SUBLINGUAL TABLET OF VORTIOXETINE HYDROBROMIDE

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ABSTRACT

The study aimed to develop and evaluate sublingual tablets of Vortioxetine Hydrobromide 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 1:2 ratio showing the highest solubility improvement. This was confirmed by DSC, 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 MCC as a binder (X1) and Croscarmellose Sodium as a superdisintegrant (X2), with tablet disintegration time (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 F9 exhibited the best results, with a disintegration time of 47 sec and 99.5% 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 sublingual tablet formulation of Vortioxetine Hydrobromide.

KEYWORDS: Vortioxetine Hydrobromide, β-Cyclodextrin, 3^2factorial design, solubility enhancement, inclusion complex, FTIR, DSC.

INTRODUCTION

Major depressive disorder (MDD) is believed to arise from a complex interplay of genetic, biochemical, environmental, and psychological factors. Traditionally, it was thought that alterations in neurotransmitters—specifically dopamine, serotonin, and norepinephrine—were the primary cause of depression. This theory is supported by the effectiveness of various antidepressants, such as selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and dopamine-norepinephrine reuptake inhibitors, in treating the condition. Additionally, low levels of serotonin metabolites have been observed in individuals experiencing suicidal thoughts. However, more recent theories propose that MDD is predominantly associated with disruptions in complex neural circuits and neuroregulatory systems, leading to secondary changes in neurotransmitter activity.

A persistently low or depressed mood, anhedonia, or a diminished interest in enjoyable activities, feelings of worthlessness or guilt, lethargy, difficulty concentrating, changes in appetite, agitation or psychomotor retardation, sleep disturbances, or suicidal thoughts are all indicators that someone has it.

Sublingual tablets represent a novel and patient-friendly oral dosage form designed to disintegrate smoothly in the sublingual 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.

The mechanism of Sublingual 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. Sublingual tablets 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.

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 Sublingual 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. Sublingual tablets are manufactured using direct compression, wet granulation, or dry granulation, depending on drug properties and formulation goals.

Advantages of Sublingual Tablet

1. It produces immediate systemic effect by enabling the drug absorbed quickly or directly through mucosal lining of the mouth beneath the tongue.
2. Rapid onset of action.
3. No need of water for administering tablet.
4. Sublingual area is much more permeable than buccal area.
5. Bypass GI tract and hepatic portal system and avoid hepatic first pass metabolism due to this bioavailability of drug get increase.
6. Due to rapidity in action these sublingual dosage forms are Widely used in emergency conditions.
7. This Route can be used by people who have difficulty in swallowing table

MATERIAL AND METHODS

Materials

Vortioxetine Hydrobromide was obtained as a gift sample from **Zydus Lifescience ltd**. All excipients used were of analytical grade and procured from reputed suppliers. These included mannitol as diluent (Research Lab FineChem Industries), HPMC K100, Spray Dried Lactose, and MCC as binders (Research Lab FineChem Industries), PEG-6000 as solubilizer (Oxford Lab FineChem LLP), croscarmellose sodium, Crospovidone, and PVPK 30 as superdisintegrants (Oxford Lab FineChem LLP), aspartame as sweetener (Research Lab FineChem Industries), magnesium stearate and talc as lubricants/glidants (Oxford Lab FineChem LLP).

Characterization and Pre-Formulation Study: Vortioxetine Hydrobromide 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, phosphate buffer (pH 6.8), and methanol. The absorption maxima (λmax) of Vortioxetine Hydrobromide were determined using UV-Visible spectrophotometry. A standard calibration curve was constructed using serial dilutions in pH 6.8 buffer at the identified λmax. Compatibility between drug and excipients was assessed by FTIR analysis to detect any possible interactions.

Preparation of Inclusion Complex: Vortioxetine Hydrobromide–β-Cyclodextrin inclusion complexes were prepared by kneading method in different molar ratios like 1:1, 1:2 and 1:3 of Vortioxetine Hydrobromide 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.

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. Sublingual tablets were then prepared by direct compression method 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 MCC (X_1) and Croscarmellose Sodium (X_2) were taken as independent variables.

Tablet Disintegration time 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 Vortioxetine Hydrobromide tablet to evaluate improvement in drug release and patient-friendly characteristics. The Sublingual 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.

Role	Ingredients	T1 (mg)	T2 (mg)	T3 (mg)	T4 (mg)	T5 (mg)	T6 (mg)	T7 (mg)	T8 (mg)	T9 (mg)
API	SD2 (Equivalent to 10mg Vortioxetine)	69.83	69.83	69.83	69.83	69.83	69.83	69.83	69.83	69.83
Diluent	Mannitol	118.17	118.17	118.17	118.17	118.17	118.17	118.17	118.17	118.17
Binder	Spray Dried Lactose	20	20	20	-	-	-	-	-	-
	HPMC K 100	-	-	-	20	20	20	-	-	-
	MCC	-	-	-	-	-	-	20	**20**	20
Solubilize r	PEG 6000	26	26	26	26	26	26	26	**26**	26
Super DT agent	PVPK 30	8	-	-	8	-	-	8	-	-
	Crosscarmel lose Sodium	-	8	-	-	8	-	-	**8**	-
	Crospovidone	-	-	8	-	-	8	-	-	8
Sweetener	Aspartame	4	4	4	4	4	4	4	**4**	4
Lubricant	MG. Stearate	2	2	2	2	2	2	2	**2**	2
Glidant	Talc	2	2	2	2	2	2	2	**2**	2
	Total Weight	250	250	250	250	250	250	250	**250**	250

Table 2: Selection of Binder Polymer Range.

INGREDIENTS	K1	K2	K3	K4	K5	K6
SD2 (Equivalent to 10 mg Vortioxetine)	69.83	69.83	69.83	69.83	69.83	69.83
MANNITOL	126.17	124.17	122.17	114.17	112.17	110.17
MCC	12	14	16	24	26	28
PEG 6000	26	26	26	26	26	26
CROSSCARMALLOSE SODIUM	8	8	8	8	8	8
ASPARTAME	4	4	4	4	4	4
MG STEARATE	2	2	2	2	2	2
TALC	2	2	2	2	2	2
TOTAL	250	250	250	250	250	250

Table 3: Composition with coded and actual value.

Independent Variable		Dependant Variable	
X1	**X2**	**Y1**	**Y2**
MCC (mg)	Crosscarmellose Sodium (mg)	Disintegration Agent (sec)	% CDR (%)
Levels	Coded Value	Independent Variable	
		X1 (mg)	X2 (mg)
Low	-1	15	6
Intermediate	0	20	8
High	1	25	10

Table 4: Factorial Design Layout.

Batches	Coded Values		Real Values	
	X1	X2	MCC (mg)	Crosscarmellose Sodium (mg)
F1	-1	-1	15	6
F2	-1	0	15	8
F3	-1	1	15	10
F4	0	-1	20	6
F5	0	0	20	8
F6	0	1	20	10
F7	1	-1	25	6
F8	1	0	25	8
F9	1	1	25	10

Table 5: Formulation Table for Factorial Batches.

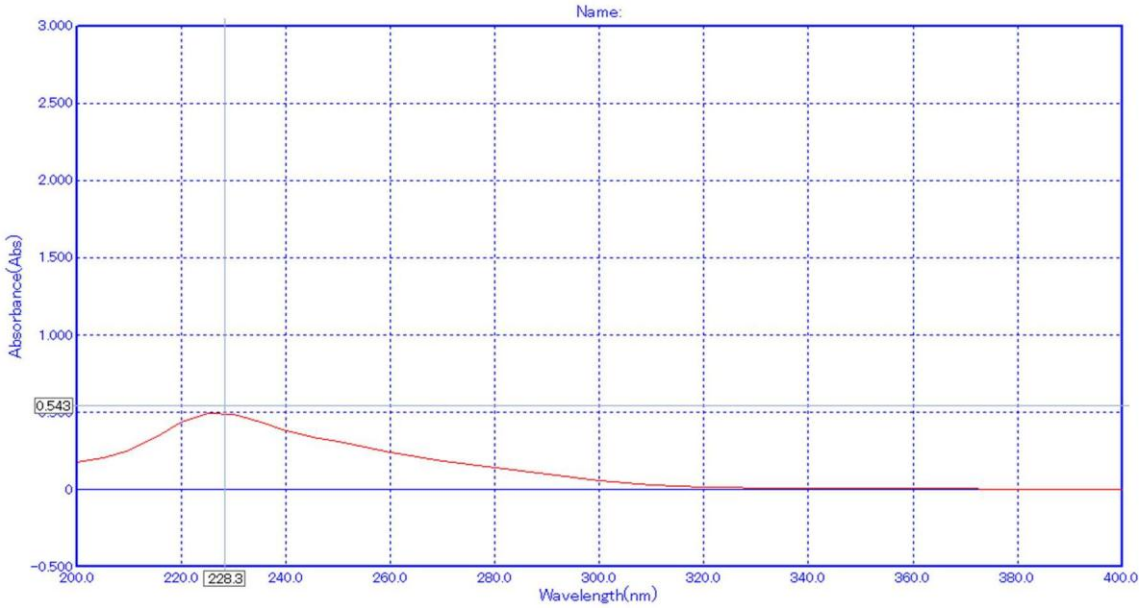
Role	Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)
API	SD2 (Equivalent to 10 mg Vortioxetine HBr)	69.83	69.83	69.83	69.83	69.83	69.83	69.83	69.83	69.83
Diluent	Mannitol	125.17	111.17	113.17	121.17	123.17	118.17	116.17	120.17	115.17
Binder	MCC	15	15	15	20	20	20	25	25	25
Solubilizer	PEG 6000	26	26	26	26	26	26	26	26	26
Super DT Agent	Crosscarmel lose Sodium	6	8	10	6	8	10	6	8	10
Sweetner	Aspartame	4	4	4	4	4	4	4	4	4
Lubricant	MG. Stearate	2	2	2	2	2	2	2	2	2
Glidant	Talc	2	2	2	2	2	2	2	2	2
	Total Weight	250	250	250	250	250	250	250	250	250

Evaluation Parameters

- **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 228 nm after dissolution in pH 6.8 buffer. 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 pH 6.8 buffer at 37 ± 0.5°C and 50 rpm for Intact tablets. Samples were withdrawn at 5, 10, 15, 20, 25, and 30 minutes, filtered, and analysed using UV spectrophotometry at 228 nm. Results were plotted as cumulative % drug release vs. time.
- **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.

RESULTS AND DISCUSSION

Absorption Maxima of Vortioxetine Hydrobromide (λmax): λmax of Vortioxetine Hydrobromide in pH 6.8 was found to be on 228.3 nm in 6 µg/ml solution.



Absorption maxima of Vortioxetine Hydrobromide shown in fig 1;

Figure 1: Absorption Maxima of Vortioxetine Hydrobromide (λmax) in pH 6.8 Solution.

Drug-Excipients Compatibility (FTIR Study) Results

Fig. 2 presents the FTIR spectrum of Vortioxetine Hydrobromide 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 Vortioxetine Hydrobromide sample was identified and the selected excipients were compatible with the drug sample.

Table 6: FTIR Data Interpretation.

Functional Group	Standard FTIR range cm^{-1}	Vortioxetine HBr (Pure Drug) Peak range cm^{-1}	Vortioxetine HBr + Excipients
C-H Stretching	3000-3100	3062.96	3105.72
C-O Stretching	1124-1205	1151.50	1120.64
C-N Stretching	1020-1360	1373.32	1336.67
C-H Bending	860-900	898.56	894.97

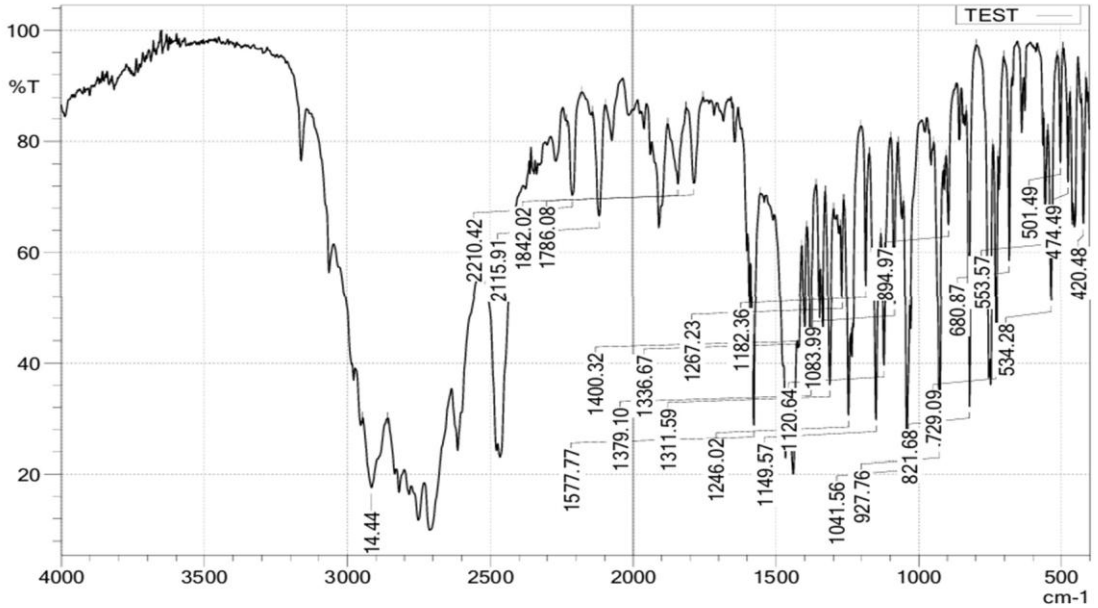


Figure 2: FTIR spectra of pure drug and drug with excipient.

Solubility Results of Inclusion Complex: Among the three inclusion complexes, IC2 (1:2 molar ratio) exhibited the highest solubility (80.64 µg/mL), making it the most suitable for formulation. For a 10 mg dose of Vortioxetine Hydrobromide (molecular weight: 379.36 g/mol), the corresponding moles are 0.02636. An equimolar amount of β-Cyclodextrin (molecular weight: 1134.9 g/mol) is required, equating to 59.83 mg. Thus, the optimized inclusion complex (IC2) consists of 10 mg of Vortioxetine Hydrobromide and 59.83 mg of β-CD, total 69.83 mg, ensuring improved solubility and drug delivery.

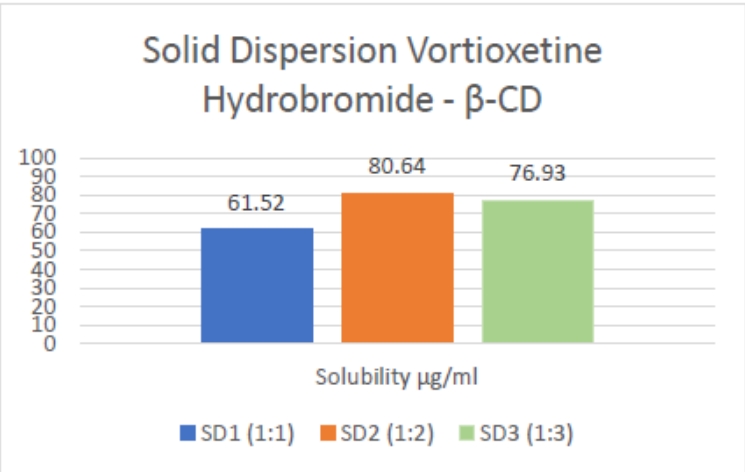


Figure 3: Bar Graph for Solubility of Inclusion Complexes.

The DSC thermogram of pure Vortioxetine Hydrobromide shows a sharp endothermic peak at 231°C, indicating high crystallinity and poor solubility. In contrast, the Vortioxetine hydrobromide-B-CD complex less intense peak, suggesting reduced crystallinity and successful drug inclusion. This transformation aligns with DSC findings, confirming improved solubility and dissolution potential.

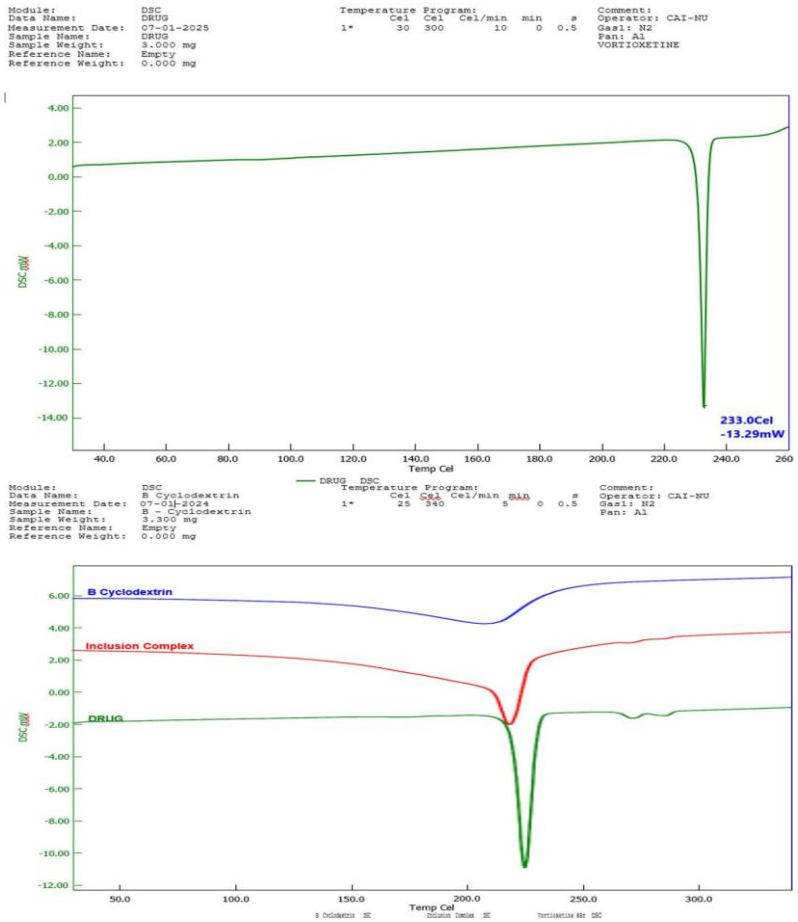


Figure 4: DSC Thermogram of Vortioxetine Hydrobromide + β-CD Inclusion Complex.

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	37.0 ± 1.2	0.44 ± 0.02	0.60 ± 0.03	1.36	26.66
T2	33.0 ± 1.0	0.44 ± 0.01	0.52 ± 0.02	1.18	15.38
T3	36.0 ± 1.1	0.49 ± 0.02	0.66 ± 0.03	1.34	25.75
T4	39.0 ± 1.3	0.54 ± 0.02	0.80 ± 0.04	1.48	32.5
T5	34.0 ± 1.0	0.43 ± 0.01	0.50 ± 0.02	1.16	14
T6	38.0 ± 1.2	0.42 ± 0.01	0.63 ± 0.03	1.5	33.3
T7	31.0 ± 0.9	0.43 ± 0.01	0.52 ± 0.02	1.2	17.3
T8	32.54 ± 0.8	0.50 ± 0.02	0.58 ± 0.03	1.16	13.79
T9	35.0 ± 1.1	0.48 ± 0.02	0.56 ± 0.02	1.17	14.28

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)	Wetting time (sec) (n=6)	Disintegration Time (sec) (n=6)	Drug Content (%) (n=3)
T1	255.4± 2.5	5.1 ± 0.2	3.7 ± 0.1	0.63 ± 0.03	37 ±0.10	79 ± 2.5	89.7 ± 1.1
T2	246.3 ± 2.3	5.3 ± 0.2	3.2 ± 0.1	0.59 ± 0.02	27 ±0.87	65 ± 2.1	96.1 ± 0.8
T3	256.2 ± 2.4	5.4 ± 0.3	3.6 ± 0.1	0.61 ± 0.03	28 ±0.76	78 ± 2.3	91.2 ± 1.0
T4	244.6 ± 2.2	5.2 ± 0.2	3.9 ± 0.1	0.57 ± 0.02	38 ±0.34	76 ± 2.2	89.9 ± 1.2
T5	252.3 ± 2.5	4.8 ± 0.2	3.3 ± 0.1	0.56 ± 0.02	32 ±0.36	66 ± 2.0	95.7 ± 0.9
T6	247.2 ± 2.1	6.0 ± 0.3	3.1 ± 0.1	0.71 ± 0.04	35 ±0.65	81 ± 2.6	91.4 ± 1.1
T7	251.5 ± 2.3	4.9 ± 0.2	3.6 ± 0.1	0.53 ± 0.02	26 ±0.53	69 ± 2.1	96.3 ± 0.7
T8	253.4 ± 1.6	5.0 ± 0.3	3.7 ± 0.1	0.55 ± 0.04	24 ±0.23	62 ± 2.1	96.7 ± 0.4
T9	254.0 ± 2.4	4.7 ± 0.2	3.4 ± 0.1	0.56 ± 0.02	26 ±0.67	68 ± 2.0	95.9 ± 0.8

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

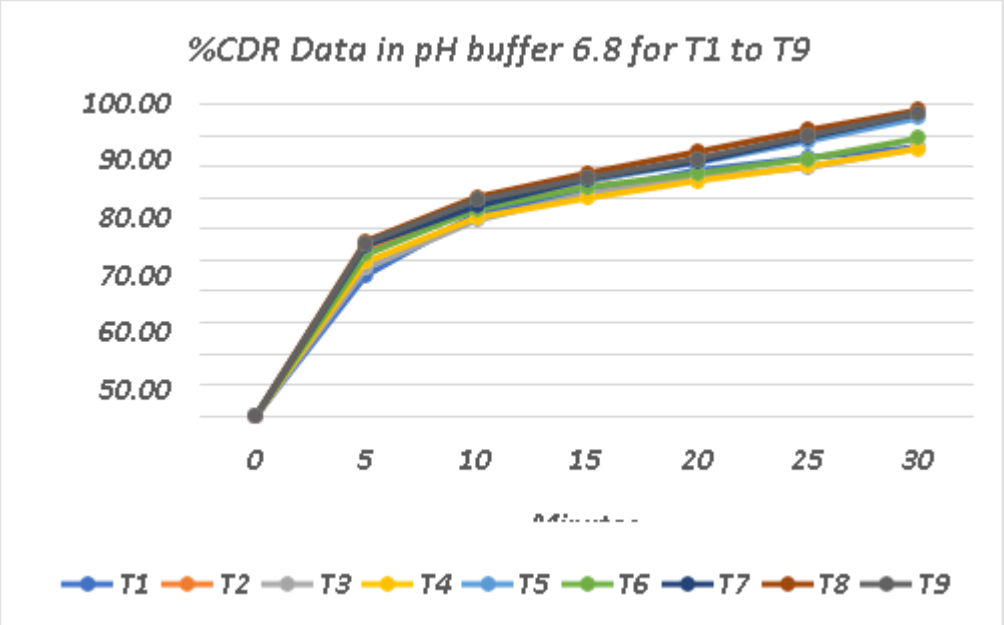


Figure 5: %CDR Data in pH 6.8 buffer for T1 to T9.

Selection of Polymer Range (K1-K6) Results

Table 9: Pre-Compression Results for K1-K6 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 (%)
K1	34.5 ± 0.5	0.44 ± 0.015	0.6 ± 0.02	1.36	36.36
K2	34.55 ± 0.6	0.42 ± 0.012	0.50 ± 0.015	1.19	16.1
K3	33.71 ± 0.7	0.43 ± 0.014	0.5 ± 0.018	1.16	16.27
K4	33.57 ± 0.5	0.44 ± 0.013	0.51 ± 0.016	1.15	15.9
K5	34.76 ± 0.6	0.578 ± 0.011	0.676 ± 0.014	1.17	14.5
K6	32.54 ± 0.8	0.43 ± 0.014	0.52 ± 0.017	1.2	20.93

Table 10: Post-Compression Results for K1-K6 batches.

Batch	Weight Variation (mg) (n=20)	Hardness (kg/cm²) (n=3)	Thickness (mm) (n=3)	Friability (%) (n=10)	Wetting time (sec) (n=6)	Disintegration Time (sec) (n=6)	Drug Content (%)
K1	250.5 ± 1.2	4.5 ± 0.3	3.9 ± 0.1	0.6 ± 0.05	33 ±0.65	99 ± 2.1	87.1 ± 0.4
K2	251.5 ± 1.5	4.7 ± 0.2	4.2 ± 0.1	0.55 ± 0.04	29 ±0.76	78 ± 1.8	91.2 ± 0.3
K3	255.2 ± 1.7	5.5 ± 0.4	4.1 ± 0.1	0.7 ± 0.06	25 ±0.45	50 ± 2.0	95.3 ± 0.5
K4	248.3 ± 1.4	5.3 ± 0.3	4.3 ± 0.1	0.65 ± 0.05	27 ±0.32	58 ± 2.2	96.6 ± 0.4
K5	247.7 ± 1.3	4.7 ± 0.3	3.8 ± 0.1	0.6 ± 0.05	28 ±0.87	71 ± 2.3	90.7 ±0.4
K6	253.4 ± 1.6	5.0 ± 0.3	3.7 ± 0.1	0.55 ± 0.04	32 ±0.26	104 ± 2.1	88.6 ± 0.3

The cumulative drug release data confirms that formulations containing MCC in the range of 15–25 mg and Croscarmellose Sodium in the range of 6-10 mg demonstrated optimal drug release. However, when MCC was used below 15 mg or above 25 mg, and Croscarmellose Sodium was used below 6 mg or above 10 mg, the formulations did not exhibit desirable release kinetics. This was evident in K1 and K6, where drug release and disintegration time were not within the expected limits. These findings emphasize the importance of maintaining the optimal concentration range of MCC and Croscarmellose Sodium to achieve consistent and effective drug release. concentration range of MCC and Croscarmellose Sodium to achieve consistent and effective drug release.

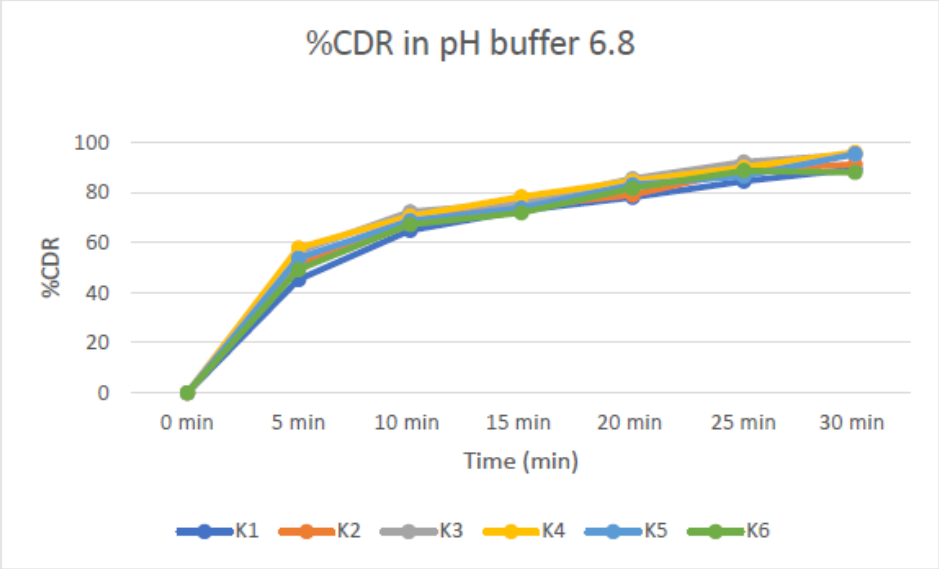


Figure 6: %CDR Data in pH 6.8 buffer for K1 to K6.

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	34.5 ± 0.5	0.564 ± 0.012	0.644 ± 0.015	1.14	12.42
F2	33.9 ± 0.5	0.567 ± 0.010	0.652 ± 0.013	1.15	13.02
F3	33.71 ± 0.7	0.569 ± 0.011	0.656 ± 0.013	1.15	13.26
F4	33.57 ± 0.5	0.587 ± 0.012	0.673 ± 0.015	1.14	12.79

F5	34.76 ± 0.6	0.543 ± 0.009	0.623 ± 0.012	1.15	12.84
F6	32.54 ± 0.8	0.578 ± 0.011	0.676 ± 0.014	1.17	14.5
F7	31.99 ± 0.7	0.553 ± 0.010	0.653 ± 0.014	1.12	11.02
F8	33.6 ± 0.6	0.562 ± 0.009	0.649 ± 0.012	1.16	13.42
F9	34.55 ± 0.6	0.580 ± 0.010	0.659 ± 0.013	1.14	12.02

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)	Wetting time (sec) (n=6)	Disintegration Time (sec) (n=6)	Drug Content (%)
F1	250.5 ± 1.2	4.5 ± 0.3	3.9 ± 0.1	0.6 ± 0.05	25 ±0.24	63 ± 2.1	95.3 ± 0.4
F2	253.1 ± 1.5	5.2 ± 0.3	4.3 ± 0.1	0.55 ± 0.04	25 ±0.43	52 ± 1.8	96.3 ± 0.3
F3	255.2 ± 1.7	5.5 ± 0.4	4.1 ± 0.1	0.7 ± 0.06	26 ±0.24	50 ± 2.0	96.3 ± 0.5
F4	248.3 ± 1.4	5.3 ± 0.3	4.3 ± 0.1	0.65 ± 0.05	24 ±0.32	58 ± 2.2	96.6 ± 0.4
F5	247.7 ± 1.3	4.7 ± 0.3	3.8 ± 0.1	0.6 ± 0.05	28 ±0.31	60 ± 2.3	95.9 ± 0.3
F6	253.4 ± 1.6	5.0 ± 0.3	3.7 ± 0.1	0.55 ± 0.04	26 ±0.57	62 ± 2.1	96.7 ± 0.4
F7	251.5 ± 1.5	4.7 ± 0.2	4.2 ± 0.1	0.55 ± 0.04	25 ±0.75	55 ± 1.8	97.2 ± 0.3
F8	251.3 ± 1.4	5.4 ± 0.3	4.4 ± 0.1	0.65 ± 0.05	27 ±0.86	64 ± 2.4	95.9 ± 0.4
F9	252.5 ± 1.5	5.3 ± 0.2	3.9 ± 0.1	0.54 ± 0.05	23 ±0.53	47 ± 1.9	98.1 ± 0.3

In vitro dissolution studies of factorial batches F1 to F9 in pH 6.8 using USP Type II apparatus revealed that sublingual tablets consistently showed faster drug release. F9 demonstrated the most favourable release behaviour, with 99.5% in 30 minutes (intact) highlighting the impact of optimized concentrations of MCC and Croscarmellose Sodium. These results emphasize that the formulation's balance of binder and superdisintegrant is critical for consistent drug release confirming the robustness of the Sublingual tablet design across all tested batches.

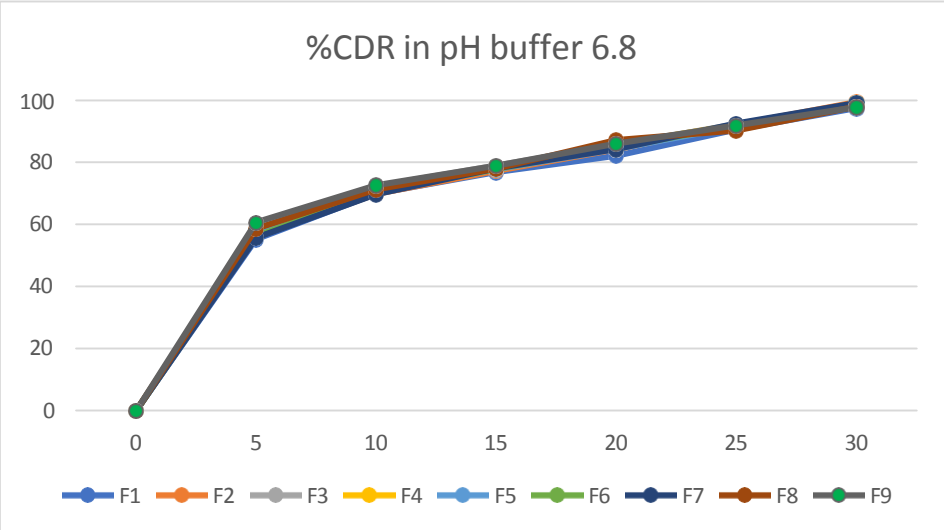


Figure 7: %CDR Data in pH 6.8 for F1 to F9 (Intact tablet).

Experimental Design Results: The statistical validation of the 3² factorial design was conducted using Design Expert software to analyse the influence of MCC (X_1) and Croscarmellose Sodium (X_2) on tablet Disintegration time (Y_1) and percent cumulative drug release (%CDR, Y_2). For Disintegration time (Y_1), a quadratic model proved statistically significant with an F- value of 20.54 and a p-value of 0.0158, confirming model reliability. The terms A^2 (MCC²) and B^2 (Croscarmellose Sodium²) were significant contributors to the response. The model displayed strong fit statistics: $R^2 = 0.9716$, adjusted $R^2 = 0.9243$, and predicted $R^2 = 0.6984$, with Adequate Precision of 12.4099, 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 71.70 and a p-value of 0.0025. Significant factors included A (MCC), B (Croscarmellose Sodium), their interaction (AB), and the quadratic term A^2. The model showed excellent robustness with $R^2 = 0.9917$, adjusted $R^2 = 0.9779$, and predicted $R^2 = 0.9002$, along with a high Adequate Precision value of 22.8508, ensuring strong predictability. Based on statistical and graphical analysis Batch F9 was identified as the optimized formulation showing a tablet Disintegration time of 47 sec and %CDR of 99.5.

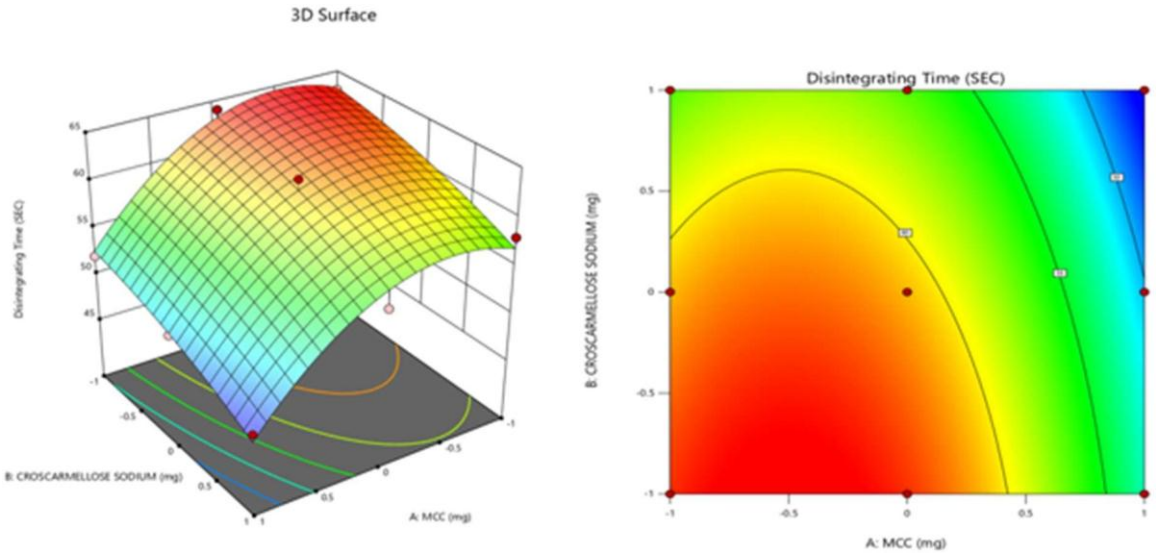


Figure 10: 3D Surface and Contour Plot for Y1-Disintegration Time.

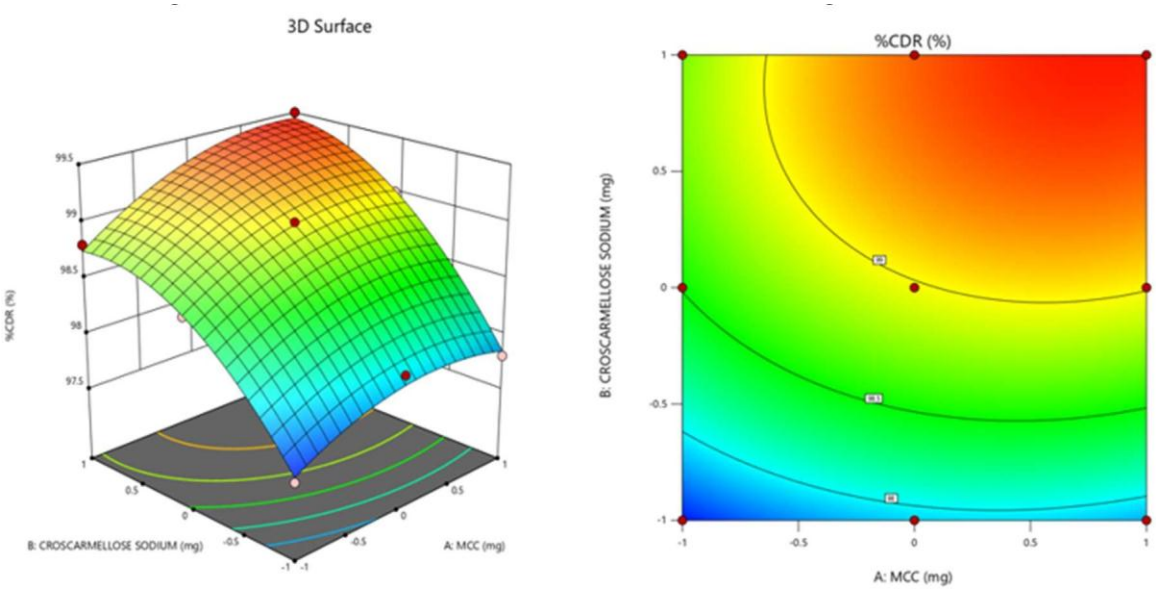


Figure 11: 3D Surface and Contour Plot for Y2-%CDR.

Y1 Disintegration Time: 60.8889 + -5.33333 * A + -3.16667 * B + -3.77768e-15 * AB + -5.33333 * A^2 + -0.833333 * B^2

Y2 %CDR: 98.9778 + 0.25 * A + 0.7 * B + 0.1 * AB + -0.216667 * A^2 + -0.366667 * B^2

Checkpoint batch analysis and optimization based on desirability: The checkpoint batch was formulated at coded values of 0.91 (24.55 mg MCC) and 1.01 (10.02 mg Croscarmellose Sodium), and its experimental evaluation showed excellent agreement with predicted values recording a Disintegration time of 47 ± 1.9 sec and a %CDR of 99.50 ± 0.39%. 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 F9 was selected as the optimized formulation of tablet disintegration time (47 sec) and %CDR (99.5%). 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**
MCC (mg)	Crosscarmellose Sodium (mg)	Disintegration Time (sec)	% CDR (%)
Coded Value: 0.91	Coded Value: 1.01	Predicted Value: 47.4	Predicted Value: 99.50
Actual Value: 24.55	Actual Value: 10.02	Observed Data: 47 ± 1.9	Observed Data: 99.50 ± 0.39

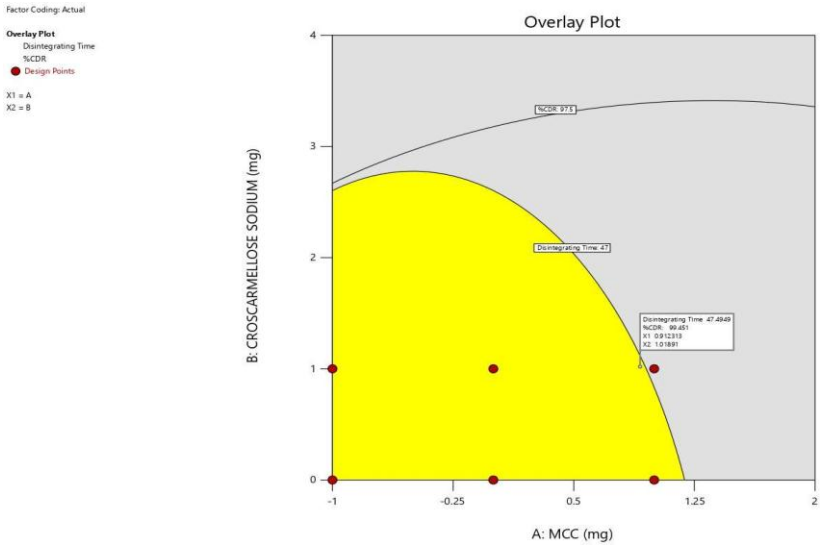


Figure 12: Check Point Batch.

Comparison with Marketed Product: The optimized formulation (Batch F9) was compared with the marketed Vortioxetine Hydrobromide product, Vortidif® (Sun Pharma), to evaluate differences in performance characteristics. Significant differences were observed in dissolution profiles, where intact forms of F9 exhibited notably faster drug release compared to Vortidif®. Intact F9 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 141.04 (intact), while f2 was 18.15, indicating that F9'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 pH 6.8 buffer, at 50rpm, 37.0°C in USP Type II (Paddle) Apparatus, (n=4)		
Time (min)	**Intact Form F9**	**Marketed Form**
0	0	0
5	56.1 ± 0.43	10.5 ±0.29
10	69.8 ± 0.51	19.7 ±0.42
15	77.3 ± 0.67	27.4 ±0.37
20	84.12 ± 0.34	34.8 ±0.55
25	92.1 ±0.46	49.6 ±0.62
30	99.5 ± 0.33	56.7 ±0.49
40		65.9 ±0.65
50		78.9 ±0.56
60		87.4 ±0.47
70		99.8 ±0.37

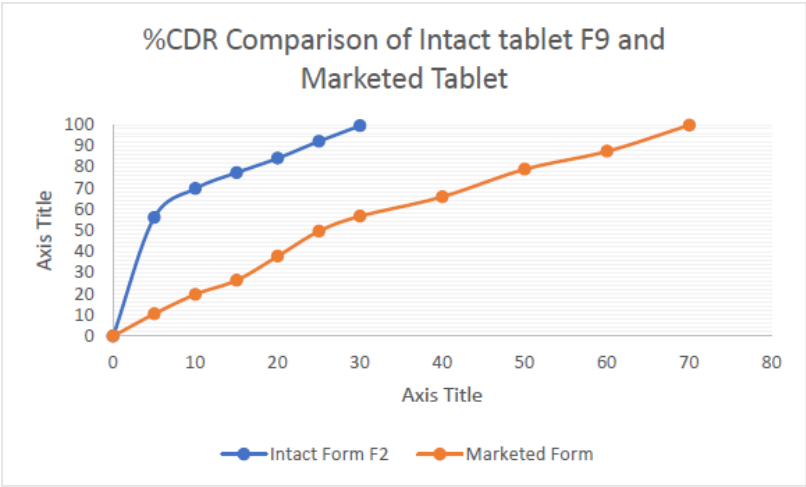


Figure 13: Release Comparison with Marketed Product.

Stability Study: Stability testing of the optimized Sublingual 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 (5.3 ± 0.1 to 5.2 ± 0.2 kg/cm²), disintegration time was within acceptable limits (47 ± 1.9 to 51 ± 3.1 seconds), and %CDR at 30 minutes was virtually unchanged (99.5% to 99.1%). 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)	5.3 ± 0.1	5.2 ± 0.2
Disintegration Time (Sec) (n=3)	47 ± 1.9	51 ± 3.1
Friability (n=10)	0.54 ± 0.05	0.5 ± 0.02
%CDR (%) at 30 minutes (n=3)	99.5 ± 0.39	99.1 ± 0.5

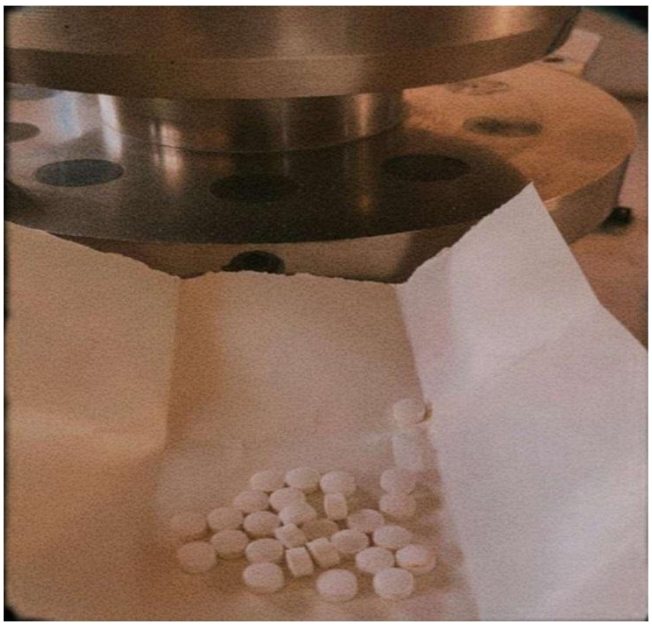


Figure 14: Prepared Sublingual Tablets.

CONCLUSION

In conclusion, the present study successfully developed and optimized a Sublingual tablet of Vortioxetine Hydrobromide 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 1:2 molar ratio showing the best results. The formulation, prepared by direct compression using MCC and Croscarmellose Sodium, was optimized using a 3^2 factorial design. Batch F9 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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