CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
SJIF Impact Factor: 7.187

Available online at: http://www.iajps.com *Research Article*

FORMULATION AND EVALUATION OF MOUTH DISSOLVING TABLETS OF CLONAZEPAM USING NATURAL AND SYNTHETIC SUPER DISINTEGRANTS

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Article Received: September 2021 **Accepted:** October 2021 **Published:** November 2021

Abstract:

In this work, natural and synthetic super disintegrants were used to produce mouth dissolving tablets for anticonvulsant drugs utilizing the direct compression method. Plantago ovate mucilage (2-8%) was employed as a natural super disintegrant, while Cross carmellose sodium (2-8%) was used as a synthetic super disintegrant in the direct compression method. Extracting the drug with 0.1 N HCl and pH 6.8 phosphate buffer and measuring the absorbance at 254nm was used to estimate the anticonvulsant drug in the produced tablet formulations.

After that, post-compression parameters were tested on the prepared formulations.

In vitro drug release pattern (0.1 N HCl and pH 6.8 phosphate buffer), stability study (at 40°C/75% RH for 6 months), drug-excipient interaction (IR spectroscopy), and in vitro dispersion time were all compared to formulations including natural super disintigrant.

The overall best formulation formulations were those that contained 8% w/w natural super disintegrant Plantago ovate mucilage (FM8).

Short-term stability analysis of potential formulations revealed that drug content and In vitro dispersion time did not change significantly. There are no drug-excipient interactions, according to IR spectroscopic tests. Natural super disintegrants were found to be superior in compression to synthetic super disintegrantes with enhanced dissolving in the current study.

***Keywords**: Clonazepam, Plantago ovata mucilage, Cross carmellose sodium.*

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Please cite this article in press Abdul Sayeed et al, ***Formulation And Evaluation Of Mouth Dissolving Tablets Of Clonazepam Using Natural And Synthetic Super Disintegrants.,*** *Indo Am. J. P. Sci, 2021; 08(11).*

INTRODUCTION:

The most commonly used solid dose forms are tablets and capsules. Many people, however, have difficulties swallowing tablets and hard gelatin capsules. Dysphasia is the term for difficulty swallowing. This issue has been seen in patients of all ages, but mainly in children and the elderly. As a result, these traditional dosage forms lead to a high rate of noncompliance and inefficient therapy in terms of swallowing, particularly in the case of juvenile, geriatric, or mentally retarded individuals [1-2].

The mentally ill, motion sickness, abrupt episodes of allergic response and coughing are some of the other groups who have difficulty with traditional oral dosage forms. Due to a lack of water, swallowing standard dosage forms can be problematic at times. To address the issues, a new type of solid oral dose form known as mouth-dissolving tablets was developed, which disintegrate and dissolve fast in saliva without the requirement for drinking water [3]. The time it takes for good MDTs to disintegrate varies from a few seconds to nearly a minute [4].

Direct compression techniques are used to create a Clonazepam mouth dissolving tablet that dissolves in the oral cavity without the use of water in seconds when placed on the tongue. "Mouth dissolving tablets are great for active people as well as people who have swallowing problems." As a result, the current study aims to produce and assess clonazepam oral dissolving tablets using various natural and synthetic superdisintegrants in order to address these issues.

Plant-derived polymers have been used as a diluent, binder, and disintegrant in tablets, thickeners, suspensions, gelling agents in gels, and bases in suppository formulations in recent years. Because of their lack of toxicity, low cost, availability, soothing action, and non-irritant nature, natural gums and mucilage are chosen over semi synthetic and synthetic excipients [5-6].

Plantago ovata mucilages were investigated in this research. Because of their high swelling index of, natural superdisntegrants were chosen [7].

This mucilage contains a variety of qualities, including binding, dissolving, and maintaining properties [8]. As a result, mucilages were employed to manufacture anticonvulsant medication fast dissolving tablets using direct compression methods, as well as to investigate the effect of functional differences between natural and synthetic superdisintegrants on tablet qualities.

The goal of this research is to create and test clonazepam mouth dissolving tablet.

- To increase patient adherence.
- To create a low-cost product.
- To speed up the beginning of action of clonazepam.
- To improve clonazepam's efficacy and safety.

Using natural and synthetic superdisintegrants, the goal is to improve the rate of dissolving by increasing the release rate of medicine from the solid oral dosage form.
Clonazepam was used as the model drug in this study.

Clonazepam increases the action of Gamma-aminobutyric acid (GABA), the central nervous system's main inhibitory neurotransmitter. It's used to treat epilepsy, anxiety, and the symptoms of alcohol withdrawal [9].

MATERIALS AND METHODS:

Clonazepam was bought from Octis Research Laboratories in Chennai, Crosscarmellose Sodium from Ascot Pharma Ltd in Mumbai, and the other materials from SD Fine Chemicals Pvt Ltd in Mumbai.

Determination of λmax and standard Calibration Curve of Clonazepam in distilled water:

10 mg of Clonazepam were carefully weighed and dissolved in 100 mL of methanol, with 20 mL of preparation being swallowed and brought up to 100 mL with distilled water. Then, in a volumetric flask, 2,4,6,8,10 ml was taken and built up to 10 ml with distilled water. The absorbance of these samples was measured using a UV spectrophotometer set to 254 nm. After that, the absorbance readings were plotted against the drug concentration, and a Clonazepam standard curve was created, as shown in table 3 and figure 1.

Determination of λmax and standard Calibration Curve of Clonazepam in pH 6.8 phosphate buffer:

Weighed 10 mg of Clonazepam into a 100 ml volumetric flask and dissolved in less amount of water and diluted with phosphate buffer of pH 6.8 up to the mark to make a 1 mg/mL stock solution. 1 ml was taken from the stock solution and diluted up to 10 ml in a volumetric flask to make a standard solution with a concentration of 100µg /ml. Dilutions of 10-50 µg/ml were prepared using phosphate buffer pH 6.8 and absorbance was measured at 254 nm as reported in Table 4 and Figure 2.

Isolation of Plantago ovate mucilage:

For the isolation of mucilage, seeds of *Plantago ovata* were used. They were soaked in distilled water for 48 hours and then boiled for 1 h for complete release of mucilage into water. The material collected was squeezed through muslin cloth for filtering and separating out the marc. Then, an equal volume of acetone was added to the filtrate so asto precipitate the mucilage. The separated mucilage was dried (in oven at temperature less than 60^0), powdered, sieved (#60) and stored in a desicator until further use [10].

FORMULATION DEVELOPMENT:

The best types of synthetic and natural superdisintegrants are incorporated in the formulation of MDTs like, Cross carmellose sodium and *Plantago ovate*. Before the tablet formulation the superdisintegrants was screened out and taken into formulation with other excipients for compression by direct compression method. The superdisintegrant shows good properties like, when the tablet comes in contact with liquid, it breaks up into smaller particles because of superdisintegrants are swells, hydrate, change the volume and produce a disruptive change in the tablet.

In this work, the direct compression method with aid of synthetic and natural superdisintegrants was attempted for the formulation development of mouth dissolving tablets of clonazepam. The clonazepam tablets are available in 0.5mg, 1mg, 2mg doses in the market. Dose of 2mg is selected for the present study.

The development of the formulation of mouth dissolving tablets in the present study was mainly based on the type and concentration of synthetic and natural superdisintegrants. Synthetic and natural super disintegrates in different concentrations (2%, 4%, 6% and 8%) were used so as to get tablets with good physical properties. Ingredients like Microcrystalline cellulose and mannitol as directly compressible diluents, magnesium stearate and talc as lubricant, aerosil as flow promoter, aspartame as sweetening agent and pineapple flavor as enhance the palatability.

Preparation of powder blends of drug and excipients:
The powder blends for mouth dissolving tablets were prepared by taking ingredients given in Table no. 1. All the ingredients were passed through 60 mesh sieve separately and collected. Then ingredients were weighed and mixed in a geometrical order. First Microcrystalline cellulose, Mannitol and Super disintegrants were weighed and mixed together in glass mortar using a pestle. Then Drug and Aspartame were mixed and added in first mixer. Then Magnesium stearate, Talc and Aerosil were added and mixed. Finally flavor (Pineapple flavor) was added and mixed for 10-20 minutes.

Before tablets preparation, the mixture blends of all the formulations were subjected for compatibility studies (IR) and pre-compression parameter like Angle of repose, Bulk density, Tapped density, Percentage compressibility and Hausner ratio.

Preparation of Clonazepam Mouth dissolving tablets by direct compression:
Clonazepam mouth dissolving tablets were prepared in nine formulations CZP0 to CZP8 using the ingredients given in the Table no.1. Keeping the total weight of the tablet (150mg) kept constant in all the formulations. All the ingredients were passed through 60 mesh sieve separately and collected. Then ingredients were weighed and mixed in a geometrical order.

First microcrystalline cellulose, mannitol and super disintegrants were weighed and mixed together in glass mortar using a pestle. Then drug and aspartame were mixed and added in first mixer. The blend was then lubricated by mixing with magnesium stearate, talc and aerosil. Finally, the mixture was blended with flavor. Then the powder blend was compressed. Tablets were prepared using 8 mm round flat-faced punches of the 16-station (Cadmach Machineries ltd.) rotary tablet compression machine. Compression force was kept constant for all formulation.

The mouth dissolving tablets were prepared and subjected to post compression parameters like hardness, friability, thickness, and weight variation, *In-vitro* dispersion time, wetting time, water absorption ratio, drug content, *In-vitro* disintegration time and *In-vitro* dissolution.

Table no. 1: Formulation of Clonazepam Mouth Dissolving Tablets

S.N0	Ingredients (mg/tab)	CZP0	CZP1	CZP2	CZP3	CZP4	CZP5	CZP6	CZP7	CZP8
1	Clonazepam	2	2	2	2	2	2	2	2	2
2	Cross carmellose sodium	---	3	6	9	12	---	---	---	---
3	Plantago ovata mucilage	---	---	---	---	---	3	6	9	12
4	Microcrystalline cellulose	50	50	50	50	50	50	50	50	50
5	Aspartame	5	5	5	5	5	5	5	5	5
6	Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
7	Talc	1	1	1	1	1	1	1	1	1
8	Aerosil	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
9	Pineapple flavour	1	1	1	1	1	1	1	1	1
10	Mannitol	89	86	83	80	77	86	83	80	77
	TOTAL	150	150	150	150	150	150	150	150	150

PRE-COMPRESSION ASSESSMENT OF POWDER BLEND [11]:
Different parameters were evaluated for prepared powder blend using following methods.

Angle of repose:
The angle of repose is calculated by using fixed funnel method. In this method the funnel was fixed to a stand at definite height (h). The graph paper was placed on a flat horizontal surface. Then powder blend was allowed to fall freely on the paper through the funnel, until the apex of the conical pile just touches the tip of the funnel.
The height and radius of pile was noted and from this angle of repose was determined with the help of given formula.
The formula for calculating angle of repose is

$$\theta = \tan^{-1}(h / r)$$
$$\tan(\theta) = h / r$$

Bulk Density:
It was measured by pouring the accurately weighed 2g of powder blend (passed through 20 mesh sieve) was placed in a 10ml graduated measuring cylinder. And then initial volume was observed, this initial volume is called as bulk volume.
From this the bulk density was calculated by using the following formula.

Bulk-density = Mass of the powder/Bulk volume.

Tapped Density:
Accurately weighed amount of powder blend was placed in a measuring cylinder and the volume was measured by tapping of powder for 500 times and the tapped volume was noted. The tapped density was calculated by using following formula.

Tapped-density= Mass of the powder/Tapped volume.

Compressibility Index:
Compressibility index is indicates the powder flow properties. It is expressed in percentage.
Compressibility index is based on the bulk density and tapped density, the percentage compressibility of the powder blend was determined by using the following formula.

Carrs Index = (Tapped-density-Bulk density/Tapped density) x 100

Hausners Ratio:
Hausner ratio is an indirect index of ease of powder flow. It was calculated by thefollowing formula.

Hausner's ratio = Tapped density/ Bulk density

POST-COMPRESSION ASSESSMENT OF POWDER BLEND [11-14]:
Thickness:
Using Digital vernier Calipers, the thickness of the tablets was assessed. The physical qualities of the material to be compressed under compression force, as well as the die filling, determine the thickness. Three tablets were chosen at random from each formulation and the mean and standard deviation were

computed. It's in millimeters.

Hardness:
The tablet hardness was determined using a Monsanto hardness tester. The tablet was held between two jaws, one fixed and the other movable. The scale was set to zero load and then steadily increased until the tablet broke. The load value at that moment is used to determine the tablet's hardness. Three tablets were chosen at random from each formulation, and the mean and standard deviation were computed. It's measured in kilogrammes per square metre.

Friability:
To determine the effect of abrasion and shocks on tablets, a friability test was done. The % friability of the tablets was calculated using the Roche friabilator. The tablet is subjected to abrasion and shock in a plastic chamber that rotates at 25 rpm and drops a tablet from a height of 6 inches every revolution. In the friabilator, a pre-weighted sample of tablets was put and turned 100 times.

%Friability= (Initial Weight- Final weight / Initial Weight) X 100

Weight Variation:
The weight variation test was carried out according to I.P. Twenty tablets were chosen at random from each batch and weighed individually. The total weight of all tablets was then used to establish the average weight. The average weight was compared to the individual weights. If no more than two tablets are outside the percentage limit and no tablet differs by more than two times the percentage limit, the tablets pass the weight variation test.

***In-vitro* Dispersion Time:**
Dropping a tablet into a Petridis containing 10ml of phosphate buffer pH 6.8 solutions at 37 ± 5^{0}c was used to determine in-vitro dispersion time. Three tablets were chosen at random from each batch and the time it took for a tablet to completely disperse was monitored. The time required for *in-vitro* dispersion is measured in seconds.

Wetting Time:
In a Petri dish (6.5cm) holding 6 ml of water, a double-folded piece of tissue paper was inserted. The tablet was placed on the paper, and the time it took for the tablet to be completely wet was recorded in seconds. By keeping the water at 370°C, the procedure was slightly adjusted. The time it takes for a tablet to disintegrate while it is held immobile in a Petri dish is called the wetting time.

Water Absorption Ratio:
In a 6.5cm Petri dish holding 6 ml of water, a piece of tissue paper folded twice was inserted. The time it took for the tissue paper to be completely wet was measured using a tablet. After that, the wetted pill was weighed.
Water absorption ratio, R, was determined using following equation.

R = 100 (Wa-Wb) / Wb

Where,
Wa = Weight of the tablet after absorption.
Wb = Weight of the tablet before absorption.

Disintegration Time:
The process of breakdown of a tablet in to a smaller particle is called as disintegration. The *in-vitro* disintegration time of a tablet was determined using disintegration apparatus as per I.P specifications.

I.P specifications:
Place one tablet in each of 6 tubes of the basket. Add a disc to each tube and run the apparatus using pH 1.2 maintained at 37°± 2°C as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute in the pH 1.2 maintained at 37° ± 2°C. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded.

Drug content:
Three tablets weighed and crushed in a mortar then weighed powder contain equivalent to 10mg of drug transferred in 100ml of phosphate buffer pH 1.2. Subsequently, the solution in volumetric flask was filtered, suitable dilutions will be carried out. And final solution was analyzed at 254nm using UV-visible spectrophotometer Shimadzu UV- 2450, Japan.

***In-vitro* Dissolution Studies of Clonazepam:**
In vitro dissolution of mouth dissolving tablets were studied in USP type-II dissolution apparatus (Electrolab) employing a paddle stirrer. 900 ml of phosphate buffer P^H 6.8 was used as dissolution medium. The stirrer was adjusted to rotate at 50 rpm. The temperature of dissolution medium was maintained at 37±0.5ºC throughout the experiment. One tablet was used in each test. Samples of dissolution medium (5 ml) were withdrawn by means of syringe fitted with pre-filter at known intervals of time and analyzed for drug release by measuring the absorbance at 254nm. The volume withdrawn at each time interval was replaced with fresh quantityof dissolution medium. Cumulative percent released was calculated and plotted against time. The results are given in table no.9 to 11 and figure no.3 to 5.

KINETIC STUDY [15]:
The results of *In vitro* release profile obtained for all the formulations were plotted in modes of data treatment as follows:

1. Zero – order kinetic model – Cumulative % drug released versus time.
2. First – order kinetic model – Log cumulative percent drug remaining versus time.
3. Higuchi model – Cumulative percent drug released versus square root of time.
4. Korsmeyer equation / Peppas model – Log cumulative percent drug released versus log time.

Zero order kinetics:
Zero order release would be predicted by the following equation:

$$\mathbf{At=A0-k0t}$$

Where,
At = Drug release at time‘t’
A0 = Initial drug concentration.
K0 = Zero-order rate constant (hr^{-1})
When the data is plotted as cumulative percent drug release versus time, if the plot is linear then the data obeys Zero – order kinetics and its slop is equal to Zero order release constant k0.

First Order Kinetics:
First – order release could be predicted by the following equation:

$$\mathbf{Log\ C = log\ Co - Kt / 2.303}$$

Where,

C = Amount of drug remained at time‘t’
C0 = Initial amount of drug.
K = First - order rate constant (hr^{-1})

When the data plotted as log cumulative percent drug remaining versus time, yields a straight line, indicating that the release follow first order kinetics. The constant ‘K1’ can be obtained by multiplying 2.303 with the slop value.

Higuchi’s Model:
Drug release from the matrix devices by diffusion has been described by following Higuchi’s classical diffusion equation:

$$Q = [D\epsilon / \iota (2A - \epsilon Cs) Cst]\ ½$$

Where,

Q = Amount of drug release at time‘t’
D = Diffusion coefficient of the drug in the matrix. A = Total amount of drug in unit volume of matrix.
Cs = Solubility of drug in the matrix.
Є = Porosity of the matrix.
ι= Tortuosity.
T = Time (hrs at which q amount of drug is released).

Above equation can be simplified as if we assume that ‘D’, ‘Cs’ and ‘A’ are constant. Then equation becomes.

$$Q = kt1/2$$

When the data is spited according to equation i.e. cumulative drug release versus square root of time yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to ‘K’.

Korsmeyer Equation / Peppas Model:
To study the mechanism of drug release from the liposomal solution, the release data was also fitted to the well- known exponential equation which is often used to describe the drug release behavior from polymeric systems.

$$Mt / M\alpha = Ktn$$

Where,

Mt / Mα = The fraction of drug released at time‘t’.

K = Constant incorporating the structural and geometrical characteristics of the drug polymer system.
n = Diffusion exponent related to the mechanism of the release.

Above equation can be simplified as follows by applying long on both sides,

$$\text{Log } Mt / M\alpha = \text{Log } K + n \text{ Log } t$$

STABILITY STUDIES [16]:
Stability studies of pharmaceutical products were done as per ICH guidelines. These studies are designed to increase the rate of chemical or physical degradation of the drug substance or product by using exaggerated storage conditions. Basically, there are two types of stability studies:

1. **Short -term stability studies**
2. **Long- term stability studies**

Table no: 2: Stability conditions according to ICH guidelines

Types	Conditions		Minimum time period at submission (month)
	Temperature (^{0}C)	Relative humidity(%)	
Short-term testing	40± 2	75 ± 5	6
Long-term testing	25 ± 2	60 ± 5	12

Method:

Selected formulations were stored at different storage conditions at elevated temperature such as 25°C± 2^{0}C / 60% ± 5% RH, and 40^{0}C ± 2^{0}C/ 75% ± 5% RH for 90 days. The samples were withdrawn at intervals of 30 days and checked for physical changes, hardness, friability, drug content and percentage drug release.

PHYSICOCHEMICAL EVALUATION OF DRIED POWDERED MUCILAGE [17-20]:

The following physicochemical tests for mucilage

- **Organoleptic properties:** Organoleptic properties such as physical appearance, colour, odour and taste of dried powdered mucilage were determined.
- **Solubility test:** The solubility of dried powdered mucilage was determined by adding a pinch in the solvent such as water.
- **Total ash:** Total ash was determined on 1 gm of dried powdered mucilage.
- **Loss on drying:** Loss on drying was determined for an appropriate quantity of dried powdered mucilage at 105^{0}C for 5 hours.

LOD (%) = (Wt of water in sample/ Wt of dry sample) × 100

- **Swelling factor:** Swelling factor was determined by putting 1 gm of the drug in the measuring cylinder (25 ml capacity) in 20 ml water with occasional shaking. The volume occupied by the seeds after 24 hours of wetting is measured.
- **Flow properties of dried mucilage powder:** The flow properties of dried mucilage powder such as Angle of repose, Bulk density, Tapped density, Cars index and Hausners ratio were determined.

TABLE NO. 3: PHYSICOCHEMICAL TESTS FOR MUCILAGE

S.no	Physico chemical parameters	*Plantago ovata* mucilage
1	Solubility	Slightly soluble in water
2	Loss on drying (%)	10±0.011
3	Swelling ratio	9±0.145
4	Total ash (%)	4±0.021
5	Angle of repose	26.56^0±0.251
6	Bulk density g/cm^3	0.42±0.055
7	Tapped density g/cm^3	0.46±0.085
8	Carrs index (%)	10.03±0.012
9	Hausners ratio	1.08±0.056

All parameters (±SD) n=3

FTIR Spectroscopy:

The interaction between drug and excipients was studied by using FTIR spectroscopy. In the preparation of tablet formulation, drug and excipients may interact as they are in close contact with each other, which could lead to the instability of drug. Preformulation studies regarding the drug-excipients interaction are therefore very critical in selecting appropriatepolymer. FTIR spectroscopy was employed to ascertain the

compatibility between drug and the selected excipients. Potassium bromide, pure drug and the excipients were heated to 105^0C for one hour in a hot air oven to remove the moisture content. Then in presence of IR lamp, potassium bromide was mixed with drug and or excipients and the spectra were taken. FTIR spectrum of drug was compared withFTIR spectra of excipients.

RESULT AND DISCUSSION:

Table 4: Standard calibration curve of Clonazepam in Distilled water.

Concentration'sµg/ml	Absorbance			
	I	II	III	Mean ± SD
0	0.000	0.000	0.000	0.000±0.000
2	0.163	0.161	0.165	0.153±0.002
4	0.285	0.287	0.283	0.295±0.004
6	0.345	0.347	0.349	0.427±0.003
8	0.476	0.480	0.484	0.573±0.002
10	0.665	0.668	0.671	0.698±0.005

Figure-1: Standard graph of clonazepam in distilled water (λmax 254 nm)

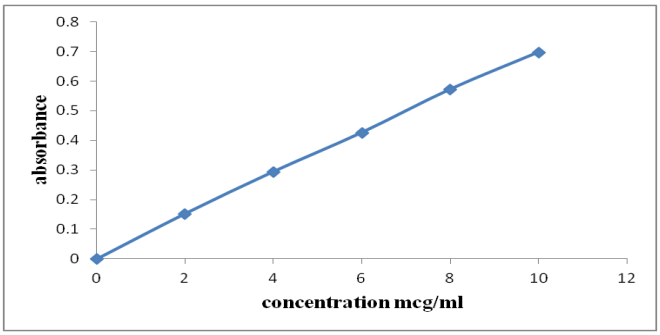
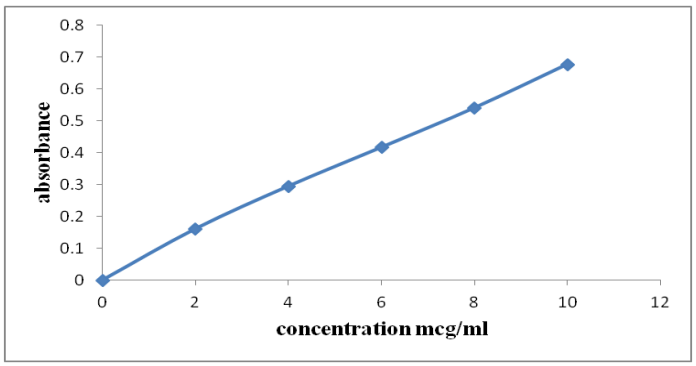


Table 5: Standard calibration curve of Clonazepam in phosphate buffer.

Concentrationsµg/ml	Absorbance			
	I	II	III	Mean±SD
0	0.000	0.000	0.000	0.000±0.000
2	0.171	0.173	0.175	0.161±0.004
4	0.297	0.294	0.296	0.295±0.006
6	0.345	0.347	0.349	0.417±0.003
8	0.588	0.592	0.590	0.541±0.005
10	0.695	0.698	0.703	0.678±0.004

Figure-2: Standard graph of clonazepam in pH 6.8 phosphate buffer (λ_{max} 254 nm)



Pre-compression parameters of Clonazepam powder blend:

Powder blend for direct compression containing drug and various excipients were subjected for pre compression parameters (micromeritic properties) to study the flow properties of powder blend to achieve uniformity of tablet weight.

The bulk density of powder blend was found to be in the range of 0.56 to 0.63 g/cc, tapped density was found to be in the range of 0.66 to 0.69 g/cc, angle of repose was found to be in the range of 20.45o to 26.48^{o}, Carr's index was found to be in the range of 5.69 % to 13.38%, Hausner's ratio was found to be in the range of 1.01 to 1.08.

All the formulations show good results and lies within the acceptable range which indicate good flow properties. The results of all the pre compression parameters are given in table no 6.

Table no: 6: Pre-compression parameters of Clonazepam powder blend CZP0– CZP8

Formulation code	Bulk Density (g/cc)	Tapped density (g/cc)	Angle of repose (degree)	Carr's index (%)	Hausner's ratio
CZP0	0.56	0.66	26.48	13.38	1.08
CZP1	0.58	0.67	23.68	11.10	1.08
CZP2	0.61	0.69	24.08	10.12	1.01
CZP3	0.60	0.66	20.45	8.89	1.03
CZP4	0.59	0.67	21.43	9.00	1.03
CZP5	0.63	0.68	23.10	8.41	1.03
CZP6	0.61	0.67	24.20	6.79	1.04
CZP7	0.62	0.69	23.72	6.26	1.02
CZP8	0.60	0.69	22.56	5.69	1.03

All results expressed as mean ± SD, n = 3

Post Compression parameters of Clonazepam Mouth dissolving tablets:

All the tablet formulations were subjected for organoleptic, physical and chemical evaluation. Shape and color, Weight Variation, Thickness, Hardness, Friability, Drug Content, Wetting time, Water absorption ratio, Disintegration time, *In vitro* dispersion time, *In-vitro* drug release studies were carried out.

Appearance of the tablets: Each formulation batch's tablets were chosen at random and evaluated under

a microscope for shape. The tablets were concave and round in shape. Without any capping or laminating, all of the tablets had a very good appearance and were considered to be satisfactory.

Thickness: The thickness of all formulations was determined to be in the range of between 2.11±0.12 mm to 2.19±0.06 mm and summarized in table no.7.

Weight Variation: The percent Weight Variation of all the formulations were summarized in table. All the tablets were passed weight variation test as the % variation was within the pharmacopoeial limits of 7.5%. It was found to be from 147.1±1.59 to 150.5±1.44 and the weight of the all tablets was found to be uniform due to good flow property and compressibility of all the formulations.

Hardness: The hardness of tablets was tested using Pfizer hardness tester to find out whether they could retain their physical shape or not. The hardness of all the tablets was found to be in the range of 2.76±0.5 kg/cm^{2}to 3.13±0.1 kg/cm^2 and the results were summarized in table no.7.

Friability: Tablet strength was tested by Roche Friabilator and the tablets of all formulations showed very good friability with less than **0.53%** which is well and within wide accepted range of Pharmacopoeial limit (1.0%) and results were given in table no.7.

Drug Content uniformity:
The uniformity of drug content was tested for all formulations, and the mean value and standard deviation of all formulations were determined; low standard deviation values suggest uniform drug content within the tablets. The percent drug content of all the pills was found to be between 98.98±1.52 and 101±2.02 percent (within permissible ranges of ±5%), as shown in table 7.

Table no: 7: Post Compression parameters of formulations CZP0-CZP8

Formulation code	Weight Variation *	Thickness*	Hardness**	Friability**	Drug Content**
CZP0	147.1±1.59	2.18±0.04	2.76±0.5	0.59	98.98±1.52
CZP1	148.5±2.59	2.16±0.01	3.10±0.5	0.55	101±1.09
CZP2	149.3±2.23	2.21±0.01	3.11±0.5	0.59	99.95±2
CZP3	150.0±1.44	2.11±0.12	3.13±0.1	0.49	99.95±1.01
CZP4	148.4±1.87	2.16±0.06	2.90±0.1	0.55	101±1.57
CZP5	150.5±0.50	2.19±0.01	2.76±0.5	0.56	99.58±1.52
CZP6	149.1±1.49	2.17±0.12	2.81±0.1	0.49	99.80±1.14
CZP7	149.5±2.21	2.19±0.06	2.83±1.4	0.56	100±1.57
CZP8	147.4±1.61	2.12±0.02	3.11±0.5	0.57	101±2.02

All results expressed as mean ± SD, n = 3

Water absorption ratio:
The water absorption ratio of all the formulations was found to be 48.22±3.8% to 144±1 %. The results were depicted in Table.No.8.

Disintegration-Time:

The disintegration time of all the formulations was found to be 18±1.12 sec to 279±1.62 sec. The results were depicted in Table.no.8.

Wetting time:

The Wetting time of all the formulations was found to be 20.98±1.5 sec to 103±4.91sec. The results were depicted in Table.no.8.

***In vitro* dispersion time:**

The *In vitro* dispersion time of all the formulations was found to be 23.11±0.15 sec to 98±1.2sec. The results were depicted in Table.no.8.

Table no 8: Post compression parameters of formulations CZP0 _ CZP8

Formulation Code	Wetting time (sec)	Water absorption ratio (%)	Disintegration time (sec)	*In vitro* dispersion time (sec)
CZP0	103±4.91	144±1	279±1.62	98±1.2
CZP1	47.11±1.0	48.22±3.8	73±0.34	48.03±2.47
CZP2	39.26±0.7	59.21±1.5	64±0.11	43.0± 2.10
CZP3	36.33±1.52	67.65±1.1	46±0.29	35.42± 1.90
CZP4	**27.19±1.5**	**78.12±1.14**	**26±0.45**	**29.94± 0.70**
CZP5	48.64±2.08	52.12±1.61	60±1.55	40.66±1.52
CZP6	39.32±1.01	66.46±2.9	48±1.82	37.66±1.52
CZP7	29.19±1.12	72.46±2.9	35±2.05	29.33±2.51
CZP8	**20.98±1.5**	**81.11±1.11**	**18±1.12**	**23.11±0.15**

All results expressed as mean ± SD, n = 3

***IN-VITRO* DRUG RELEASE STUDIES:**

Tablets containing clonazepam were studied for *In-vitro* drug release studies as per the procedure described in methodology. All formulations were subjected for dissolution studies. The samples were withdrawn at specified time intervals and analyzed by UV-Visible Spectrophotometer at 254nm.

Drug release profile was studied using percentage drug release versus time (hr) plot. The results were depicted in Table No.9 to 11 and figure no 3 to 5. Formulations CZP0,CZP1,CZP2,CZP3,CZP4 and CZP5, CZP6, CZP7, CZP8 showed 36.84±0.6%,68.56±1.67%,73.30±1. 78%,80.66±1.54%,85.53±1.54%, and73.56±1.67%,76.30±1.8% 83.66±1.54%,97.93±1.54% respectively at 30 minutes.

Among all formulations CZP8 containing 8% plantago ovate mucilage as natural super disintigrant was found to be promising and has shown faster release of drug.

Table no. 9: *In –Vitro* drug release characteristics of Clonazepam without Superdisintegrant (CZP0)

Time (Min)	**Cumulative % of drug release without Superdisintegrant (CZP0)**
0	0
05	12.27±1.4
10	16.21±0.5
15	22.07±1.2
20	26.19±1.4
25	32.61±1.9
30	36.84±0.6

All results expressed as mean ± SD, n = 3

Figure. No.3 : %Cumulative amount of drug release Vs Time of CZP0.

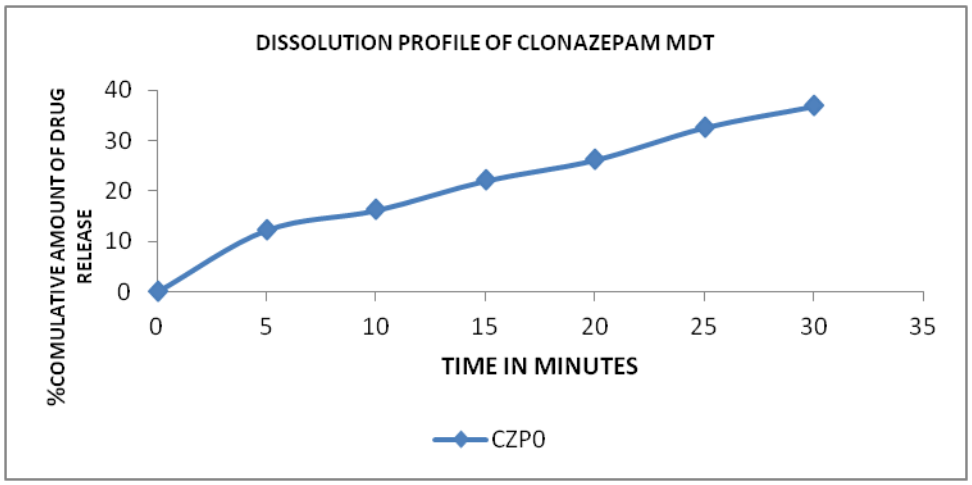


Table no 10: *In –Vitro* drug release characteristics of Clonazepam with Croscarmellose sodium (CZP1–CZP4)

Time (Min)	**Cumulative % of drug release with Croscarmellose sodium**			
	CZP1	**CZP2**	**CZP3**	**CZP4**
0	0	0	0	0
05	20.34±1.00	26.75±1.54	31.05±0.54	36.55±1.24
10	28.70±1.34	34.20±1.43	44.92±1.37	52.83±2.04
15	37.39±2.01	45.16±2.17	59.23±2.05	64.80±1.51
20	49.50±2.67	57.92±2.53	66.73±0.84	72.77±1.58
25	56.22±1.45	64.70±1.73	76.80±1.54	78.52±1.05
30	68.56±1.67	73.30±1.78	80.66±1.54	85.53±1.54

All results expressed as mean ± SD, n = 3

Figure. No.4: %Cumulative amount of drug release Vs Time of CZP1 to CZP4.

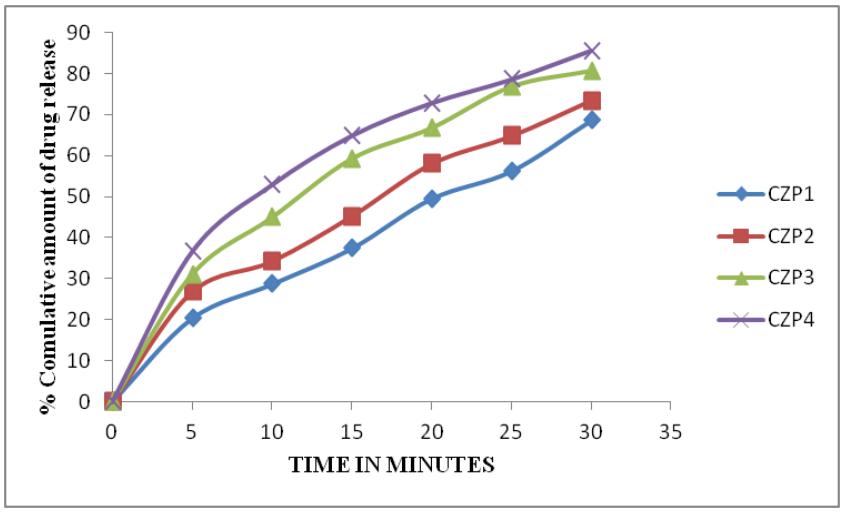
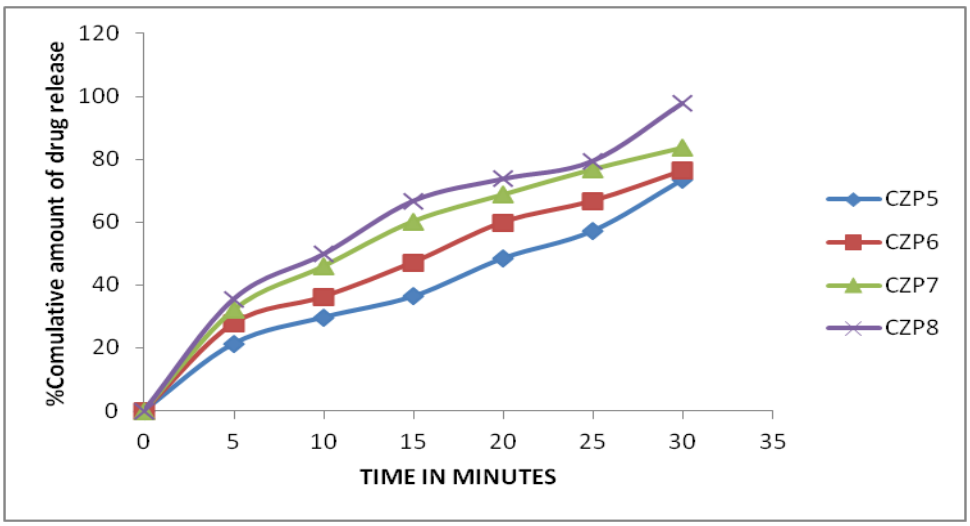


Table no 11: *In –Vitro* drug release characteristics of Clonazepam with Plantago ovate mucilage. (CZP5–CZP8)

Time (Min)	Cumulative % of drug release with Plantago ovate mucilage.			
	CZP5	CZP6	CZP7	CZP8
0	0	0	0	0
05	21.34±1.00	27.75±1.54	32.05±0.54	35.55±1.24
10	29.70±1.34	36.20±1.43	45.92±1.37	49.83±2.04
15	36.39±2.01	47.16±2.17	60.23±2.05	66.80±1.51
20	48.50±2.67	59.92±2.53	68.73±0.84	73.77±1.58
25	57.22±1.45	66.70±1.73	76.80±1.54	79.52±1.05
30	73.56±1.67	76.30±1.78	83.66±1.54	97.93±1.54

All results expressed as mean ± SD, n = 3

Figure. No.5 :%Cumulative amount of drug release Vs Time of CZP5 to CZP8.



STABILITY STUDIES:

Short-term stability studies conducted on formulation (CZP8) at 40^0C/ 75% RH for 3 months have shown no significant changes in physical appearance, drug content and *in vitro* dispersion time and dissolution and results were summarized in table no. 12.

Table no 12: Stability data for formulation Clonazepam (CZP8)

Name of Test	Initial	1st month	2nd month	3rd month	6th month
Physical Changes	No changes	No changes	No changes	No changes	No changes
Dissolution					
05 minutes	49.08±2.6	48.62±2.4	48.56±2.2	48.52±2.1	48.46±2.2
10 minutes	73.67±2.6	72.48±2.1	72.35±2.3	72.29±2.2	72.18±2.1
15 minutes	88.11±2.7	86.76±2.3	86.54±2.2	86.47±2.3	86.32±2.1
20 minutes	92.38±2.6	91.38±2.6	91.38±2.6	91.38±2.6	90.98±2.6
25 minutes	95.27±2.7	94.92±2.3	94.86±2.1	94.73±2.2	94.59±2.3
30 minutes	97.93±2.3	97.57±0.43	97.22±0.26	97.18±0.32	97.11±0.63
Assay (%)	99.89±0.39	98.57±0.43	98.22±0.26	98.18±0.32	98.11±0.63
Friability (%)	0.57±0.13	0.56±0.13	0.56±0.42	0.56±0.33	0.56±0.51
Disintegration (Sec)	18±1.2	18±1.2	18±1.1	18±1.0	18±1.0
Dispersion time(Sec)	24.11±0.15	24.11±0.15	24.11±0.15	24.10±0.15	24.10±0.15

All results expressed as mean ± SD, n = 3

KINETICS STUDIES:

The *In-vitro* drug release data of the fast dissolving tablets were evaluated kinetically, by Zero order, First order, Higuchhi, Peppas,. The data were processed for regression analysis using PCP DISSO V3 Software. The regression coefficient (R) value for Zero order, First order, Higuchhi, Peppas, for all the formulations were shown in Table. No.13. the formulations CZP8 follows zero order kinetics. The release of drug may be depends on disintegration time.

TABLE NO:13: KINETIC STUDIES OF CLONAZEPAM MOUTH DISSOLVING TABLETS

Formulation code	Zero order (R^2 value)	First order (R^2 value)	Higuchi (R^2 value)	Korsmeyer-Peppas (R^2 value)
CZPO	0.9963	0.9926	0.9920	0.9899
CZP1	0.9951	0.9669	0.9849	0.9892
CZP2	0.9926	0.9847	0.9960	0.9847
CZP3	0.9679	0.9946	0.9858	0.9850
CZP4	0.9588	0.9954	0.9944	0.9973
CZP5	0.9809	0.9155	0.9550	0.9894
CZP6	0.9945	0.9809	0.9959	0.9894
CZP7	0.9759	0.9960	0.9942	0.9997
CZP8	0.9732	0.7580	0.9542	0.9014

DRUG-POLYMER COMPATIBILITY STUDIES:

IR Spectroscopy was used to investigate the interaction of Carriers and polymers with Clonazepam in this compatibility research. The compatibility of the medication and polymers was determined using FTIR spectroscopy. All of the IR spectra have distinct peaks. By correlating the data, it can be concluded that the medicine is compatible with the formulation components. The FTIR spectrum analysis revealed that there was no drug interaction with the tablet's formulation additives since there was no fluctuation or shift in bands, implying that there was no drug-polymer interaction**.**

Extraction of mucilage from seeds of *Plantago ovat (IsapghulaSeed*):

The extraction method described in the methodology section, table no.7. The compatibility study was performed by IR-Spectroscopy to study the interaction of extracted product (dried powder) and Clonazepam. The FTIR-Spectroscopy was employed to ascertain the compatibility between the drug and extracted products (dried powder). By correlation, the interpreting the results, it indicates that there was no drug interaction with formulations additives of the tablet as there is no variation and shift in bands, it can be justified there is no interaction between drug and extracted products (dried powder).

CONCLUSION:

- Clonazepam mouth disintegrating tablets were effectively manufactured using the direct compression method and natural and synthetic Super disintegrants.
- First, plantago ovata mucilage was extracted and employed as a natural super disintegrating agent.
- Pre-compression and post-compression evaluations were carried out according to pharmacopoeia standards, and compatibility testing was carried out using the FTIR method.
- The following conclusions can be taken from the preceding investigations.
- The medicine was found to be compatible with the carriers, polymers, and other excipients employed in the dosage form in FTIR analyses.
- The findings of the pre-compression parameters revealed good flow characteristics.
- Mouth dissolving tablets of Clonazepam were prepared by direct compression method.
- Croscarmellose Sodium used as synthetic super disintegrants.
- Magnesium stearate is used as a lubricant. Talc is used as a glidant.
- Aspartame is used as sweetening agent.
- Post-Compression parameter results found to be optimum. Thus hardness of the tablets shown sufficient to withstand the shock. All the formulations tablets were found uniformity in weight.
- The drug content was uniform in all the tablet formulations indicating uniform distribution of drug within the matrices.
- Based on the *in-vitro* disintegration time and dissolution studies of clonazepam CZP8 containing Superdisintegrant as seeds of plantago ovate mucilage were found to be promising and showed a disintegration time 18±1.2 sec and drug release profile 97.93±1.54 respectively, when compared to the synthetic super disintigrant .
- The formulations subjected for kinetic studies and shown zero order kinetics.
- The stability studies carried out as per ICH guidelines for 3 months. Results showed that the formulations were stable and intact without any interaction.
- Finally, it was concluded that the MDTs of Clonazepam formulations containing Superdisintegrant as seeds of plantago ovata mucilage showed less disintegration time and *in-vitro* drug release study faster than the synthetic super disintegrant.
- Formulations were found to be complying with all the properties of tablets and the formulations were satisfactory.

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