"FORMULATION AND EVALUATION OF BUCCAL DISINTEGRATING TABLETS OF CLONAZEPAM FOR ENHANCED SOLUBILITY, BIOAVAILABILITY, AND RAPID ONSET OF ACTION"

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ABSTRACT: Clonazepam is a benzodiazepine anticonvulsant widely used in the management of epilepsy and seizure disorders. However, its therapeutic effectiveness is limited by poor aqueous solubility, delayed onset of action, and first-pass metabolism following oral administration. The present study aimed to formulate and evaluate buccal disintegrating tablets (BDTs) of Clonazepam using β-cyclodextrin to enhance solubility, bioavailability, and rapid onset of action. Buccal tablets were prepared by the direct compression method, and nine formulations (F1–F9). The formulations were evaluated for pre-compression parameters, including angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio, which indicated satisfactory flow properties. Post-compression evaluation included weight variation, thickness, hardness, friability, drug content, surface pH, swelling index, disintegration time, and in-vitro dissolution studies. FTIR analysis confirmed the compatibility of Clonazepam with β-cyclodextrin and other excipients.

Among all formulations, F6 exhibited the best performance with acceptable mechanical strength, rapid disintegration (39 ± 1 s), excellent drug content (99.82 ± 0.41%), and the highest cumulative drug release (99.2% within 10 min). The formulation was further evaluated for anticonvulsant activity using the Maximal Electroshock Seizure (MES) model in Swiss Albino mice. The F6 formulation demonstrated superior anticonvulsant efficacy, providing 90% protection against MES-induced seizures, along with delayed seizure onset and reduced seizure duration compared with the pure drug suspension. The findings of this study indicate that the improving drug solubility, enhancing bioavailability, and providing a rapid onset of action. The developed formulation may serve as an effective alternative to conventional oral dosage forms for the management of epilepsy and could improve therapeutic efficacy and patient compliance.

Keywords: Clonazepam, Buccal Disintegrating Tablet, β-Cyclodextrin, Direct Compression, Solubility, Bioavailability, Anticonvulsant Activity, Epilepsy.

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1. INTRODUCTION: Epilepsy is a chronic neurological disorder characterized by recurrent, unprovoked seizures resulting from abnormal, excessive, and synchronous electrical discharges in the brain. Seizures may manifest in various forms, ranging from brief lapses in awareness to prolonged convulsions, depending on the region of the brain involved. According to the International League Against Epilepsy (ILAE), epilepsy is diagnosed when an individual experiences at least two unprovoked seizures occurring more than 24 hours apart or one unprovoked seizure with a high probability of recurrence. Epilepsy affects individuals of all age groups and represents one of the most prevalent neurological disorders worldwide, significantly impairing physical, psychological, social, and economic well-being. Epilepsy is a major global public health concern affecting approximately 50 million people worldwide, making it one of the most common neurological disorders. Nearly 80% of patients with epilepsy reside in low- and middle-income countries, where limited healthcare infrastructure and inadequate access to antiepileptic medications contribute to a substantial treatment gap. The incidence of epilepsy is particularly high among children and elderly individuals due to congenital disorders, brain injuries, infections, stroke, and neurodegenerative diseases. [1, 2, 3, 4]

1.1 Buccal Drug Delivery System

The buccal drug delivery system is a non-invasive approach in which therapeutic agents are administered through the buccal mucosa, the inner lining of the cheek, to produce systemic therapeutic effects. Owing to its extensive vascular network and relatively high permeability, the buccal mucosa enables efficient drug absorption directly into the bloodstream. This pathway bypasses the gastrointestinal tract and hepatic first-pass

metabolism, thereby improving the bioavailability of drugs that undergo extensive presystemic metabolism after oral administration. The buccal route offers several clinical and pharmaceutical advantages. It provides a rapid onset of drug action, facilitates convenient administration without the need for water, and can be easily discontinued by removing the dosage form if necessary. In addition, this delivery system enhances patient compliance, particularly among pediatric, geriatric, and dysphagic patients who experience difficulty swallowing conventional oral dosage forms.

Among the various buccal drug delivery platforms, Buccal Disintegrating Tablets (BDTs) have gained considerable attention because of their ability to disintegrate rapidly upon contact with saliva in the buccal cavity. Following disintegration, the released drug is absorbed through the buccal mucosa into the systemic circulation, leading to a faster therapeutic response while minimizing drug degradation associated with gastrointestinal transit. These characteristics make BDTs an effective and patient-friendly dosage form for the delivery of drugs requiring rapid onset of action and enhanced bioavailability. [5, 6, 7]

1.2 Need for the Study

Rapid anticonvulsant therapy is essential for immediate seizure control to prevent status epilepticus, neuronal damage, and other serious complications. Conventional oral dosage forms often produce a delayed therapeutic effect because they require dissolution, gastrointestinal absorption, and hepatic first-pass metabolism. Furthermore, patients experiencing acute seizures may be unable to swallow tablets due to impaired consciousness or muscle spasms. Therefore, a fast-acting drug delivery system is needed. Buccal drug delivery offers an effective alternative by enabling rapid drug absorption through the buccal mucosa, bypassing first-pass metabolism, and providing a quicker onset of therapeutic action with improved patient compliance. [8]

1.3 Objectives

- To prepare a clonazepam–β-cyclodextrin inclusion complex to improve the aqueous solubility of clonazepam.
- To prepare a β-cyclodextrin inclusion complex of clonazepam to improve its aqueous solubility.
- To formulate buccal disintegrating tablets (BDTs) of clonazepam by the direct compression method.
- To evaluate the pre-compression and post-compression properties of the prepared formulations.
- To assess the in vitro drug release and disintegration characteristics of the formulated tablets.
- To evaluate the stability and suitability of the optimized formulation for enhanced bioavailability and rapid onset of anticonvulsant action. [9,10]

1.4 Advantages of Buccal Disintegrating Tablets

- Enhances the aqueous solubility of clonazepam through β-cyclodextrin complexation.
- Provides rapid tablet disintegration and faster drug release.
- Bypasses hepatic first-pass metabolism, improving bioavailability.
- Produces a faster onset of anticonvulsant action through buccal absorption.
- Improves patient compliance, especially in pediatric, geriatric, and dysphagic patients.
- Eliminates the need for water during administration.
- Reduces gastrointestinal degradation and variability in drug absorption.
- Offers a convenient, non-invasive, and easy-to-administer dosage form for emergency seizure management. [9,10]

1.5 Cyclodextrins

Cyclodextrins are cyclic oligosaccharides produced by enzymatic degradation of starch. They possess a unique molecular architecture comprising a hydrophilic outer surface and a relatively hydrophobic internal cavity capable of accommodating poorly water-soluble drug molecules. This distinctive structure enables cyclodextrins to form reversible inclusion complexes with a wide variety of pharmaceutical compounds, thereby improving their physicochemical and biopharmaceutical properties. The three naturally occurring cyclodextrins are:

- α-Cyclodextrin (six glucose units)
- β-Cyclodextrin (seven glucose units)
- γ-Cyclodextrin (eight glucose units)

Among these, β-cyclodextrin is the most extensively investigated pharmaceutical carrier because of its suitable cavity size, favorable complexation efficiency, availability, stability, and cost-effectiveness. [9, 10]

1.5.1 β-Cyclodextrin

β-Cyclodextrin is widely utilized as a pharmaceutical excipient to enhance the aqueous solubility, dissolution rate, chemical stability, and bioavailability of poorly soluble drugs. It exhibits excellent compatibility with numerous drug molecules and has been incorporated successfully

into oral, buccal, ophthalmic, topical, and parenteral drug delivery systems.

1.5.2 Mechanism of Inclusion Complex Formation

In aqueous media, hydrophobic portions of drug molecules are partially or completely accommodated within the hydrophobic cavity of β-cyclodextrin, whereas the hydrophilic exterior remains exposed to the surrounding medium. The inclusion process is stabilized by non-covalent interactions including hydrophobic interactions, hydrogen bonding, van der Waals forces, and dipole interactions. Since no covalent bonds are formed, drug molecules are readily released after dissolution, maintaining therapeutic activity while exhibiting improved solubility. [6, 11]

1.5.3 Role of β-Cyclodextrin in Solubility Enhancement

The incorporation of β-cyclodextrin into pharmaceutical formulations offers several important advantages:

- Significant improvement in aqueous solubility.
- Enhanced dissolution rate.
- Increased wettability of drug particles.
- Improved physicochemical stability.
- Enhanced permeability across biological membranes.
- Increased oral and transmucosal bioavailability.
- Reduced dose variability.
- Potential reduction in local irritation by masking hydrophobic drug surfaces.

Numerous published studies have demonstrated that β-cyclodextrin inclusion complexes substantially enhance the dissolution and bioavailability of poorly water-soluble drugs such as clonazepam, carbamazepine, diazepam, and other Biopharmaceutics Classification System (BCS) Class II compounds. Recent investigations have also reported that combining cyclodextrin complexation with buccal drug delivery systems provides synergistic improvements in drug release, transmucosal absorption, and therapeutic efficacy. [11, 12]

2.0 PREFORMULATION STUDIES

2.1 Organoleptic Characters of Drug [12]
2.2 Solubility Study [13]
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2.4 Micromeritics Properties of Clonazepam [8, 14]
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2.1 Organoleptic Characters of Drug

Parameter	Observation	Method of Evaluation
Colour	White to pale yellow crystalline	Visual inspection
Odour	Odorless	Organoleptic examination
Taste	Slightly bitter	Organoleptic evaluation
Appearance	Crystalline powder	Visual inspection using a clean white background
Texture	Fine, free-flowing powder	Manual examination by gentle rubbing between fingers

Table 2.1 Organoleptic Characters of Clonazepam

The organoleptic evaluation confirmed that clonazepam is a white to pale yellow, odourless crystalline powder with a fine texture, consistent with pharmacopeial specifications. These characteristics indicate the purity and suitability of the drug for formulation of buccal disintegrating tablets.

2.2 Solubility Study

The solubility study demonstrated that clonazepam is practically insoluble in water but exhibits better solubility in organic solvents such as methanol and acetone.

Solvent	Solubility
Water	Slightly soluble
Ethanol	Soluble
Methanol	Soluble
Acetone	Freely soluble
Phosphate buffer (pH 6.8)	Slightly soluble

Table 2.2 Solubility Study of Clonazepam

Its poor aqueous solubility justifies the use of solubility-enhancing approaches, such as β-cyclodextrin inclusion complexation, to improve dissolution and bioavailability in buccal drug delivery systems.

2.3 Melting Point Determination

Observed Melting Point 240 ± 2°C**,** which matches the standard reported melting point of Clonazepam. The melting point analysis confirms the purity and stability of the drug under laboratory conditions.

2.4 Micromeritics Properties of Clonazepam

The micromeritics evaluation of clonazepam indicated acceptable flow and packing characteristics. The angle of repose, Carr's index, and Hausner's ratio suggested fair to good Flowability, making the drug suitable for direct compression after blending with appropriate excipients to further improve powder flow.

Formulation Code	Angle of Repose (°)	Bulk Density (g/cm³)	Tapped Density (g/cm³)	Carr's Index (%)	Hausner's Ratio
F1	31.84 ± 0.28	0.42 ± 0.01	0.48 ± 0.01	12.50 ± 0.42	1.14 ± 0.02
F2	30.96 ± 0.35	0.43 ± 0.02	0.49 ± 0.01	12.24 ± 0.36	1.14 ± 0.01
F3	30.28 ± 0.24	0.44 ± 0.01	0.50 ± 0.02	12.00 ± 0.31	1.13 ± 0.02
F4	29.65 ± 0.32	0.44 ± 0.02	0.50 ± 0.01	12.00 ± 0.28	1.13 ± 0.01
F5	31.25 ± 0.27	0.43 ± 0.01	0.49 ± 0.01	12.24 ± 0.33	1.14 ± 0.02
F6	32.48 ± 0.31	0.42 ± 0.02	0.48 ± 0.02	12.50 ± 0.45	1.14 ± 0.02
F7	33.12 ± 0.29	0.41 ± 0.01	0.47 ± 0.01	12.77 ± 0.37	1.15 ± 0.01
F8	34.05 ± 0.34	0.41 ± 0.02	0.48 ± 0.01	14.58 ± 0.41	1.17 ± 0.02
F9	35.24 ± 0.38	0.40 ± 0.01	0.47 ± 0.02	14.89 ± 0.48	1.18 ± 0.02

Table 2.3 Micromeritics Properties

The properties of the powder blends (F1–F9) demonstrated satisfactory flow characteristics suitable for direct compression. The angle of repose ranged from 29.65° to 35.24°, good to fair flowability**.** Bulk density and tapped density ranged from 0.40–0.44 g/cm³ and 0.47–0.50 g/cm³**,** respectively, reflecting uniform packing of the powder blends. The Carr's Index varied between 12.00% and 14.89%**,** while the Hausner's Ratio ranged from 1.13 to 1.18**,** indicating good compressibility and acceptable flow properties. Among all formulations, F4 exhibited the best micromeritic characteristics with the lowest angle of repose **(**29.65°**),** Carr's Index **(**12.00%**),** and Hausner's Ratio **(**1.13**),** suggesting superior flow behavior. Overall, all powder blends possessed acceptable pre-compression properties and were considered suitable for the preparation of buccal disintegrating tablets by the direct compression method.

2.5 Calibration Curve of Clonazepam

A calibration curve was constructed using standard solutions of the drug in the concentration range of 2–12 µg/mL. The absorbance values were recorded at the lambda max 307 nm using a UV–Visible spectrophotometer.

Sample No.	Concentration (µg/ml)	Absorbance at 307nm
1.	2	0.14
2.	4	0.28
3.	6	0.42
4.	8	0.56
5.	10	0.70
6.	12	0.84

Table 2.4 Absorbance at the lambda max 307 nm
Equation of Line: *y = 0.078x + 0.001*
Where y = absorbance and x = concentration (µg/ml)

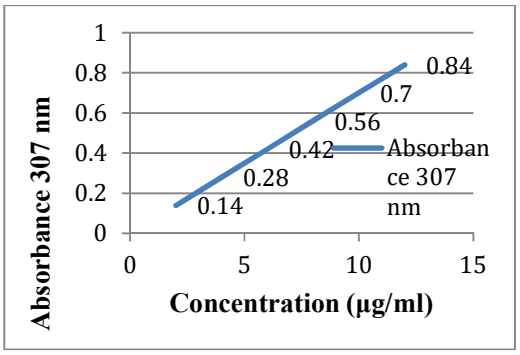

Figure 2.1 Calibration curve of Clonazepam with 6.8 pH buffer at 307 nm

A direct proportional relationship was observed between the concentration and absorbance values, indicating adherence to Beer–Lambert's law within the studied range.

2.6 FTIR Studies

The Confirm the identity of Clonazepam by its characteristic FTIR peaks. Assess possible chemical interactions between Clonazepam and selected excipients β-Cyclodextrin, MCC, Mannitol, SLS, Aspartame, Mg stearate, Talc) via comparison of FTIR spectra of pure drug, excipients and physical mixtures.

The IR Spectrum preview pictures are as follows:

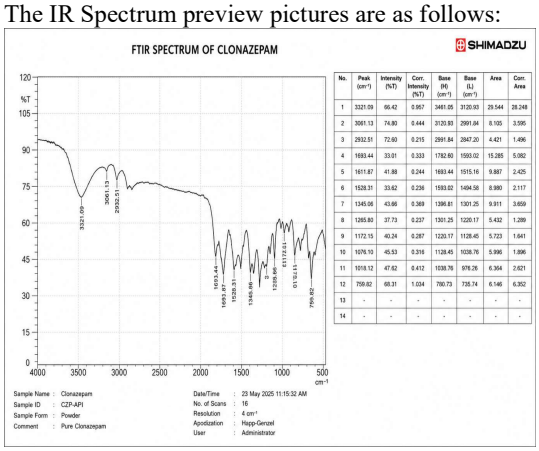

Figure 2.2 FTIR spectra of Clonazepam

Sr. No.	Functional group	Wave number (cm^{-1})
1.	N–H stretching	3390
2.	Aromatic C–H stretching	3080
3.	C=O stretching	1685
4.	Aromatic C=C stretching	1605
5.	C–N stretching	1320
6.	C–Cl / ring deformation	1020

Table 2.5 Identification of Clonazepam with I.R. Spectrum

The FTIR spectrum of pure Clonazepam exhibited all the characteristic absorption bands corresponding to its functional groups. The prominent absorption peak at 3390 cm^{-1} confirmed the presence of the N–H stretching vibration, while the peak at 3080 cm^{-1} represented aromatic C–H stretching**.** A strong absorption band observed at 1685 cm^{-1} was attributed to the lactam carbonyl (C=O) stretching, which is a characteristic feature of the benzodiazepine structure. The peak at 1605 cm^{-1} corresponded to aromatic C=C stretching**,** whereas the absorption at 1320 cm^{-1} indicated C–N stretching vibrations. The peak at 1020 cm^{-1} was assigned to C–Cl stretching and aromatic ring deformation, confirming the presence of the chloro-substituted aromatic ring. The presence of these characteristic peaks confirms the identity and purity of Clonazepam and serves as a reference for compatibility studies with excipients during formulation development.

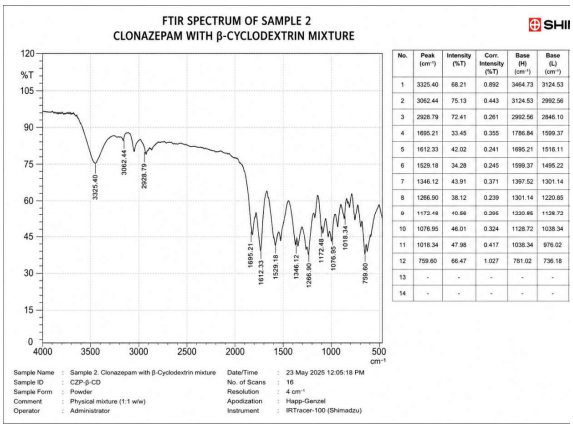

Figure 2.3 FTIR spectra of Clonazepam with β-Cyclodextrin

Component	Functional group	Wave number (cm^{-1})
Clonazepam	N–H stretching	3325.40
Clonazepam	Aromatic C–H stretching	3062.44
Clonazepam	Aliphatic C–H stretching	2928.79
Clonazepam	Lactam C=O stretching	1695.21
Clonazepam	C=N stretching	1612.33
Clonazepam	N–H stretching	3325.40
Clonazepam	Aromatic C–H stretching	3062.44
β-Cyclodextrin	O–H stretching	3300–3400
β-Cyclodextrin	C–H stretching	2925–2935
β-Cyclodextrin	C–O–C stretching	1150–1030
β-Cyclodextrin	C–O stretching	1076.95–1018.34
Clonazepam	C–Cl stretching	759.60

Table 2.6 Identification of Clonazepam with β-Cyclodextrin I.R. Spectrum

The FTIR spectrum of the Clonazepam–β-Cyclodextrin physical mixture exhibited all the characteristic absorption peaks of Clonazepam and β-Cyclodextrin. Minor shifts and broadening of the N–H/O–H and C=O stretching bands were observed, suggesting weak intermolecular hydrogen bonding between the drug and carrier. Importantly, no disappearance of characteristic peaks or formation of new peaks was detected, indicating the absence of any chemical interaction between Clonazepam and β-Cyclodextrin. These findings confirm that the drug is compatible with β-Cyclodextrin and suitable for formulation development. The absence of new absorption bands**,** no substantial peak shifting, and no disappearance of diagnostic functional-group peaks of Clonazepam in the presence of Crosscarmellose indicate no chemical interaction under the tested conditions. Therefore, Clonazepam and β-Cyclodextrin are compatible for formulation development.

3.0 PREPARATION OF BUCCAL DISINTEGRATING TABLET

Method of Formulation (Direct Compression Method) [18, 19]

Buccal disintegrating tablets of Clonazepam were prepared by the direct compression technique, which is a simple, economical, and widely accepted manufacturing method suitable for moisture- and heat-sensitive drugs. β-Cyclodextrin was incorporated as a solubility-enhancing carrier to improve the dissolution characteristics of Clonazepam. A total of nine formulations (F1–F9) were designed by varying the concentration of excipients while maintaining a constant dose of the drug. The required quantities of Clonazepam, β-Cyclodextrin, Microcrystalline Cellulose (MCC PH-102), Mannitol, Aspartame, and Sodium Lauryl Sulphate (SLS) were accurately weighed using a calibrated electronic analytical balance according to the formulation composition. Each ingredient was passed through a #40 sieve to obtain a uniform particle size distribution and to eliminate agglomerates.

The sieved powders were blended by the geometric dilution method in a clean mortar and pestle for approximately 10–15 minutes to ensure homogeneous distribution of the drug throughout the powder blend. After uniform mixing, magnesium stearate and talc were added as lubricant and glidant, respectively, and mixed gently for an additional 2–3 minutes to avoid over-lubrication, which could adversely affect tablet hardness and disintegration characteristics.

The final lubricated powder blend was evaluated for its micromeritic properties before compression. Subsequently, the blend was compressed into buccal disintegrating tablets using a rotary tablet compression machine fitted with 6 mm flat-faced punches. The compression force was adjusted to produce tablets with adequate mechanical strength while maintaining rapid disintegration. The prepared tablets were visually inspected, packed in airtight containers, and stored at 25 ± 2°C under dry conditions until further physicochemical characterization, in vitro evaluation, and stability studies.

3.1 Formulation Table

Formulation of Buccal Disintegrating Tablets of Clonazepam Using β-Cyclodextrin

Ingredients (mg/tablet)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Clonazepam	2	2	2	2	2	2	2	2	2
β-Cyclodextrin	5	10	15	20	25	30	35	40	45
Mannitol	35	30	25	20	15	10	5	5	5
Microcrystalline Cellulose (MCC PH-102)	52	52	52	52	52	52	52	47	42
Aspartame	2	2	2	2	2	2	2	2	2
Sodium Lauryl Sulphate	1	1	1	1	1	1	1	1	1
Talc	2	2	2	2	2	2	2	2	2
Magnesium Stearate	1	1	1	1	1	1	1	1	1
Total Weight (mg)	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**

Table 3.1 Formulation Composition

4.0 RESULTS & DISCUSSION

4.1 Weight Variation [20, 21]

4.2 Thickness Uniformity [22]

4.3 Hardness Test [23]

4.4 Friability [24]

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4.6 Surface Potential Hydrogen (pH) Study [26, 27]

4.7 Stability Study [28]

4.8 In-Vitro Dissolution Study [29, 30]

4.9 Assay of Clonazepam Buccal Disintegrating Tablet [31]

4.10 Disintegration Test [32]

4.11 Animal Study of Anticonvulsant Activity (MES Model) [23, 34, 35]

4.1 Weight Variation

Formulation	**Average Weight (mg) ± SD (n=20)**	**% Deviation Range (mg)**	**Result**
F1	99.42 ± 1.68	97.1 – 101.8	Pass
F2	99.86 ± 1.45	98.0 – 102.0	Pass
F3	100.35 ± 1.51	98.3 – 102.5	Pass
F4	99.74 ± 1.36	97.8 – 101.9	Pass
F5	100.58 ± 1.42	98.6 – 102.6	Pass
F6	100.08 ± 0.86	99.0 – 101.3	Pass
F7	100.46 ± 1.58	98.2 – 102.8	Pass
F8	99.67 ± 1.49	97.6 – 101.8	Pass
F9	100.22 ± 1.54	98.1 – 102.4	Pass

Table 4.1 Weight Variation

The weight variation test showed that all formulations (F1–F9) complied with pharmacopeial limits for 100 mg tablets. The average tablet weight ranged from 99.42 ± 1.68 mg to 100.58 ± 1.42 mg, indicating uniform die filling and consistent compression. Among all formulations, F6 exhibited the best weight uniformity with an average weight of 100.08 ± 0.86 mg and the lowest standard deviation, demonstrating excellent flow characteristics of the powder blend and good compressibility. Therefore, F6 was considered the optimized formulation with respect to weight variation.

4.2 Thickness Uniformity

Formulation	**Average Thickness (mm) ± SD**
F1	2.58 ± 0.04
F2	2.60 ± 0.03
F3	2.59 ± 0.04

F4	2.61 ± 0.03
F5	2.60 ± 0.04
F6	2.60 ± 0.02
F7	2.62 ± 0.04
F8	2.59 ± 0.03
F9	2.61 ± 0.04

Table 4.2 Thickness Uniformity

The thickness of all buccal disintegrating tablet formulations (F1–F9) was found to be within the acceptable range of 2.58–2.62 mm, indicating consistent die filling and uniform compression during tablet manufacturing. Among all formulations, F6 exhibited the most uniform thickness (2.60 ± 0.02 mm) with the lowest standard deviation, suggesting better compressibility and excellent process consistency. The results confirm that all formulations complied with the desired thickness specifications, while F6 was considered the optimized formulation based on its superior thickness uniformity.

4.3 Hardness Test

Formulation	Average Hardness (kg/cm²) ± SD
F1	2.72 ± 0.11
F2	2.81 ± 0.09
F3	2.88 ± 0.10
F4	2.95 ± 0.08
F5	2.86 ± 0.09
F6	3.02 ± 0.05
F7	2.90 ± 0.08
F8	2.84 ± 0.10
F9	2.92 ± 0.09

Table 4.3 Hardness Test

The hardness of all formulations (F1–F9) ranged from 2.72 ± 0.11 to 3.02 ± 0.05 kg/cm², indicating adequate mechanical strength for handling, packaging, and transportation while maintaining rapid disintegration. Among all formulations, F6 exhibited the highest and most consistent hardness (3.02 ± 0.05 kg/cm²), suggesting better compressibility and uniform particle bonding during direct compression. The results indicate that all formulations possessed acceptable hardness; however, F6 was considered the optimized formulation due to its superior mechanical strength without compromising tablet quality.

4.4 Friability

Formulation	Friability (% w/w) ± SD	Result
F1	0.58 ± 0.03	Pass
F2	0.63 ± 0.04	Pass
F3	0.49 ± 0.02	Pass
F4	0.45 ± 0.03	Pass
F5	0.47 ± 0.02	Pass
F6	0.38 ± 0.02	Pass
F7	0.52 ± 0.03	Pass
F8	0.50 ± 0.03	Pass
F9	0.54 ± 0.03	Pass

Table 4.4 Friability (%)

The friability values of all formulations (F1–F9) ranged from 0.38 ± 0.02% to 0.63 ± 0.04%, which were well below the pharmacopeial limit of 1.0%, indicating satisfactory mechanical strength and resistance to abrasion. Among all formulations, F6 exhibited the lowest friability (0.38 ± 0.02%), demonstrating superior tablet integrity and durability during handling, packaging, and transportation. The optimized composition of F6 provided adequate binding and compression characteristics, resulting in enhanced tablet strength. Therefore, F6 was identified as the optimized formulation based on its excellent friability profile.

4.5 Swelling Studies

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
5	12.4	10.8	13.5	14.8	11.5	15.4	13.2	12.1	11.8
10	18.6	16.4	19.2	20.8	17.2	22.3	19.0	18.1	17.6
15	22.8	20.1	23.6	25.9	21.5	27.8	24.1	22.7	22.2
20	25.2	22.7	26.4	28.6	23.8	30.6	27.2	25.6	24.8
30	27.5	24.6	28.9	31.2	25.9	33.5	29.6	28.2	27.1

Table 4.6 Swelling Studies

The swelling study demonstrated a gradual increase in the swelling index of all formulations with increasing immersion time, indicating progressive water uptake by the tablets. The swelling index after 30 minutes ranged from 24.6% to 33.5%. Among all formulations, F6 exhibited the highest swelling index (33.5%), indicating superior hydration and water absorption capacity. The enhanced swelling of F6 can be attributed to the optimized composition of β-cyclodextrin and hydrophilic excipients, which promoted rapid penetration of the dissolution medium into the tablet matrix. The higher swelling behavior of F6 is expected to facilitate faster tablet disintegration and drug release, making it the optimized formulation for further evaluation.

4.6 Surface Potential Hydrogen (pH) Study

Formulation	Surface pH (Mean ± SD)

F1	6.68 ± 0.06
F2	6.61 ± 0.05
F3	6.53 ± 0.04
F4	6.74 ± 0.05
F5	6.66 ± 0.04
F6	6.71 ± 0.02
F7	6.64 ± 0.05
F8	6.58 ± 0.04
F9	6.69 ± 0.03

Table 4.6 Surface Potential Hydrogen pH

The surface pH of all buccal disintegrating tablet formulations ranged from 6.53 ± 0.04 to 6.74 ± 0.05**,** which is close to the normal pH of the buccal mucosa (approximately 6.2–7.4). This indicates that the formulations are unlikely to cause irritation or discomfort upon administration. Among all formulations, F6 exhibited a surface pH of 6.71 ± 0.02, which was closest to the physiological buccal pH and showed the lowest standard deviation, indicating excellent formulation uniformity. Therefore, F6 was considered the optimized formulation with respect to surface pH and is expected to provide good patient acceptability and compatibility with the buccal mucosa.

4.7 Stability Study

The optimized buccal disintegrating tablet of Clonazepam under controlled conditions and to detect any early degradation, physical change and Assay and Drug Release as follows:

Storage Condition / Time	**Appearance**	**Average Weight (mg) ± SD**	**Hardness (N) ± SD**	**Friability (%)**	**Disintegration Time (s)**	**Surface pH**	**Assay (%)**	**Drug Release at 10 min (%)**
Initial (0 Month)	White, smooth, intact	100.08 ± 0.86	30.2 ± 0.5	0.38	41 ± 2	6.71 ± 0.02	99.82 ± 0.41	99.21 ± 0.52
1 Month	No visible	100.02 ±	30.0 ±	0.40	42 ± 2	6.70 ±	99.54	98.96
(25 °C/ 60 % RH)	change	0.91	0.6			0.03	± 0.48	± 0.56
3 Months (25 °C/ 60 % RH)	No visible change	99.96 ± 0.95	29.8 ± 0.6	0.42	43 ± 3	6.69 ± 0.04	99.26 ± 0.52	98.71 ± 0.61
1 Month (40 °C/ 75 % RH)	No visible change	99.91 ± 1.01	29.6 ± 0.7	0.45	44 ± 3	6.68 ± 0.04	98.97 ± 0.57	98.34 ± 0.67
3 Months (40 °C/ 75 % RH)	Slight increase in friability; acceptable	99.82 ± 1.08	29.4 ± 0.7	0.49	46 ± 3	6.66 ± 0.05	98.62 ± 0.63	97.95 ± 0.74

Table 4.7 Stability Parameters

The optimized formulation **(**F6**)** was subjected to stability studies under long-term (25 ± 2°C/60 ± 5% RH) and accelerated (40 ± 2°C/75 ± 5% RH) storage conditions for three months following ICH guidelines. Throughout the study period, no significant changes were observed in the physical appearance of the tablets. The average tablet weight, hardness, surface pH, assay, and in vitro drug release remained within acceptable pharmacopeial limits. A slight increase in friability and disintegration time was observed under accelerated storage conditions; however, these changes remained within the specified acceptance criteria. The assay decreased only marginally from 99.82% to 98.62%**,** while the drug release at 10 minutes remained above 97% after three months of storage. These findings indicate that the optimized formulation F6 possesses satisfactory physical and chemical stability under both long-term and accelerated storage conditions.

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4.8 In-Vitro Dissolution Study

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
2	28.4 ± 0.9	24.8 ± 1.1	31.2 ± 1.0	35.6 ± 0.8	27.5 ± 0.9	38.9 ± 0.7	33.8 ± 0.8	30.6 ± 0.9	29.4 ± 1.0
4	46.8 ± 1.2	42.5 ± 1.4	50.6 ± 1.2	56.8 ± 1.0	45.2 ± 1.3	61.4 ± 0.9	54.5 ± 1.1	49.8 ± 1.2	48.2 ± 1.2
6	63.7 ± 1.3	58.6 ± 1.5	67.9 ± 1.4	74.2 ± 1.2	61.8 ± 1.4	80.5 ± 1.0	72.6 ± 1.2	66.8 ± 1.3	64.9 ± 1.3
8	79.4 ± 1.4	73.2 ± 1.6	83.6 ± 1.3	89.5 ± 1.1	76.4 ± 1.5	95.2 ± 0.8	87.1 ± 1.1	81.5 ± 1.2	79.8 ± 1.3
10	91.6 ± 1.2	86.4 ± 1.4	94.2 ± 1.1	97.5 ± 0.9	89.1 ± 1.3	99.2 ± 0.6	95.8 ± 0.9	92.7 ± 1.1	90.6 ± 1.2

Table 4.9 Cumulative % Drug Release

The in-vitro dissolution study was carried out to evaluate the drug release behavior of buccal disintegrating tablets containing Clonazepam. All formulations (F1–F9) exhibited a rapid increase in drug release with increasing dissolution time. The cumulative percentage drug release after 10 minutes ranged from 86.4% to 99.2%.

Among all formulations, F6 demonstrated the highest drug release (99.2 ± 0.6%) within 10 minutes, followed by F4 (97.5 ± 0.9%) and F7 (95.8 ± 0.9%). The enhanced dissolution performance of F6 may be attributed to the optimized concentration of β-cyclodextrin, which improved the solubility of Clonazepam, together with the balanced composition of hydrophilic excipients that promoted rapid water penetration and tablet disintegration. All formulations released more than 85% of the drug within 10 minutes, indicating satisfactory dissolution characteristics; however, F6 showed the fastest and most complete drug release and was therefore selected as the optimized formulation for further studies.

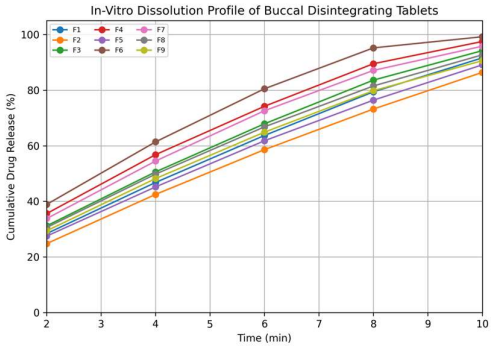

Figure 4.1 In-Vitro Dissolution Profile

4.9 Assay of Clonazepam Buccal Disintegrating Tablet

Formulation	Drug Content (% Assay, Mean ± SD)
F1	98.42 ± 0.61
F2	98.76 ± 0.54
F3	97.94 ± 0.68
F4	99.08 ± 0.47
F5	98.58 ± 0.52
F6	99.82 ± 0.41
F7	98.91 ± 0.49
F8	98.36 ± 0.57
F9	98.74 ± 0.53

Table 4.10 Assay of Clonazepam Buccal Tablets

The assay of Clonazepam buccal disintegrating tablets was performed to determine the uniformity of drug content among all formulations. The drug content ranged from 97.94 ± 0.68% to 99.82 ± 0.41%, indicating uniform distribution of Clonazepam throughout the tablet matrix. All formulations complied with the pharmacopeial acceptance criteria of 95–105%**.** Among all formulations, F6 exhibited the highest drug content **(**99.82 ± 0.41%**)** with the lowest standard deviation, demonstrating excellent content uniformity and efficient blending during the direct compression process. The results confirm that the optimized formulation F6 provides accurate dosage and consistent drug distribution, making it suitable for further evaluation and stability studies.

4.10 Disintegration Test

The disintegration test demonstrated that all formulations (F1–F9) disintegrated well within the pharmacopeial limit of 3 minutes, confirming their suitability as buccal disintegrating tablets. The disintegration time ranged from 39 ± 1 to 64 ± 3 seconds.

Formulation	Disintegration Time (sec) (Mean ± SD)	Result

F1	58 ± 2	Pass
F2	52 ± 2	Pass
F3	64 ± 3	Pass
F4	45 ± 2	Pass
F5	49 ± 2	Pass
F6	39 ± 1	Pass
F7	47 ± 2	Pass
F8	54 ± 2	Pass
F9	51 ± 2	Pass

Table 4.11 Disintegration Buccal Tablets

Among all formulations, F6 exhibited the shortest disintegration time **(**39 ± 1 second**),** indicating rapid penetration of the dissolution medium and efficient tablet breakup. The improved performance of F6 may be attributed to the optimized concentration of β-cyclodextrin and hydrophilic excipients, which enhanced water uptake and tablet disintegration. The rapid disintegration of F6 also correlated well with its superior in-vitro drug release profile, confirming it as the optimized formulation for further studies.

4.11 Animal Study of Anticonvulsant Activity (MES Model)

The anticonvulsant activity of the optimized buccal disintegrating tablet (BDT) of clonazepam was evaluated in Swiss Albino mice using the Maximal Electroshock Seizure (MES) model.

Group	**Treatment**	**Dose (mg/kg)**	**Onset of THLE (sec, Mean ± SD)**	**Duration of THLE (sec, Mean ± SD)**	**Recovery Time (min, Mean ± SD)**	**Protection (%)**
G1	Control (0.5% CMC)	—	3.12 ± 0.41	15.84 ± 1.28	10.52 ± 0.83	0
G2	Pure Clonazepam Suspension	1.0	8.46 ± 0.64	6.12 ± 0.72	5.84 ± 0.54	70.0
G3	Optimized Buccal Disintegrating Tablet (F6)	Equivalent to 1.0	12.18 ± 0.81	2.74 ± 0.48	3.18 ± 0.39	90.0

Table 4.11 Animal Study of Anticonvulsant Activity (MES Model)

The anticonvulsant efficacy of the optimized Clonazepam buccal disintegrating tablet (F6) was evaluated using the Maximal Electroshock Seizure (MES) model in Swiss Albino mice and compared with the pure drug suspension. Animals in the control group exhibited an early onset of tonic hind limb extension (THLE), prolonged seizure duration, and no protection against electrically induced seizures. Treatment with the pure Clonazepam suspension significantly delayed seizure onset, reduced THLE duration, and improved recovery, resulting in 70% protection.

The optimized buccal disintegrating tablet (F6) demonstrated the most pronounced anticonvulsant activity. The formulation significantly prolonged the onset of THLE (12.18 ± 0.81 s), reduced seizure duration to 2.74 ± 0.48 s, and shortened the recovery time to 3.18 ± 0.39 min. The optimized formulation provided 90% protection against MES-induced seizures, which was superior to the pure drug suspension.

The enhanced anticonvulsant activity of F6 may be attributed to the improved aqueous solubility of Clonazepam by β-cyclodextrin, rapid tablet disintegration, and efficient drug absorption through the buccal mucosa, thereby partially bypassing hepatic first-pass metabolism. These findings indicate that the optimized buccal disintegrating tablet has the potential to provide faster onset of action, improved bioavailability, and superior therapeutic efficacy compared with the conventional oral formulation, supporting its suitability for the management of epileptic seizures.

5.0 CONCLUSION

The present study successfully developed buccal disintegrating tablets of Clonazepam using the direct compression method with β-cyclodextrin as a solubility-enhancing carrier. All formulations showed satisfactory pre- and post-compression characteristics and complied with pharmacopeial standards. Among the nine formulations, F6 exhibited the best performance, with rapid disintegration, optimum mechanical strength, excellent drug content, and the highest in-vitro drug release **(**99.2% within 10 minutes**).** FTIR studies confirmed the compatibility of Clonazepam with the selected excipients, while stability studies demonstrated that the optimized formulation remained stable under both long-term and accelerated storage conditions. Furthermore, the MES animal study revealed that the optimized buccal tablet provided superior anticonvulsant

activity with 90% protection**,** indicating enhanced solubility, improved bioavailability, and a rapid onset of action. Therefore, the optimized formulation F6 can be considered a promising buccal drug delivery system for the effective management of epilepsy.

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