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Formulation and Evaluation of Orodispersible Tablets of Clonazepam using Natural Superdisintegrants.

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Abstract: *Present study is aimed at the development of oro-dispersible tablets of clonazepam using natural superdisintegrants. Mucilage of Hibiscus rosa sinensis leaf and seeds of Ocimum basilicum were extracted, evaluated for the organoleptic, physicochemical parameters. The dried mucilage was used as superdisintegrant for the preparation of orodispersible tablets by direct compression method. The blends were evaluated for the pre-compression parameters and all the formulations were found to possess good flow properties. Tablets were compressed by direct compression technique, evaluated for weight variation, hardness, thickness, friability, water absorption, disintegration time, dispersion time, drug content and dissolution studies. The drug release profiles of the two superdisintegrants were compared. The optimized formula F10 was subjected to wet granulation using PVP in IPA as the dry binder. The tablets containing 5%w/w dried mucilage of Ocimum basilicum as superdisintegrant prepared by direct compression technique was found to be the best which disintegrated in 22 sec. with 99.8%drug release. The tablets were found to be stable during the accelerated stability studies conducted for three months at 40±2^{0}C/75±5% RH.*

Keywords: *oro dispersible tablets, Clonazepam, Hibiscus leaf mucilage, Ocimum seed mucilage, natural superdisintegrants, direct compression tablets.*

I. Introduction

Orodispersible tablets are solid unit dosage forms like conventional tablets, but are composed of super disintegrants, which help them to dissolve the tablets within a minute in the mouth in the presence of saliva without any difficulty of swallowing. These are the best suit for the drugs that are to be given to unconscious, pediatric, geriatrics and in the emergency conditions where the patient compliance and immediate release are required.

Epileptic seizures result from abnormal, excessive or hypersynchronous[1] neuronal activity in the brain. Clonazepam is approved by the FDA for treatment of status epilepticus[2] and Panic Disorder. It is classified as a high potency benzodiazepine and is a class II agent. The dried mucilages of Hibiscus leaf [3] and the seeds of Ocimum has the property of swelling in water and this helps them to work as the superdisintegrants.

S. B shrisand etal.and Bhalero etal.worked on development of fast dissolving tablets of clonazepam using synthetic superdisintegrants. Prajapati Amit et al. developed and compared FDT of clonazepam prepared by spray dried, direct compression technique and sublimation techniques using crospovidone as superdisintegrant.

Direct compression is one of the popular techniques for preparation of these dosage forms and wet granulation technique imparts good flow properties to the formulation.

II. Materials and methods:

Clonazepam was obtained from Octis Research laboratories, the leaves of Hibiscus rosa sinensis and Ocimum basilicum seeds were collected locally and from herbal drug store respectively and were authenticated before use. All the other chemicals were procured from S.D. Fine chemicals Pvt Ltd, Mumbai.

A. Calibration curve for Clonazepam :[4]

10mg of Clonazepam was accurately weighted & dissolved in 100 ml of Methanol. 20ml of preparation was taken and made up to 100ml using distilled water. Then 2,4,6,8,10 ml was taken and made upto 10 ml in volumetric flask with distilled water. These were then analyzed by UV spectrophotometer at 254 nm and absorbance was noted. Then the absorbance values were plotted against drug concentration and standard curve of Clonazepam was produced as shown in figure-1.

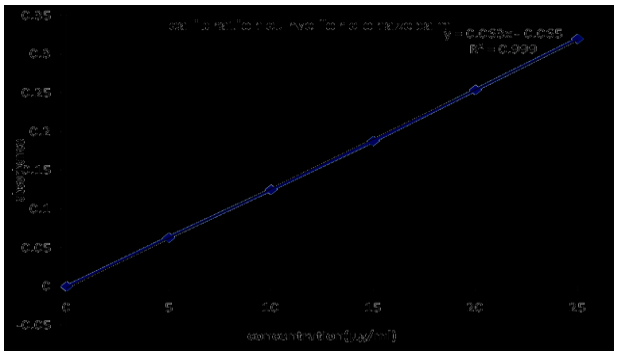


Figure-1: Calibration curve for Clonazepam

B. Isolation of mucilage from Hibiscus rosa sinensis:[5]

The fresh leaves of Hibiscus rosasinensis Linn. Were collected and washed with water to remove dirt and debris. The leaves were soaked in water for 5-6 hrs, boiled for 30 minutes and left to stand for 1hour to allow complete release of mucilage into water and were extracted using multilayer muslin cloth. Acetone was added to precipitate the mucilage and was separated, dried, in an oven at 400^0C, collected, ground, passed through #80 sieve and stored in dessicator at room temperature for further use.

C. Isolation of mucilage from seeds of Ocimum basilicum :[6]

The basil seeds obtained from local herbal drug store, air-dried and cleaned. These were ground in a mortar to obtain coarse powder and is defatted using Petroleum ether ($60\text{-}80^0$c), and activated for 1hr at a temperature $100\text{-}120^0$C. These were soaked in 6^{th} part of chloroform water for 24 hrs. The material was squeezed in a muslin bag to remove marc from the filtrate. To the filtrate an equal volume of alcohol (95%) was added to precipitate the excipient. The excipients were separated, dried in oven at temperature less than 50 ± 2^0C.

D. Characterization of dried mucilage:[5,6,7,8]

The mucilage extracted was subjected to organoleptic evaluation such as color, odour, taste etc., physico chemical evaluation was done to determine the ash value, swelling index, P^H , Viscosity and Solubility of the mucilages. Phyto chemical screening tests were performed for the detection of alkaloids, carbohydrates, glycosides, saponins, phytosterols, phenols, tannins, flavonoids, amino acids, diterpenes etc.

E. Formulation development:

Table-1: Formulation development table:

Ingredients (in mg.)	F1	F2	F3	F4	F5	F6	F7	F8	F9	$F10_d$	$F10_w$
Clonazepam	2	2	2	2	2	2	2	2	2	2	2
Hibiscus rosa sinensis	2	4	6	8	10	-	-	-	-	-	-
Osimum basilicum	-	-	-	-	-	2	4	6	8	10	10
Microcrystalline cellulose	100	100	100	100	100	100	100	100	100	100	100
MagnesiumStearate	2	2	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2	2	2
Mannitol	91	89	87	85	83	91	89	87	85	83	81
Aspartame	1	1	1	1	1	1	1	1	1	1	1
PVP	-	-	-	-	-	-	-	-	-	-	2
Total	200	200	200	200	200	200	200	200	200	200	200

F. Pre compression evaluation:

Bulk density: Ratio of weight of the sample to the volume it occupied was calculated.

$$Bulk\ density = \frac{mass\ (m)}{bulk\ volume(Vb)}$$

Tapped density: Tapped density was measured by transferring a known quantity of blend into a graduated cylinder and was placed on the tapped density apparatus. The initial volume was noted. The apparatus was set for 500, 750 and 1250 taps. The tapped density was determined.

$$Tapped\ density = \frac{mass(m)}{tapped\ volume(Vt)}$$

Compressibility index: It is the propensity of a powder to be compressed. Based on the apparent bulk density and tapped density the percentage compressibility of the blend was determined using the following formula.

$$Compressibility\ index = \frac{tapped\ density - bulk\ density\ X100}{tapped\ density}$$

Hausner's ratio: It indicates the flow properties of the powder. The ratio of tapped density to the bulk density of the powders is called Hausner ratio.

$$Hausner's\ ratio = \frac{tapped\ density}{bulk\ density}$$

Angle of repose: The Angle of repose was determined by passing the blend through a funnel fixed to a burette stand at a particular height (4 cm). The height and radius of the pile was measured. Angle of repose of the blend was calculated using the formula:

$$Angle\ of\ repose\ (\Theta) = tan^{-1}\frac{h}{r}$$

Where, h = Height of the pile
r = Radius of the pile

G. Preparation of tablets:

For F1-F10$_d$, the ingredients were weighed accurately as specified in the formula, mixed and sieved through 40 mesh. The prepared blends were evaluated for precompression parameters. The tablets were directly compressed using 7mm round flat punches on eight station rotary tablet compression machine.
For the formula F10$_w$ PVP in ethanol was added dropwise and granules were prepared using 20 mesh. The granules were dried and compressed using 7mm round flat punches on eight station rotary tablet compression machine.

H. Post compression evaluation parameters:[9]
Thickness: Thickness was determined for 20 pre-weighed tablets of each batch using a digital vernier scale and the average thickness was determined in mm**.** The tablet thickness should be controlled within a ± 5% variation of a standard.

Weight variation: 20 tablets were selected randomly from a batch and were individually weighed and then the average weight was calculated.

Hardness test: The crushing load which is the force required to break the tablet in the radial direction was measured using a Pfier hardness tester. The hardness of 10 tablets was noted and the average hardness was calculated. It is given in kp or kg/cm^2.

Percentage friability: In friability testing the tablets are subjected to abrasion and shock. The tablets were rotated in the Roche Friabilator for 100 revolutions at 25 rpm. The tablets were dedusted and reweighed. The percentage friability is expressed as the loss of weight and is calculated by the formula:

$$\%\ friability = \frac{w_0 - w_f}{w_0} x100$$

Where w_0 = Initial weight of tablets
w_f = Final weight of tablet

Drug Content Uniformity: A quantity of powder equivalent to 2 mg of clonazepam was extracted into methanol and liquid was filtered (0.22µm membrane filter disc (Millipore Corporation). The CZ content was determined by measuring the absorbance at 254 nm (using UV-vis spectrophotometer, Shimadzu 1700).

Disintegration time: Disintegration time is the time taken by the tablet to breakup into smaller particles. The disintegration test is carried out in saliva buffer ph 6.8 in an apparatus containing a basket rack assembly with six glass tubes of 7.75 cm in length and 2.15 mm in diameter, the bottom of which consists of a #10 mesh sieve at 37±2^{0}C. The disintegration time that patients can experience for oral disintegrating tablets ranges from 5 to 30 seconds.

In Vitro Dispersion Time: One tablet was placed in a beaker containing 10 ml of ph 6.8 phosphate buffer at 37±0.5ºc and the time required for complete dispersion was determined .

Fitness of dispersion: this test was performed by placing 2 tablets in 100ml of water and stir it gently till the tablets gets completely dispersed. The formulation is considered to form a smooth dispersion if it passes through the sieve of nominal mesh 710microns without leaving residue on the mesh.

Wetting Time: Twice folded tissue paper was placed in a petri-dish having an internal diameter of 5 cm containing 6 ml of water. A tablet having a small amount of rosalin powder on uppersurface was placed on tissue paper. The time required to develop red colour on upper surface of the paper was considered as the wetting time.

Water Absorption Ratio (R): The weight of the tablet prior to placement in the petri-dish was noted utilizing a digital balance (ELB 300). The wetted tablet was removed and reweighed. Water absorption ratio (R) was then determined according to the following equation:

$$\% R = \frac{w_a - w_b}{w_b} x100$$

Where, w_a and w_b were tablet weights before and after water absorption respectively.

Dissolution studies: In vitro dissolution studies of the orodisperible tablets of clonazepam was performed in 900ml of water[10] at 37±2° C using USP type II paddle apparatus. Aliquots of the dissolution medium (water) were withdrawn at specific time intervals (5,10,15,30min.) And replaced immediately with equal volume of fresh medium. The samples were filtered through 0.22µm membrane filter disc and analyzed for drug content by measuring the absorbance at 254 nm.

Release Kinetics: To study the release kinetics, data obtained form in vitro drug release studies were plotted in various kinetic models:

Zero order kinetics: Plot was drawn for the cumulative percentage of drug release vs. Time**.**

$$Q\,t = Q0 + K0\,t$$

Where, Q_t = amount of drug dissolved in time t,
Q_o = initial amount of drug in the solution
K_o = zero order release constant.

First order: Plot was drawn for log % drug remained unreleased vs. Time.

$$logQ\,t = logQ0 + K1\frac{t}{2.303}$$

Where Qt is the amount of drug released in time t,
Qo is the initial amount of drug in the solution,
K1 is the first order release constant.

III. Results and discussions

Isolation of the mucilages was done and Characterization of the mucilage was performed. The results were as given in table- 2.

The bulk density of the blends with superdisintegrants were found to be in the range of 0.36 and 0.42gm/cm^3 and the tapped density in the range 0.39-0.57 gm/cm^3. The compressibility index of various blends was found to be in the range 4.44-15.21 and the Hausner's ratio 1.04-1.25. The angle of repose of various powder blends, prepared with different super disintegrants was found to be in the range 24.5^0 and 30^0 which indicated excellent to good flow.

The thickness of the tablets was found in the range 2.9-3mm . Uniform thickness was obtained due to uniform die fill. Tablets were evaluated by using Pfizer Hardness tester. Hardness of the tablets was found in the range 2.93-3.4 kg/cm^2. Uniform hardness was obtained due to equal compression force.

Tablets were evaluated for drug content, wetting time, invitro dispersion time, fitness of dispersion, disintegration time, and water absorption ratio and the results were as shown in the table -3 **.** The drug release profiles were as shown in table-4.The comparative drug release profiles and the kinetic study results for direct compression and wet granulation were as shown in the figures- 2 and 3.

Table-2: Organoleptic and Physico chemical evaluation of mucilage:

Parameter	Hibiscus mucilage	Ocimum mucilage
Appereance	Greenish Amorphous Powder	Brownish ash like hygroscopic powder
Odour	Characteristic	Characteristic
Taste	Mucilageneous	Mucilageneous

Ash value Sulphated ash	2% 0.6%	12% 5.2%
Swelling ratio	28%	35%
Weight LOD	8.5%	6.5%
Ph	6.8	6.2
Viscosity	205cps	235cps
Solubility	Slightly soluble in water	Swells in water

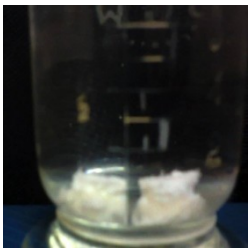
Table-3: Post compression evaluation of orodispersible tablets of clonazepam:

Formulation code	Assay (%)	Wetting time (sec.)	Invitro dispersion time (sec.)	Fitness of dispersion	Disintegration time (sec.)	Water absorption ratio
F1	98.35±0.2	52±2	260±30	Failed	42±2	52.42
F2	99.25±0.2	48±1	230 ±22	Failed	29±2	32.33
F3	98.12±0.3	42±2	208 ±15	Failed	32±2	42.96
F4	99.75±0.2	33±2	190 ±20	Failed	40±2	38.21
F5	98.65±0.4	25±2	150 ±20	Passed	28±2	42.73
F6	99.25±0.5	51±2	185 ±28	Failed	35±2	32.54
F7	100.12±0.2	46±2	150 ±30	Failed	33±2	43.1
F8	98.99±0.3	40±2	130 ±25	Failed	36±2	32.67
F9	99.85±0.2	31±2	115±10	Passed	29±2	52.11
F10(d)	100.25±0.3	22±2	70±20	Passed	22±2	72.51
F10(w)	98.99±0.25	33±2	208 ±20	Failed	40±2	22.54

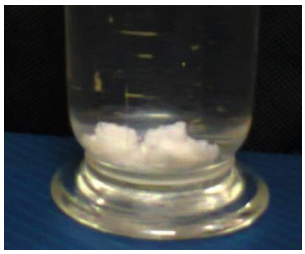
Table-4: Drug release data :

Time (min)	Cumulative percentage of drug release (%)										
	F-1	**F-2**	**F-3**	**F-4**	**F-5**	**F-6**	**F-7**	**F-8**	**F-9**	**F-10$_d$**	**F-10$_w$**
0	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
5	38.5±2	39.4±1	42.2±2	36.2±2	26.8±2	40.2±2	35.2±1	28.5±2	37.1±2	28.2±2	15.5±1
10	43.2±1	46.3±2	55.3±1	39.2±2	38.2±2	49.6±1	48.1±2	36.2±1	48.3±2	42.3±2	32.2±2
15	51.3±2	52.8±3	68.2±2	52.4±1	49.3±4	58.3±2	51.5±3	49.2±2	52.2±1	56.4±4	40.6±2
20	59.3±3	68.2±2	71.8±1	67.2±2	66.5±2	63.5±3	65.2±2	58.4±1	68.5±2	71.5±2	51.3±2
25	68.2±1	71.4±1	79.9±2	73.8±1	72.2±3	75.2±1	70.1±1	73.4±2	76.1±1	85.2±3	62.5±2
30	79.3±2	82.7±1	83.3±1	87.4±2	98.6±2	81.5±2	88.2±1	85.4±1	92.3±2	99.8±2	75.8±1

All the values are expressed as mean ±Standard deviation; n=6



At 0 sec.



At 40 sec.

At 70 sec.

Figure-2: Fitness for dispersion for F10$_d$

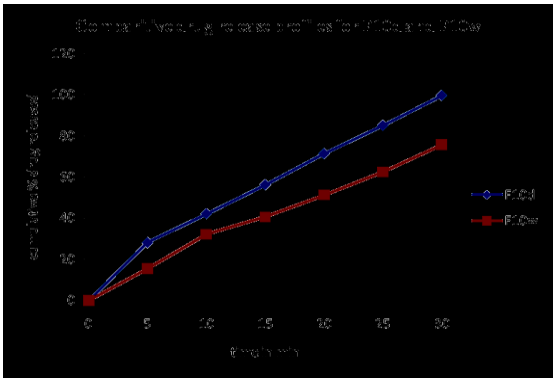


Figure-3: Comparitive drug release profiles for direct compressed and wet granulated orodispersible tablets of clonazepam

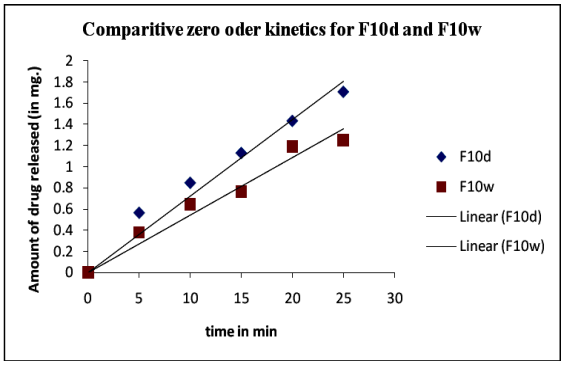


Figure-4: Comparitive zero order kinetic profiles for direct compressed and wet granulated orodispersible tablets of clonazepam.

IV. Conclusion

All the formulations prepared by the natural superdisintegrants were found to posess good flow properties. From the drug release studies and disintegration studies, the tablets prepared with 5%w/w Ocimum seed mucilage were found to be the optimized formula. The accelerated stability study at 40 ± 2^0C/75±5% RH indicated that the formulation $F10_d$ was stable during the study.

V. Acknowledgements

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