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Preparation and Evaluation of Ziprasidone Fast Dissolving Tablets by Direct Compression Method

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ABSTRACT:

The aim of this study was to prepare fast disintegrating tablets of Ziprasidone by using various superdisintegrant. The tablets were prepared using mannitol as diluent and Kyron T-134 as taste masking agent along with three different levels of superdisintegrant. The superdisintegrant used in this study were Crosspovidone, Crosscarmelose sodium and Sodium starch glycolate. The tablets were evaluated for weight variation, hardness, friability, wetting time, water absorption ratio, disintegration time (DT) and dissolution study. Using the same excipients, the tablets were prepared by direct compression and were evaluated in the similar way. From the results obtained, it can be concluded that the tablet formulation prepared with 9% Crosspovidone showed Disintegration time of 12 seconds.. Also the hardness, friability, dissolution rate (ZD3) were found to be acceptable according to standard limits.

KEY WORDS: Ziprasidone, Fast disintegrating tablets (FDT's), Direct Compression, Kyron T-134.

INTRODUCTION:

The concept of fast dissolving drug delivery system emerged from the desired to provide patient with conventional means of taking their medication. Fast dissolving dosage form can be disintegrated, dissolved or suspended by saliva in mouth. The fast dissolving tablets disintegrates instantaneously when placed on tongue and releases the drug dissolve or disperses In saliva.[1] The fast dissolving tablets are useful in patients,[2,3] like pediatric, geriatric, bedridden or mentally disabled, who may face difficulty in swallowing conventional tablet or capsule4 leading to ineffective therapy,[5] Most pharmaceutical forms for oral administration are formulated for direct ingestion or for chewing or for prior dispersion/dissolution in water. Some of them are absorbed in mouth (sublingual or buccal tablet) to obviate the problem associated with convential dosage forms orally fast dissolving tablet have been developed which combine hardness, dosage uniformity, stability and other parameters, since no water is required for swallowing the tablets and they are thus suitable for geriatric, pediatric and travelling patients.[6]

The fast dissolving tablet formulation is defined by the food and drug administration (FDA) as, "A solid dosage form containing medicinal substances which disintegrates rapidly, usually within matter of seconds, when placed upon the tongue."[7] It is difficult for many patient to swallow tablets and hard gelatine capsule hence they do not comply with prescription, which results in high incidence of non compliance and ineffective therapy. Such problem can be resolved by mean of fast dissolving tablet. These FDT are designed to dissolve or disintegrates rapidly in saliva generally within <60 second.[8]

Ziprasidone is an novel atypical antipsychotic with unique

pharmacological profile and is approved by FDA in Feb 2001 for the treatment of psychotic disorder.[9] Half life of ziprasidone is 7 hours and undergoes extensive first pass metabolism, Oral ziprasidone appear efficacious and has been shown to have some clinical advantages over chlorpromazine and haloperidol.[10] Ziprasidone oral bioavailability is about 60%in healthy volunteers when taken with food, which increases absorption by more than 50%. Peak plasma concentration occur in 3.7-4.7 hours.[11]

Hence in the present work Ziprasidone fast dissolving tablets were prepared by direct compression technique by using different superdisintegrants.

MATERIALS AND METHODS

Ziprasidone was gifted by Dr.Reddy's Labs Hyderabad, crospovidone; croscarmelose sodium and sodium starch glycolate were received as gift samples from Maple Biotech, Pune, Kyron T-134 was received from Coral Labs,Ahamadabad and all other chemicals and reagents were of analytical grade.

Preparation of Ziprasidone fast dissolving tablets: [12]

Fast dissolving tablets of Ziprasidone were prepared by direct compression method according to the formula given in Table no. All the ingredients were passed through 60 mesh sieve separately. The drug and mannitol was mixed by small portion of both each time and blending it to get a uniform mixture kept aside. Then the ingredients were weighed and mixed in geometrical order and tablets were compressed of 6mm sizes flat round punch to get tablet using Rimek Compression Machine.

Evaluation of tablets[13-14]

Angle of repose (θ):

Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and horizontal plane. The frictional force in a loose powder or granules can be measured by angle of repose.

$$\tan \theta = h / r$$

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

Where, 'θ' is the angle of repose
'h' is height of pile
'r' is radius of the base of pile

Bulk density is defined as the mass of a powder divided by the bulk volume. The bulk density of a powder depends primarily on particle size distribution, particle shape, and the tendency of the particles to adhere to one another.

The measuring cylinder containing a known mass of blend was tapped for a fixed time. The minimum volume (V_t) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density (ρ_t) was calculated using the following formula

$$\rho_t = \frac{M}{V_t}$$

Hausner's ratio:

Hausner ratio is an indirect index of ease of power flow. It is calculated by the following formula.

$$\text{Hausner ratio} = \frac{\rho_t}{\rho_d}$$

Where ρ_t is tapped density and ρ_d is bulk density. Lower Hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25).

Carr's compressibility index:

The compressibility index of the granules was determined by Carr's compressibility index.

(%) Carr's Index can be calculated by using the following formula

$$\text{Carr's Index (\%)} = \frac{TD - BD}{TD} \times 100$$

Hardness test:

Tablets require a certain amount of strength, or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture, packaging and shipping. The hardness of the tablets was determined using Monsanto Hardness tester. It is expressed in Kg/cm^2. Three tablets were randomly picked from each formulation and the mean and standard deviation values were calculated.

Friability test:

It is the phenomenon whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition. The friability of tablets were determined by using Veego Friabilator. It is expressed in percentage (%).

Twenty tablets were initially weighed ($W_{initial}$) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W_{final}). The percentage friability was then calculated by,

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} x100$$

% Friability of tablets less than 1% is considered acceptable.

Weight variation test:

The tablets were selected randomly from each formulation and weighed individually to check for weight variation. The U.S Pharmacopoeia allows a little variation in the weight of a tablet. The following percentage deviation in weight variation is allowed.

Uniformity of thickness:

The crown thickness of individual tablet may be measured with a micrometer, which permits accurate measurements and provides information on the variation between tablets. Other technique employed in production control involves placing 5 or 10 tablets in a holding tray, where their total crown thickness may be measured with a sliding caliper scale. The tablet thickness was measured using screw gauge.

Drug content uniformity:

Four tablets weighted and crushed in a mortar then weighed powder contain equivalent to 100mg of drug transferred in 100ml distill water. Its concentration 1000 mcg/ml. 10ml from this stock solution taken and diluted to 100ml distilled water, it makes 100μg/ml. Then 20μg/ml solution prepared by taking 2ml from stock solution and diluted to 10ml. Absorbance measure at 223nm.

Wetting time:

The method was applied to measure tablet wetting time. A piece of tissue paper folded twice was placed in a small petri dish (i.d. = 6.5 cm) containing 10 ml of water, a tablet was placed on the paper, and the time for complete wetting was measured. Three trials for each batch were performed and standard deviation was also determined. The method was reported by Yunxia Bi et al.

Water absorption ratio:

A piece of tissue paper folded twice was placed in a small petri dish containing 6ml of water. A tablet was put on the paper and time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio, R was determined using following equation.

$$R = 100 (W_a – W_b)/ W_b$$

Where, W_b – weight of tablet before absorption
W_a – weight of tablet after absorption

Three tablets from each formulation were performed and standard deviation was also determined.

***In vitro* disintegration time:**

The process of breakdown of a tablet into smaller particles is called as disintegration. The in-vitro disintegration time of a tablet was determined using disintegration test apparatus as per I.P. specifications.

I.P. Specifications: Place one tablet in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using pH 7.4 (simulated saliva fluid) maintained at 37° ± 2°C as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute in the pH 7.4 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.

***In vitro* dissolution studies:**

Dissolution rate was studied by using USP type-II apparatus (USP XXIII Dissolution Test Apparatus at 50 rmp) using 900ml of phosphate buffer pH (7.4) as dissolution medium. Temperature of the dissolution medium was maintained at 37 ± 0.5°C, aliquot of dissolution medium was withdrawn at every 1 min interval and filtered. The absorbance of filtered solution was measured by UV spectrophotometric method at 223 nm and concentration of the drug was determined from standard calibration curve.

Results and Disscussion:

The values of pre and postcompression parameters evaluated were within prescribed limits and indicated a good free flowing property. Results are shown in **Table 2**. The post compression parameters such as hardness, friability, thickness, disintegration time, wetting time, drug content are shown in **Table 3**, and t_{50}%, t_{90}% are shown in **Table 4**.

The weight variation results of prepared tablets were found in the range 98 to 102 mg , which is below ±7.5%, hardness range were between 3 to 3.5 kg/cm², percentage friability value between 0.41 to 0.74%, *in vitro* disintegration time of 12 to 50 sec, drug content uniformity was in between 98.91 to 100.80%, water absorption ration were found between 45 to 60% and wetting time between 54 to 98 sec. In all the formulations, hardness test indicates good mechanical strength. Friability of all formulations were less than 1%, which indicated that the tablets had a good mechanical resistance Drug release from the formulations prepared by using crospovidone (ZD1-ZD3) were faster than formulations prepared by sodium starch glycolate (ZD4-ZD6) and Crosscarmelose sodium (ZD7-ZD9). It may be due to the more wicking and swelling action of crospovidone than other used superdisintegrants.

CONCLUSION:

From the results it was concluded that the tablets prepared by using 9% crosspovidone shows good result with respect to precomprational parameter and post compressional parameter due to the more wicking action of crospovidone as compared to other used superdisintegrants. All the formulation shows the result with respect to IP limits.

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Table 1: Composition of Ziprasidonefast dissolving tablets.

Ingredients (mg)	Formulations code								
	ZD_1	ZD_2	ZD_3	ZD_4	ZD_5	ZD_6	ZD_7	ZD_8	ZD_9
Ziprasidone	20	20	20	20	20	20	20	20	20
Crosprovidone	3	6	9	-	-	-	-	-	-
Sodium starch glycolate	-	-	-	3	6	9	-	-	-
Crosscarmilose Sodium	-	-	-	-	-	-	3	6	9
Mannitol	70	67	64	70	67	64	70	67	64
Kyron-T 134	5	5	5	5	5	5	5	5	5
Magnesium Stearate	1	1	1	1	1	1	1	1	1
Talc	1	1	1	1	1	1	1	1	1
Total Wight	100	100	100	100	100	100	100	100	100

Table 2: Precompressional Parameters of Ziprasidone fast dissolving tablets.

forrmulations	Bulk density* (g/cc) ± SD, n=3	Tapped Density* (g/cc) ± SD, n=3	Angle of repose* (degree) ± SD, n=3	Carr's Index* (%) ± SD, n=3	Hausner's Ratio* ± SD, n=3
ZD_1	0.40 ± 0.06	0.512 ± 0.01	23.19 ± 1.27	22.00 ± 1.23	1.28 ± 0.03
ZD_2	0.398 ± 0.06	0.51 ± 0.01	25.28 ± 1.19	21.95 ± 1.02	1.28 ± 0.02
ZD_3	0.401± 0.06	0.513 ± 0.01	27.20 ± 1.30	21.82 ± 1.03	1.27 ± 0.03
ZD_4	0.392 ± 0.06	0.504 ± 0.02	25.14 ± 1.01	22.21 ± 1.25	1.29 ± 0.03
ZD_5	0.402 ± 0.06	0.498 ± 0.01	28.56 ± 1.45	19.49 ± 1.36	1.24 ± 0.03
ZD_6	0.443 ± 0.06	0.508 ± 0.02	26.41 ± 1.56	19.49 ± 1.29	1.23 ± 0.03
ZD_7	0.398 ± 0.06	0.499 ± 0.01	26.38 ± 1.20	20.25 ± 1.89	1.25 ± 0.03
ZD_8	0.395 ± 0.06	0.50 ± 0.02	26.01 ± 1.15	21.01 ± 1.56	1.26 ± 0.03
ZD_9	0.389 ± 0.06	0.501 ± 0.02	28.46 ± 1.29	22.20 ± 1.57	1.25 ± 0.02

Table 3: Precompressional Parameters of Ziprasidonefast dissolvingtablets

Parameters	Formulations code								
	ZD_1	ZD_2	ZD_3	ZD_4	ZD_5	ZD_6	ZD_7	ZD_8	ZD_9
Hardness ($kg/cm^{2)}$ ± SD	3.0 ± 0.12	3.5 ± 0.17	3.5 ± 0.23	3.5 ± 0.27	3.5 ± 0.14	3.0 ± 0.15	3.0 ± 0.23	3.5 ± 0.25	3.0 ± 0.30
Friability (%)	0.61	0.65	0.74	0.69	0.41	0.52	0.47	0.62	0.43
Thickness* (mm) ± SD	3.12 ± 0.10	3.08 ± 0.02	3.14 ± 0.10	3.14 ± 0.20	3.13 ± 0.14	3.13 ± 0.14	3.12 ± 0.14	3.14 0.31	3.13 ±0.20
Weight variation* (mg) ± SD	100 ± 0.11	101 ± 0.23	98± 0.56	99 ± 0.45	100 ± 0.55	101 ± 0.34	101 ± 0.45	100± 0.65	102 ±0.86
In vitro disintegration time* (sec) ± SD	25 ± 1.56	19 ± 2.36	12 ± 1.36	50 ± 1.59	35 ± 1.28	30 ± 1.53	30 ± 1.29	28 ± 1.44	20 ± 1.46
Wetting time* (sec)± SD	87 ± 1.25	69 ± 1.37	54 ± 1.53	98 ± 1.54	87 ± 1.35	76 ± 1.23	84 ± 2.09	74 ± 2.45	70 ± 2.03
Water absorption ratio* ± S.D	51 ± 1.22	52 ± 1.52	60 ± 1.33	52 ± 1.95	54± 1.66	45 ± 1.30	59 ± 1.43	55 ± 1.52	46 ± 1.29
Drug Content* (%) ± SD	99.20 ± 0.75	100.8±0.40	100.47± 0.53	99.85 ±1.02	99.93 ±1.90	100.1 ±1.20	98.91 ±1.17	99.4±0.9	99.1 ±1.31

Table1 4: Release profile of the Ziprasidone fast dissolving tablets.

Formulations	$T_{50\%}$ (min)	$t_{90\%}$ (min)
ZD_1	4.00 ± 0.12	7.21 ± 0.29
ZD_2	3.00 ± 0.21	5.40 ± 0.32
ZD_3	2.01 ± 0.39	3.63 ± 0.56
ZD_4	4.58 ± 0.51	8.02 ± 0.18
ZD_5	4.06 ± 0.54	7.32 ± 0.27
ZD_6	3.00 ± 0.45	5.04 ± 0.34
ZD_7	5.02 ± 0.43	9.03 ± 0.54
ZD_8	3.98 ± 0.29	7.17 ± 1.25
ZD_9	3.49 ± 0.43	6.28 ± 0.59

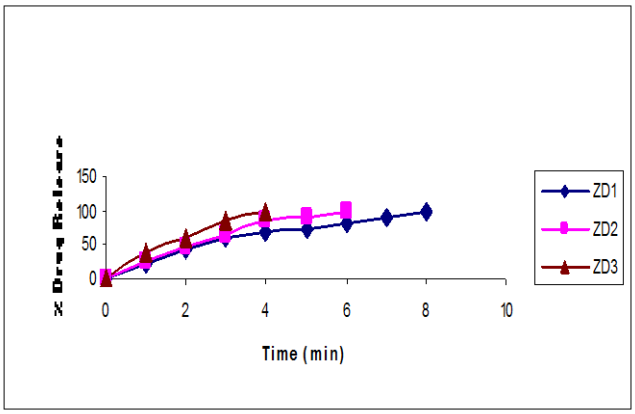

Figure 1: Release profile of Ziprasidone FDT's prepared using crosspovidone.

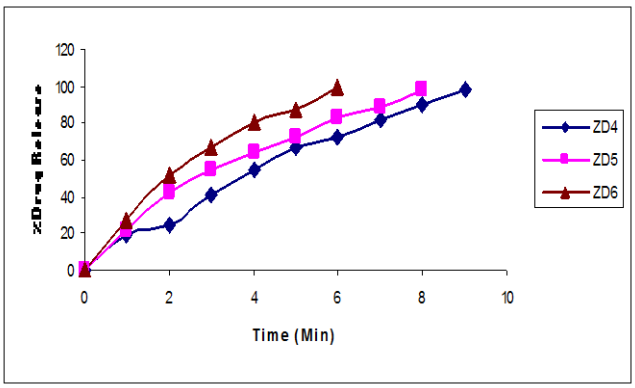

Figure 2: Release profile of Ziprasidone FDT's using sodium starch glycolate.

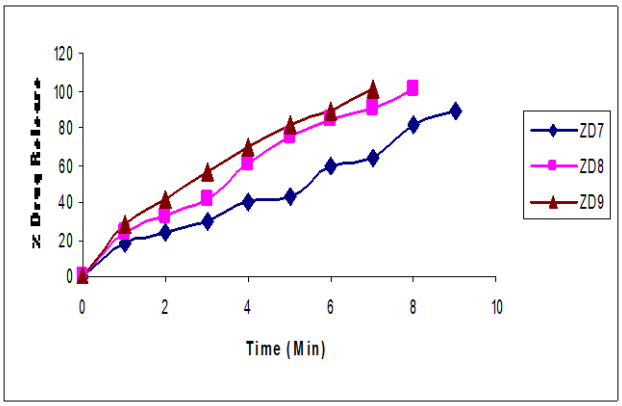

Figure 3: Release profile of Ziprasidone FDT's using crosscaemelose sodium.