

Research article**DESIGN AND DEVELOPMENT OF ZIPRASIDONE FAST DISSOLVING TABLETS BY VACUUM DRYING TECHNIQUE****Hariprasanna R.C, Hrushikesh Dewalkar, Upendra kulkarni, Basawaraj S Patil, Ravi Yachwad, Mahesh More**

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ABSTRACT:

The objective of this research was to formulate fast dissolving tablet of Ziprasidone for rapid action. Vacuum drying method was adapted to prepare the tablets by using two different Sublimating agents. All formulations are evaluated for pre and post-compression parameters like Angle of repose, Bulk density, Tapped density, Housners ratio, Hardness, Weight variation, wetting time, water absorption ratio, Disintegration time, Drug content. The results obtained showed that the quantity of camphor significantly affect response variables. The results indicate that the optimized tablet formulation provides a short DT of 13 sec with sufficient crushing strength and acceptable friability.

Keywords: Ziprasidone, Camphor, Menthol, vacuum drying, Fast dissolving tablets.

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INTRODUCTION:

Many patients especially children and elderly have difficulty in swallowing tablets and capsules and consequently unable to take medicine as prescribed. Almost 50% of the population is affected by such problem, resulting in the high incidence of non compliance and ineffective therapy.¹

Most pharmaceutical forms for oral administration are formulated for direct ingestion, or for chewing, or for prior dispersion and/or dissolution in water; some of them are absorbed in the mouth (sublingual or buccal tablets). To obviate the problems associated with conventional dosage forms, orally fast disintegrating tablets have been developed, which combine hardness, dosage uniformity, stability and other parameters, with extremely easy administration, since no water is required for swallowing the tablets and they are thus suitable for geriatric, pediatric and traveling patients.²

FDTs can be prepared by different methods as direct compression, freeze-drying, spray drying, vacuum drying and wet granulation method.³ The aim of this study was to formulate FDTs with sufficient mechanical integrity and to achieve faster disintegration in the oral cavity without water. To achieve this goal, Lactose used as sweetening agent and Microcrystalline cellulose as diluent for the formulation of tablets. Attempts were made to

enhance dissolution rate along with faster disintegration using sublimating agent like Camphor and Menthol in the formulation of tablets.

Ziprasidone is an novel atypical antipsychotic with unique pharmacological profile and is approved by FDA in Feb 2001 for the treatment of psychotic disorder.⁴ 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.⁵ 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.⁶

Hence in the present work Ziprasidone fast dissolving tablets were prepared by vacuum drying technique by using different sublimating agent.

MATERIALS AND METHODS

Ziprasidone was gifted by Dr.Reddy's Labs Hyderabad; MCC and crospovidone were obtained from Maple biotech Pvt Ltd, Pune, India. Camphor, Menthol, Lactose, Talc, Magnesium stearate were purchased from S.D Fine chemicals ltd, Mumbai, India and all other chemicals and reagents were of analytical grade.

Preparation of Ziprasidone tablets⁷:

Ziprasidone tablets were prepared by vacuum drying technique. The basic principle involved in preparing fast dissolving tablets by vacuum drying technique is inert solid subliming ingredients (E.g. camphor, menthol) were added to other tablet excipients and the blend was compressed into tablet.

Removal of volatile material by vacuum drying generated a porous structure. Compressed tablets containing mannitol and camphor have been prepared by vacuum drying technique. The tablets dissolve within 10-20 seconds and exhibit sufficient mechanical strength for practical use.

Six formulations were developed by varying concentration of subliming agent i.e. camphor and Menthol.

Accurately weighed ingredients were sifted through sieve no.44 and thoroughly mixed for 10 min and magnesium stearate and other ingredients were added to the blend and thoroughly mixed. The tablets were compressed using Rimek tablet punching machine. The compressed tablets were then subjected to vacuum drying by keeping the tablets in vacume dryer at 60°C for 3 hrs. The tablets were removed and evaluated for post compression parameter.

Evaluation of tablets⁸⁻⁹

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

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

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,

$$F = \frac{W_{\text{initial}} - W_{\text{final}}}{W_{\text{initial}}} \times 100$$

% 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 $37^\circ \pm 2^\circ\text{C}$ as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute in the pH 7.4 maintained at $37^\circ \pm 2^\circ\text{C}$. 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 rpm) using 900ml of phosphate buffer pH (7.4) as dissolution medium. Temperature of the dissolution medium was maintained at $37 \pm 0.5^\circ\text{C}$, 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.

RESULT AND DISCUSSION:

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. As the subliming agent concentration was increased the hardness of the tablets were decreased. It may be due to the formation of additional pores after vacuum drying. Disintegration time and wetting time of tablets decreased as the concentration of subliming agent was increased. It may be due to the effect of low hardness.

Table 1: Composition of Ziprasidone fast dissolving tablets.

Ingredients (mg)	Formulations code					
	ZS ₁	ZS ₂	ZS ₃	ZS ₄	ZS ₅	ZS ₆
Ziprasidone	20.00	20.00	20.00	20.00	20.00	20.00
crospovidone	5	5	5	5	5	5
Camphor	3	6	9	-	-	-
Menthol	-	-	-	3	6	9
Lactose	50.0	47.0	44.0	50.0	47.0	44.0
MCC	20	20	20	20	20	20
Mg stearate	1	1	1	1	1	1
Talc	1	1	1	1	1	1
Total Weight	100	100	100	100	100	100

Table 2: Precompressional Parameters of Ziprasidone fast dissolving tablets.

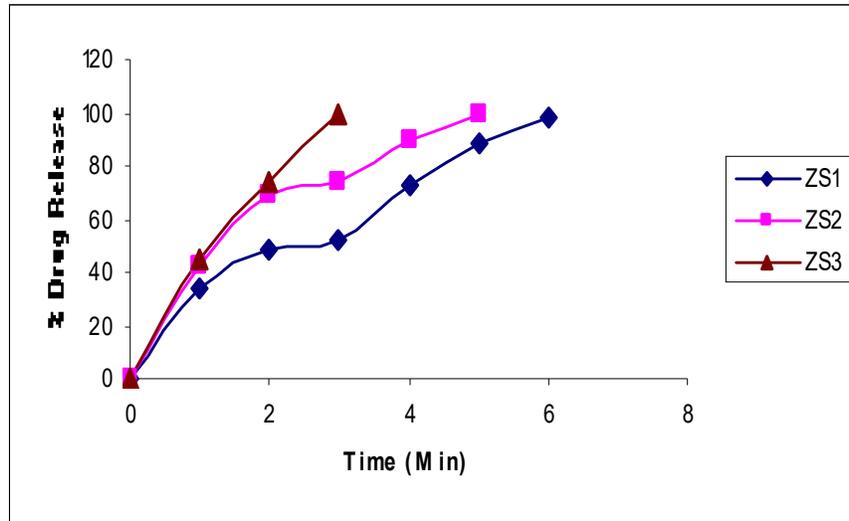
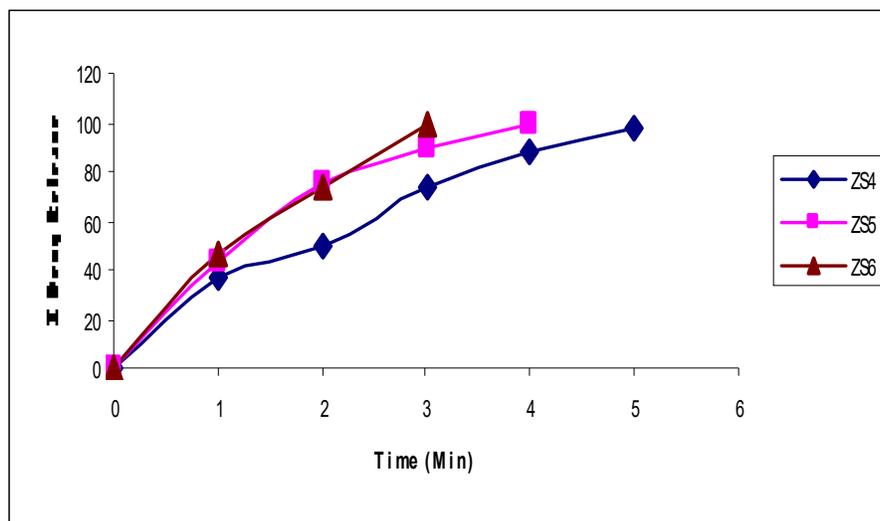
Formulation code	Bulk density* (g/cc) ± SD, n=3	Tapped Density* (g/cc) ± SD, n=3	Angle of repose* (degree) ± SD, n=3	Carr's Index* (%) ± SD, n=3	Hausner's Ratio* ± SD, n=3
ZS ₁	0.322 ± 0.06	0.420 ± 0.01	29.21 ± 1.71	16.44 ± 1.23	1.19 ± 0.03
ZS ₂	0.320 ± 0.06	0.425 ± 0.01	27.34 ± 1.58	16.31 ± 1.02	1.17 ± 0.02
ZS ₃	0.325 ± 0.06	0.428 ± 0.01	28.11 ± 1.30	15.96 ± 1.03	1.18 ± 0.03
ZS ₄	0.356 ± 0.06	0.561 ± 0.02	27.78 ± 1.29	14.68 ± 1.25	1.17 ± 0.03
ZS ₅	0.359 ± 0.06	0.554 ± 0.01	28.54 ± 1.49	13.76 ± 1.36	1.16 ± 0.03
ZS ₆	0.367 ± 0.06	0.570 ± 0.02	26.61 ± 1.25	16.98 ± 1.29	1.18 ± 0.03

Table 3: Post compressional Parameters of Ziprasidone fast dissolving tablets .

Parameters	Formulations code					
	ZS ₁	ZS ₂	ZS ₃	ZS ₄	ZS ₅	ZS ₆
Hardness (kg/cm ²) ± SD	3.1 ± 0.09	3.0 ± 0.05	2.5 ± 0.20	3.0 ± 0.15	2.9 ± 0.30	2.5 ± 0.29
Friability (%)	0.59	0.53	0.71	0.47	0.54	0.27
Thickness* (mm) ± SD	3.18 ± 0.15	3.28 ± 0.10	3.20 ± 0.05	3.31 ± 0.09	3.23 ± 0.10	3.07 ± 0.14
Weight variation* (mg) ± SD	99 ± 0.64	98 ± 0.92	100 ± 0.38	99 ± 0.36	100 ± 0.20	101 ± 0.40
<i>In vitro</i> disintegration time* (sec) ± SD	46 ± 1.75	31 ± 1.54	13 ± 1.44	58 ± 1.59	41 ± 1.18	27 ± 1.33
Wetting time* (sec) ± SD	79 ± 1.25	65 ± 1.37	43 ± 1.53	93 ± 1.54	85 ± 1.35	65 ± 1.23
Water absorption ratio* ± S.D	85 ± 1.20	81 ± 1.33	87 ± 1.59	85 ± 1.78	84 ± 1.89	82 ± 1.10
Drug Content* (%) ± SD	98.90 ± 0.85	98.17 ± 0.80	99.27 ± 0.75	100.03 ± 1.22	101.10 ± 1.87	99.50 ± 1.96

Table 1 4: Release profile of the Ziprasidone fast dissolving tablets.

Formulation Code	$t_{50\%}$ (min)	$t_{90\%}$ (min)
ZS ₁	2.55 ± 0.12	4.59 ± 0.29
ZS ₂	2.00 ± 0.21	3.60 ± 0.32
ZS ₃	1.50 ± 0.39	2.71 ± 0.56
ZS ₄	3.05 ± 0.51	5.49 ± 0.18
ZS ₅	2.50 ± 0.54	4.50 ± 0.27
ZS ₆	2.01 ± 0.45	3.63 ± 0.34

**Fig. 1: Release profile of Ziprasidone FDT's prepared by vacuum drying using camphor****Fig. 2: Release profile of Ziprasidone FDT's prepared by vacuum drying using menthol**

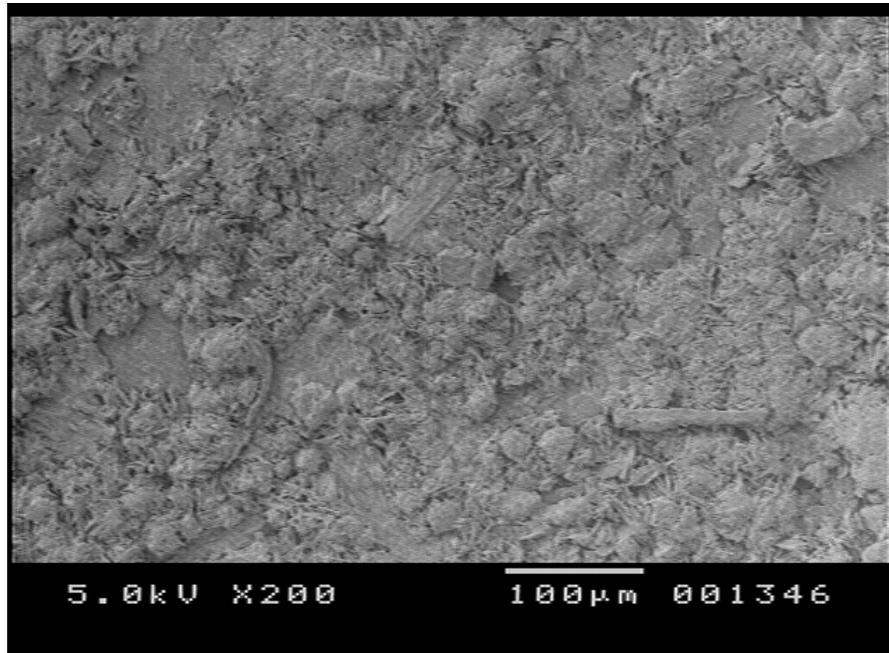


Fig 3: SEM of Ziprasidone tablet without activation

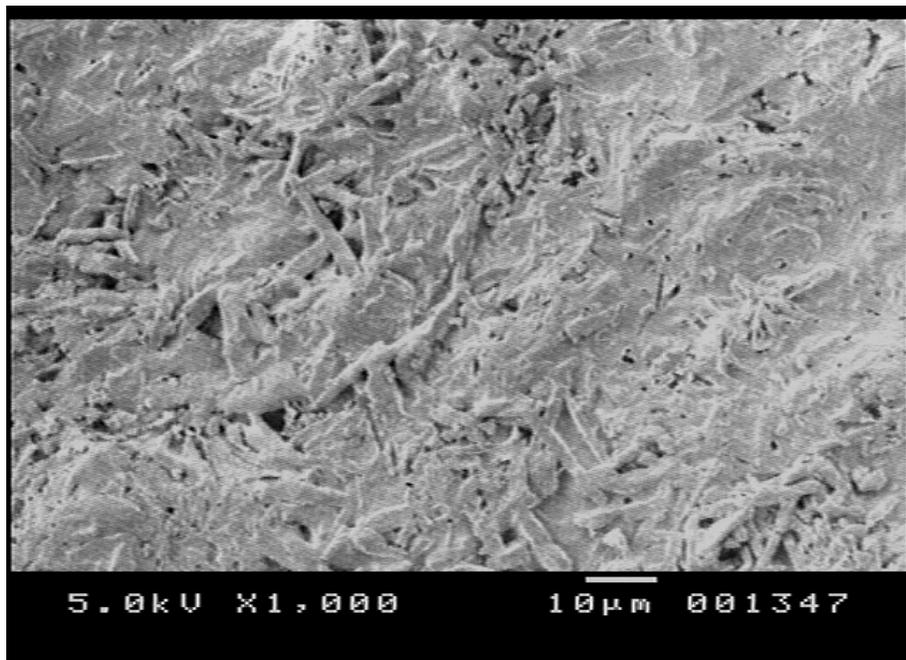


Fig 4: SEM of Ziprasidone tablet with activation

All the prepared tablets passes the weight variation test and was found in the range of 98 to 101 mg which is below $\pm 7.5\%$, , percentage friability was found between 0.27 to 0.71%, *in vitro* disintegration time of 13 to 58 sec, drug content uniformity was in between

98.17 to 101.10%, water absorption ration were found between 81 to 87% and wetting time between 43 to 93 sec. and Shows maximum drug release within 3 min.

In vitro drug release studies showed that as the concentration of subliming agent increased, the rate of dissolution also increased. It may be due to the formation of additional pores and low hardness of the tablets. Drug release from the formulations prepared by using Camphor (ZS1-ZS3) were faster than formulations prepared by Menthol (ZS4-ZS6).

SEM analysis: Before subjecting to vacuum drying the tablets images were taken with scanning electro microscopy and found that there was no formation of pores in the tablets. After vacuum drying process the tablet were also subjected to scan in the SEM and yields the image with formation of pores. When these tablets comes and contact with dissolution medium, immediately medium will enters the body of the tablets due to availability of pores and leads to breaking of the tablets with the influence of crospovidone.

CONCLUSION:

Thus it is concluded that fast disintegrating tablets can be prepared with a view of obtaining faster action of the drug and would be advantageous in compilations to the currently available conventional dosage forms. With the adopted vacuum drying technique an optimum point can be reached in the shortest time with minimum efforts and this technique would be an effective alternative approach compared with the use of more expensive adjuvant in the formulation of fast disintegrating tablets. Finally it can be concluded that the superdisintegrant and volatile substances had played an important role to decrease disintegration time and to enhance the dissolution rate in vacuum drying technique, hence could be used to prepare the Fast Dissolving Tablets.

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