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FORMULATION AND *IN VITRO* EVALUATION OF MOUTH DISSOLVING TABLETS OF ANTI EPILEPTIC DRUG USING NATURAL AND SYNTHETIC SUPER DISINTEGRANTS

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Abstract

The mouth-dissolving tablets for the anti-emetic drug in the current investigation were made utilizing the direct compression method using both natural and synthetic super disintegrants. Sodium starch glycolate (2–8%) and ocimum basilicum seed mucilage (2–8%) were utilized as synthetic and natural super disintegrants, respectively, in the direct compression method. By extracting the drug with 0.1 N HCl and pH 6.8 phosphate buffer and measuring the absorbance at 254 nm, the anti-epileptic drug content in the prepared tablet formulations was determined.

The prepared formulations were further tested for post compression paremeters.

In vitro drug release pattern (0.1 N HCl and pH 6.8 phosphate buffer),stability study (at 40ºC/ 75% RH for 6 months),drug-excipient interaction (IR spectroscopy) in vitro dispersion time respectively in comparison with formulations containing natural super disintigrant.

The promising formulations containing 8% w/w Synthetic super disintigrant Sodium starch glycolate emerged as the overall best formulation formulations (FCZ4).

Short-term stability studies of promising formulations indicated that there are no significant changes in drug content and in vitro dispersion time ($p<0.05$).IR-spectroscopic studies indicated that there are no drug-excipient interactions. It can be concluded from the present work that synthetic super disintigrant were found to be superior in compression with natural super disintegrante with improved dissolution.

Keywords: *Clonazepam, Ocimum basilicum seed mucilage,Sodium starch glycolate etc.*

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1. INTRODUCTION:

Oral routes of drug administration have wide acceptance up to 50-60% of total dosage forms. Solid dosage forms are popular because of ease of administration, accurate dosage, self medication, pain avoidance and most importantly the patient compliance. One of the important drawbacks of this dosage forms for some patients, is the difficulty to swallow (Dysphasia)[1-2].Drinking water plays an important role in the swallowing of oral dosage forms.

Oftentimes people experience inconvenience in swallowing conventional dosage forms such as tablet when water is not available, in the case of the motion sickness and sudden episode s of coughing during the common cold, allergic condition and bronchitis. For these reason, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention.

Mouth dissolving tablets are not only indicated for people who have swallowing difficulties, but also are ideal for active people.

MDTs are known by various names such as" fast-melting, Fast dissolving, oral disintegrating or orodispersible".The European Pharmacopoeia defines the term "mouth dissolving" as a tablet that can be placed in the mouth where it disperses rapidly before swallowing. Fast dissolving tablets are those when put on tongue disintegrate instantaneously releasing the drug which dissolve or disperses in the saliva.

The faster the drug into solution, quicker the absorption and onset of clinical effect[3].

2. MATERIALS AND METHODS:

Clonazepam was procured from Octis research laboratories, Chennai; Sodium Starch Glycolate was procured from Vijlak Pharma Ltd.,Mumbai,all other ingredients obtained from SD Fine Chemicals Pvt Ltd, Mumbai.

Preparation of a Clonazepam calibration curve in distilled water:

10 mg of Clonazepam was accurately weighed and dissolved in 100ml of methnol; 20 ml of preparation was taken and made up to 100ml in a volumetric flask using distilled water; 2, 4, 6, 8, and 10 ml was taken and made up to 10 ml in a volumetric flask using distilled water. A UV spectrophotometer set to 254 nm was used to measure the absorbance of these samples).The absorbance data of the concentrations are shown in table no.4 and figure no.1.

Preparation of a Clonazepam calibration curve in a pH 6.8 phosphate buffer:

Weighed 10 mg of Clonazepam into a 100 mL volumetric flask, dissolved in less water, then diluted with phosphate buffer at 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 100 µg/ml. Using phosphate buffer pH 6.8, dilutions of 10-50 µg/ml were prepared, and absorbance was measured at 254 nm. The absorbance data of the concentrations are shown in table no.5 and figure no.2.

Ocimum basilicum seed mucilage isolation:

To eliminate extraneous particles, basil seeds were washed with water. For 20 minutes, seeds were soaked in water (seed: water = 1:10). To separate the gel layer from the seeds, the swelled seeds were treated to intense agitation using a homogenizer at 1500 rpm. To eliminate undesirable particles, the separated gel layer was passed through muslin cloth and then precipitated with acetone. The precipitate was washed in ethanol and dried at 40°C in a hot air oven. The powdered mucilage was kept in an airtight container [4].

FORMULATION DEVELOPMENT:

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 availablein0.5mg, 1mg, and 2mgdoses 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 indifferent 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, aerosol 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 for10-20 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 FCZ0 toFCZ8 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.

Tableno. 1: Formulation of Clonazepam Mouth Dissolving Tablets

S.N0	Ingredients (mg/tab)	FCZ0	FCZ1	FCZ2	FCZ3	FCZ4	FCZ5	FCZ6	FCZ7	FCZ8
1	Clonazepam	2	2	2	2	2	2	2	2	2
2	Sodium starch glycolate	---	3	6	9	12	---	---	---	---
3	Ocimum basilicum seed 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 flavor	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[5]

Different parameters were evaluated for prepared powder blend using following methods.

Angle of repose

Angle of repose is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane.

The friction force in a loose powder can be measured by the angle of repose (θ). It is an indicative of the flow properties of the powder.

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

tan (θ)= h/ r

θ= tan-1 (h / r)

Bulk Density

Bulk density is the ratio of total mass of powder to the bulk volume of powder. 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

Tapped density is the ratio of total mass of powder to the tapped volume of powder. 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 the following formula.

Hausners ratio = Tapped density/ Bulk density

POST-COMPRESSION ASSESSMENT OF POWDER BLEND[6-9]

Thickness:

The thickness of the tablets was determined by using Digital vernier Calipers. Thickness mainly depends upon the die filling, physical properties of material to be compressed under compression force. Three tablets were randomly taken from each formulation, mean and standard deviation values were calculated. It is expressed in mm.

Hardness

The Monsanto hardness tester was used to determine the tablet hardness. The tablet was held between a fixed and moving jaw. Scale was adjusted to zero load was gradually increased until the tablet fractured. The value of the load at that point gives a measure of hardness of the tablet. Three tablets were randomly taken from each formulation, mean and standard deviation values were calculated. It is expressed in kg/cm$^{2.}$

Friability

The friability test for tablets was performed to assess the effect of abrasion and shocks. Roche friabilator was used for the percent friability of the tablets. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at a height of 6 inches in each revolution. Pre-weighted sample of tablets was placed in the friabilator and were subjected to the100 revolutions.

Then the tablets were removed and de dusted by using a soft muslin cloth and reweighed. The weight lost should not exceed the limit 1.0%.Thepercentage friability was measured by using the following formula.

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

Weight Variation

The weight variation test was performed as per I.P. Twenty tablets were randomly selected from each batch and individually weighed. And then average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight. The tablets passes the test for weight variation test if no more than two tablets are outside the percentage limit and if no tablet differs by more than two times the percentage limit.

***In-vitro* Dispersion Time**

In-vitro dispersion time was measured by dropping a tablet into a Petridis containing10ml of phosphate buffer pH 6.8 solutions at 37± 0.5^0c. Three tablets from each batch were randomly selected and tested the time required for complete dispersion of a tablet was measured. The *in-vitro* dispersion time is expressed in seconds.

Wetting Time

A piece of tissue paper folded double was placed in a Petri dish (6.5cm) containing 6 ml of water .the tablet was placed on the paper, and the time for complete wetting of the tablet was measured in seconds. The method was slightly modified by maintaining water at 37^0c.Wettingtime corresponding to the time taken for the tablet to disintegrate when kept motionless on the Petri dish.

Water Absorption Ratio

A piece of tissue paper folded twice was placed in Petri dish (6.5cm) containing 6mlof water. A tablet was put on the tissue paper and the time required for the complete wetting was measured. The wetted tablet was then 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 272.6nm 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 at37±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 254 nm.The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. Cumulative percent released was calculated and plotted against time. The results are given in table no.9 to 11and figure no.3 to 5.

KINETIC STUDY[10]

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:

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 constantk0.

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

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 slopvalue.

Higuchi’s Model:

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

Q = [DЄ /ι (2A – ЄCs) 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 / Mα = 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,

Log Mt / Mα = Log K + n Log t

STABILITY STUDIES[11]

Stability is defined as “the capacity of the drug product to remain within specifications established to ensure its identity, strength, quality and purity” (FDA1987).
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 temperatures such as 25^{o}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.

PHYSICO CHEMICAL EVALUATION OF DRIED POWDERED MUCILAGE[12-14]

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 on1gm of dried powdered mucilage.
- **Loss on drying:** Loss on drying was determined for an appropriate quantity of dried powdered mucilage at105^{0}Cfor5hours.

  LOD (%) = (Wt of water in sample/Wt of dry sample) ×100
- **Swelling factor:** Swelling factor was determined by putting 1gm of the drug in the measuring cylinder (25 ml capacity) in 20 ml water with occasional shaking. The volume occupied by the seeds after 24hours 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: PHYSICO CHEMICAL TESTS FOR MUCILAGE

S.no	Physicochemical parameters	*Ocimum basilicum* Seed mucilage
1	Solubility	Slightly soluble in water
2	Loss on drying (%)	4±0.05
3	Swelling ratio	8.2±0.022
4	Total ash (%)	3.1±0.062
5	Angle of repose	20.44^0±0.133
6	Bulk density g/cm^3	0.73±0.045
7	Tapped density g/cm^3	0.84±0.015
8	Carrs index (%)	12.6±0.11
9	Hausners ratio	1.14±0.07

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 interacts they are in close contact with each other, which could lead to the instability of drug. Preformulation studies regarding the drug-excipients interaction are there for every critical in selecting appropriate polymer.FTIR spectroscopy was employed to ascertain the compatibility between drug and the selected excipients. Potassium bromide, pure drug and the excipients were heated to105^{0}C 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 with FTIR spectra of excipients.

3. RESULT AND DISCUSSION:

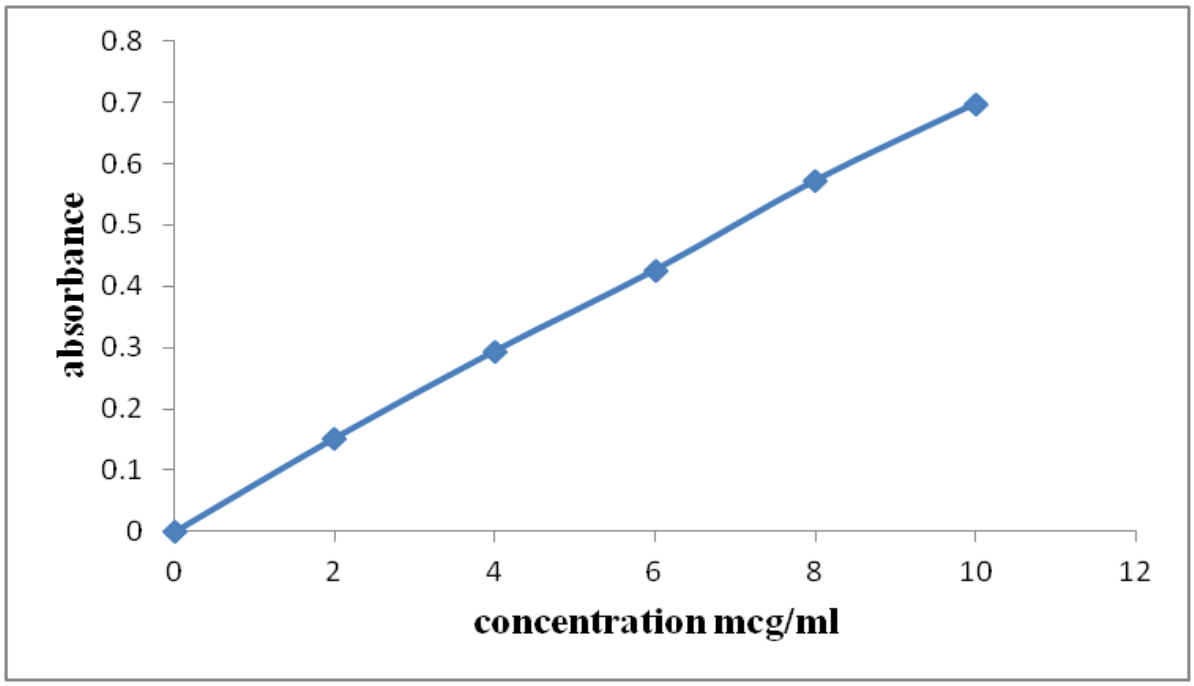
Determination of standard Calibration Curve and λmax of Clonazepam in distilled water:

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 no.4 and figure no.1.

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

Concentrations µg/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)



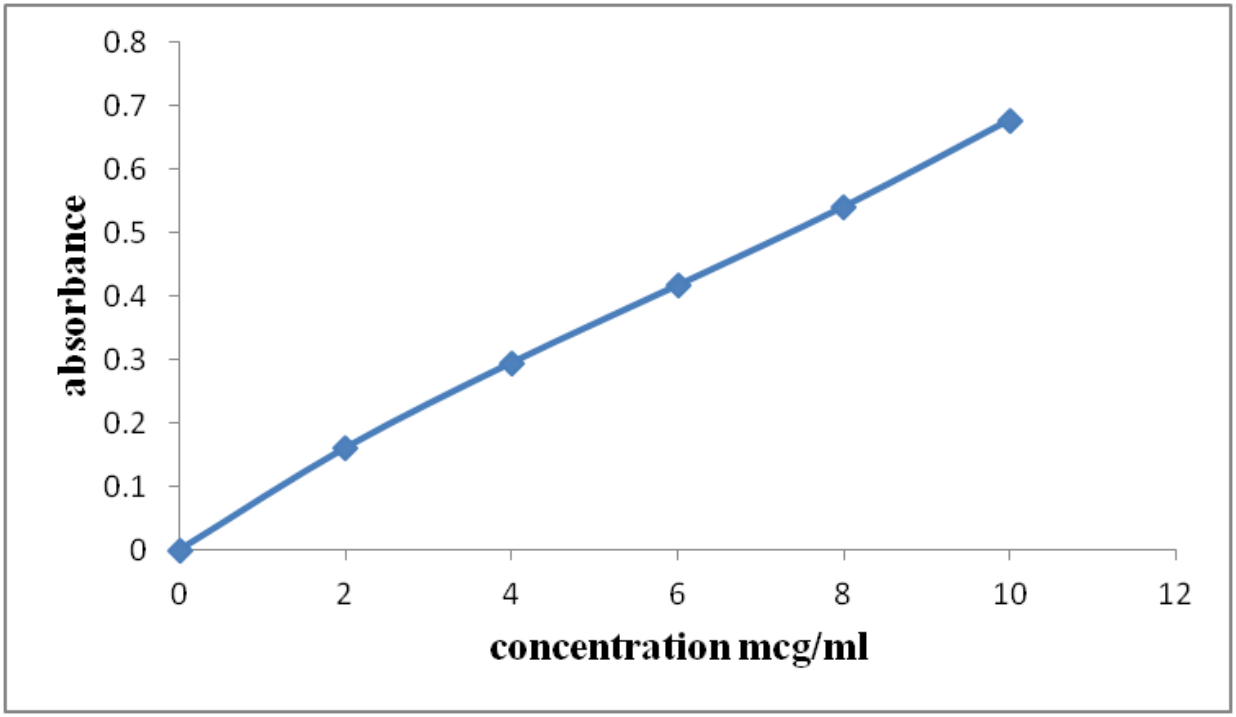
Determination of standard Calibration and λmax Curve of Clonazepam in pH 6.8 phosphate buffer:

Weighed 10 mg of Clonazepam into a 100 mL volumetric flask, dissolved in less water, then diluted with phosphate buffer at 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 100 g/ml. As stated in table no.2 and Figure no.2, further dilutions of 10-50 g/ml were prepared using phosphate buffer pH 6.8 and absorbance was measured at 254 nm.

Table5: Standard calibration curve of Clonazepam in phosphate buffer.

Concentrations µg /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 pH6.8phosphatebuffer (λ_{max}254nm)



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 0.64 g/cc, tapped density was found to be in the range of 0.64 to 0.74 g/cc, angle of repose was found to be in the range of 20.45to 26.48º, Carr's index was found to be in the range of 5.41% 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 FCZ0 – FCZ8

Formulation code	Bulk Density (g/cc)	Tapped density (g/cc)	Angle of repose (degree)	Carr's index (%)	Hausner's ratio
FM0	0.56	0.66	26.48	13.38	1.08
FM1	0.60	0.71	22.13	11.58	1.05
FM2	0.59	0.70	21.12	10.75	1.10
FM3	0.61	0.74	24.56	12.47	1.06
FM4	0.59	0.68	22.96	10.21	1.04
FM5	0.64	0.72	22.90	6.89	1.01
FM6	0.59	0.67	23.78	6.49	1.04
FM7	0.61	0.64	24.18	5.41	1.03
FM8	0.63	0.69	20.45	6.79	1.01

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 colour, Weight Variation, Thickness, Hardness, Friability, Drug Content, Wetting time, Water absorption ratio, Disintegration time, *In vitro* dispersion time, *and In-vitro* drug release studies were carried out.

Appearance of the tablets: Tablets were selected randomly from each formulation batch and examined under lens for shape and in presence of light for colour. Tablets showed concave, circular shape in white color and all tablets showed very good appearance without any capping or lamination and found satisfactory.

Thickness: Thickness of all the formulations were found in the range between 2.17±0.05 mm to 2.20±0.05 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 147.9±1.59 to 150.4±1.31, 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 of2.76±0.5 kg/cm^{2}to 3.13±0.5 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 Pharmacopoeia limit (1.0%) and results were given in table no.7.

Drug Content uniformity: The drug content uniformity was performed for all the formulations, the mean value and standard deviation of all the formulations were calculated, the low values of standard deviation indicates uniform drug content within the tablets. The percent drug content of all the tablets was found to be in the range of 98.39±1.04 to 100±2.02 percent (which was within the acceptable limits of ±5%) and results were given in table no.7.

Table no 7: Post Compression parameters of formulations FCZ0-FCZ8

Formulation code	Weight Variation	Thickness	Hardness	Friability	Drug Content
FMC0	147.1±1.59	2.18±0.04	2.76±0.5	0.59	98.98±1.52
FMC1	150.4±1.31	2.19±0.05	2.81±0.1	0.66	98.39±1.04
FMC2	148.6±2.45	2.17±0.05	2.93±1.4	0.68	100±1.59
FMC3	148.1±2.11	2.19±0.01	3.04±0.5	0.67	100±2.02
FMC4	148.9±2.86	2.20±0.05	3.05±0.5	0.61	99.88±0.07
FMC5	148.9±2.86	2.19±0.01	3.13±0.9	0.49	99.77±0.01
FMC6	149.6±2.59	2.19±0.04	3.05±0.5	0.56	100±1.09
FMC7	149.9±2.23	2.18±0.02	3.10±0.5	0.49	99.95±2.10
FMC8	150.0±1.494	2.20±0.02	3.03±0.1	0.46	99.85±1.01

All results expressed as mean ± SD, n = 3

Water absorption ratio:
The water absorption ratio of all the formulations was found to be 56.22±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 22±0.12 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 22.99±0.5 sec to 103±4.91**sec**. 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 25.11±0.15sec to 98±1.2 sec. The results were depicted in Table.no.8.

Table no 8: Post compression parameters of formulations FCZ0- FCZ8

Formulation Code	Wetting time (sec)	Water absorption ratio (%)	Disintegration time (sec)	*In vitro* dispersion time (sec)
FCZ0	103±4.91	144±1	279±1.62	98±1.2
FCZ1	45.66±2.08	56.22±3.8	69±0.10	46.61±1.52
FCZ2	37.66±1.52	67.01±1.8	51±1.26	39.63±1.52
FCZ3	32.33±1.52	73.12±2.11	37±1.27	30.31±2.51
FCZ4	**22.99±0.5**	**84.75±1.12**	**22±0.12**	**25.11±0.15**
FCZ5	51.66±2.08	59.22±3.8	79±1.55	65.03±2.47
FCZ6	46.19±1.0	68.21±1.5	68±1.82	56.12±2.11
FCZ7	40.66±1.15	79.98±1.01	49±2.05	48.42±1.90
FCZ8	**31.72±1.0**	**85.95±1.14**	**29±1.15**	**37.14±0.70**

All results expressed as mean ± SD, n = 3

***In-vitro* drug release studies**

In-vitro drug release experiments on tablets containing clonazepam were performed as specified in the technique. Dissolution tests were performed on all formulations. The samples were taken at predetermined intervals and evaluated with a UV-Visible Spectrophotometer at a wavelength of 254nm.

The % drug release vs time (hr) plot was used to investigate the drug release profile. Table No.9 to 11 and Figure No.3 to 5 presented the findings. FCZ0, FCZ1, FCZ2, FCZ3, and FCZ4 exhibited 36.84±0.6, 72.08±2.78, 78.24±2.43, 86.37±1.52, and 90.25±1.65 percent, Release of drug respectively at 30min.

Formulations FCZ5, FCZ6, FCZ7, FCZ8 Showed 62.01±2.3%,70.24±2.4%,82.95±2.7%, 89.72±1.1% respectively.

Among all formulations FCZ4 containing 8% Sodium starch glycolate as synthetic 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 Super disintegrant (FCZO)

Time (min)	Cumulative % of drug release without Super disintegrant (FCZO)
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

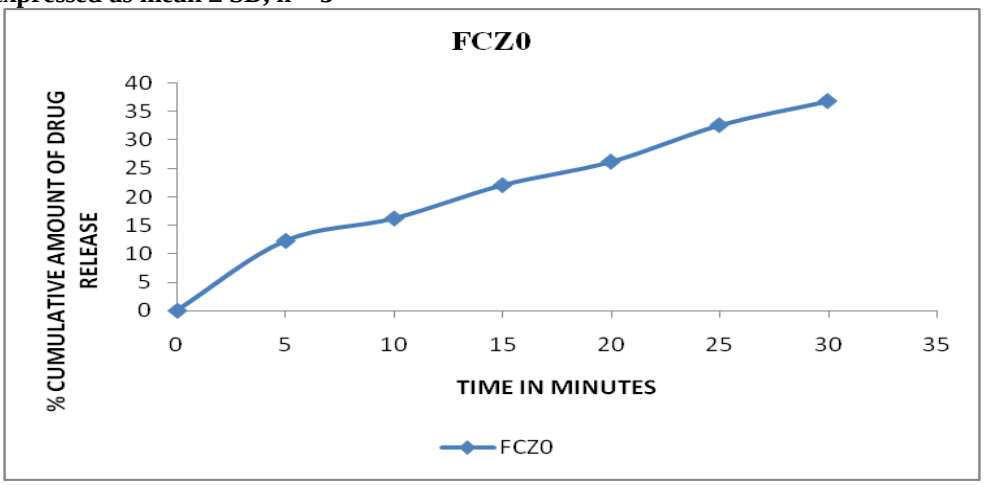


Figure. No.3. %Cumulative drug release Vs Time of FCZ0.

Table no 10: *In –Vitro* drug release characteristics of Clonazepam with Sodium starch glycolate (FCZ1– FCZ4)

Time (Min)	Cumulative % of drug release with Sodium starch glycolate			
	FCZ1	FCZ2	FCZ3	FCZ4
0	0	0	0	0
05	28.08±1.73	30.37±1.56	36.42±1.02	41.82±1.65
10	36.54±2.74	42.37±2.34	54.01±1.39	59.78±2.64
15	47.26±2.46	53.91±2.68	64.32±1.75	66.83±2.73
20	59.98±2.39	65.47±2.47	73.89±1.91	77.05±2.78
25	66.32±1.87	73.65±1.47	80.92±2.36	84.17±2.18
30	72.08±2.78	78.24±2.43	86.37±1.52	90.25±1.65

All results expressed as mean ± SD, n = 3

Figure no.4:%Cumulative amount of drug release Vs Time of FCZ1 to FCZ4

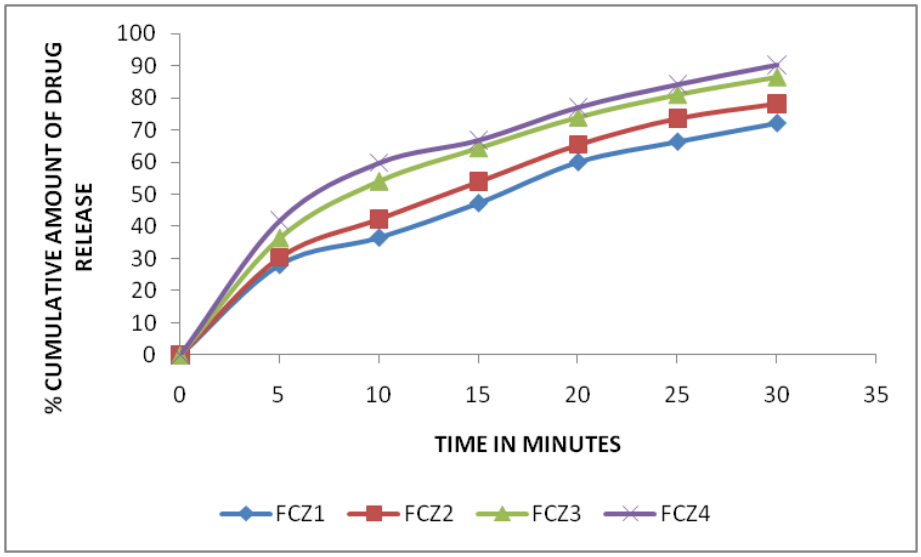
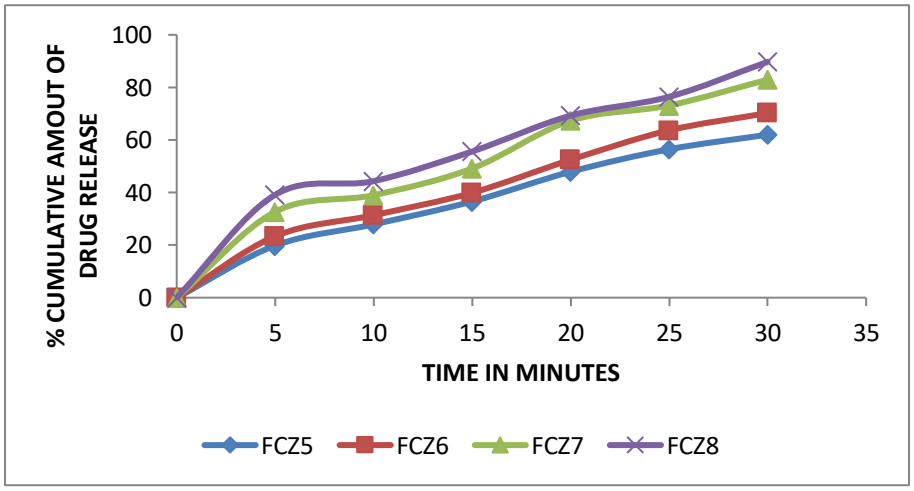


Table no 11: *In –Vitro* drug release characteristics of Clonazepam with Ocimum basilicum seed mucilage. (FCZ5– FCZ8)

Time (Min)	Cumulative % of drug release with Ocimum basilicum seed mucilage.			
	FCZ5	FCZ6	FCZ7	FCZ8
0	0	0	0	0
05	19.82±2.7	23.37±1.5	32.67±2.5	39.15.±1.8
10	27.89±1.6	31.37±2.3	39.00±1.3	44.34±2.0
15	36.59±1.3	39.91±2.6	49.16±2.4	55.62 ± 2.5
20	47.91±2.5	52.47±2.4	67.34±2.5	69.26 ± 1.6
25	56.45±1.8	63.65±1.4	73.13±2.6	76.43 ± 1.2
30	62.01±2.3	70.24±2.4	82.95±2.7	89.72 ± 1.1

All results expressed as mean ± SD, n = 3

Figure no.5: %Cumulative drug release Vs Time of FCZP5 to FCZP8



STABILITY STUDIES:

Short-term stability studies conducted on formulation (FCZ4) 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 12.

Table no 12: Stability data for formulation Clonazepam (FCZ4)

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 FCZ4 follows zero order kinetics. The release of drug may be depends on disintegration time.

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

Formulation code	Zero order (R^2 value)	First order (R^2 value)	Higuchi (R^2 value)	Korsmeyer-Peppas (R^2 value)
FCZ0	0.9963	0.9926	0.9920	0.9899
FCZ1	0.9845	0.9915	0.9896	0.9732
FCZ2	0.9802	0.9956	0.9911	0.9817
FCZ3	0.9597	0.9986	0.9971	0.9956
FCZ4	0.9648	0.9861	0.9936	0.9957
FCZ5	0.9931	0.9913	0.9940	0.9858
FCZ6	0.9930	0.9778	0.9897	0.9892
FCZ7	0.9799	0.9595	0.9821	0.9564
FCZ8	0.9879	0.9053	0.9904	0.9881

4. CONCLUSION:

- Mouth dissolving tablets of clonazepam were successfully formulated by employing direct compression method, using natural and synthetic Super disintegrants.
- Firstly extraction of Ocimum basilicum seed mucilage used as a natural super disintegrating agents.
- The physicochemical parameters like pre-compression and post-compression evaluation were performed as per pharmacopeia standards and compatibility study was done by FTIR method.

Based on the above studies, following conclusions can be drawn.

- The FTIR studies indicated that the drug was compatible with the carriers, polymers and other excipients used in the dosage form.
- Pre-compression parameter results showed good flow properties.
- Mouth dissolving tablets of clonazepam were prepared by direct compression method.

- Sodium starch glycolate 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 formulations FCZ4 containing Super disintegrant Sodium starch glycolate were found to be promising and showed a disintegration time 21±0.45 sec and drug release profile 96.25±1.65 respectively, when compared to the natural 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 synthetic Super disintegrant Sodium starch glycolate showed less disintegration time and *in-vitro* drug release study faster than the natural super disintegrant.
- Formulations were found to be complying with all the properties of tablets and the formulations were satisfactory.

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