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Design and development of fast dissolving tablets containing ziprasidone by solid dispersion method

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ABSTRACT:

This present work investigates enhancement of the dissolution profile of Ziprasidone using solid dispersion (SD) with crospovidone, Mannitol, Polyethylene glycol by using solvent evaporation technique. Solid dispersions were prepared by solvent evaporation method using solvent methanol in 1:1, 1:2, 1:4, and 1:9 ratio. Dissolution studies using the USP paddle method were performed for solid dispersions of Ziprasidone at 37 ± 0.5^0c and 50 rpm in Phosphate buffer pH 7.4 Fourier transformer infrared (FTIR) spectroscopy were performed to identify the physicochemical interaction between drug and carrier, hence its effect on dissolution. Dissolution of Ziprasidone solid dispersion in crosspovidone improved significantly in solid dispersion the 1:9 (ZC8). Thus, the solid dispersion technique can be successfully used for improvement of dissolution of Ziprasidone.

KEY WORDS: Solid dispersion, Ziprasidone, crospovidone, dissolution enhancement,fast- dissolving tablets.

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INTRODUCTION:

Oral bioavailability of a drug depends on its solubility and/or dissolution rate, and dissolution may be rate determining step for appearance of medicinal effect, therefore efforts to increase dissolution of drug with limited water solubility is often needed. Many methods are available to improve these characteristics, including salt formation, micronization and addition of solvent or surface active agents. Solid dispersion (SD) is one of these methods, and involved a dispersion of one or more active ingredients in an inner carrier or matrix in solid state prepared by melting, dissolution in solvent or melting solvent method.1 Solid dispersion technique has been used for a wide variety of poorly aqueous soluble drugs such as nimesulide, ketoprofen, tenoxicam, nifedipine, nimodipine.[(1)]

The progress in treatment of diseases has been evident within upsurge in development of new drugs. An estimated 40% of these drugs are poorly water soluble. Although most of the drugs have encouraging experimental data obtained in vitro, the in vivo results have been disappointing. The attributes include

1. Poor absorption, rapid degradation, and lamination (peptides and protein) resulting in insufficient concentration,
2. Drug distribution to other tissues with high drug toxicities (anticancer drugs)
3. Poor solubility of drugs, and
4. Fluctuations in plasma levels owing to unpredictable bioavailability.

The enhancement of oral bioavailability of such poorly water soluble drugs remains one of the most challenging aspects of drug development. The development of solid dispersions as a practically viable method to enhance bioavailability of poorly water-soluble drugs overcame the limitations of previous approaches such as salt formation, solubalization by cosolvents, and particle size reduction.[2] Studies revealed that drugs in solid dispersion need not necessarily exist in the micronized state. A fraction of the drug might molecularly disperse in the matrix, thereby forming a solid dispersion.[3-4] when the solid dispersion is exposed to aqueous media, the carrier dissolves and the drug releases as fine colloidal particles. The resulting enhanced surface area produces higher dissolution rate and bioavailability of poorly water-soluble drugs. In addition, in solid dispersions, a portion of drug dissolves immediately to saturate the gastrointestinal tract fluid, and excess drug precipitates as fine colloidal particles or oily globules of submicron size. In spite of these advantages, only 2 products have been marketed since the development of this technology 4 decades ago.

The limitations of this technology have been a drawback for the commercialization of solid dispersions. The limitations include

1. Laborious and expensive methods of preparation,
2. Reproducibility of physicochemical characteristics,
3. Difficulty in incorporating into formulation of dosage forms,
4. Scale-up of manufacturing process, and

   Stability of the drug and vehicle.

Solid Dispersions

The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles [5-6] therefore, based on their molecular arrangement, six different types of solid dispersions can be distinguished. They are described in Table 2. Moreover, certain combinations can be encountered, i.e. in the same sample; some molecules are present in clusters while some are molecularly dispersed.

Moreover, not the preparation method but the molecular arrangement governs the properties of solid dispersions.

MATERIALS AND METHODS

Ziprasidone was gifted by Dr.Reddy's Labs Hyderabad, crospovidone, sodium starch glycolate and polyethylene glycol 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: [7]

Solid dispersion of Ziprasidone was prepared by solvent evaporation method using various carriers such as (Mannitol, PEG-6000 and Crospovidone in different ratio 1:1, 1:2, 1:4, and 1:9). The weighed quientety of drug and mannitol (1:1) was taken in china dish; to which methanol was added. The solvent was evaporated at room temperature and dried in hot air oven at 50 ^{0}C for 4 hrs. The resultant mass was passed through sieve no.60 and stored in desiccators. The procedure was repeated with other carriers.

Evaluation of tablets [8-9]

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

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

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.

SEM Studies:

Image of pure drug Ziprasidone, Mannitol and solid dispersion of ziprasidone in mannitol (1:9) are shown in figure. Images shows that Ziprasidone and mannitol in crystalline form but in the case of solid dispersion drug and polymer converted into amorphous form, indicates that the crystalline form is converted to amorphous form. Conversion to amorphous form is essential to increase the drug solubility.

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**.

Results revealed that all formulations have acceptable physical parameters .The tablet prepared by solid dispersion method passes weight variation was found in the range 248 to 251 mg which is below ±7.5%, hardness 3 to 3.5 Kg/cm^2, percentage friability of 0.42 to 0.77 %, *in vitro* disintegration time of 13 to 89 sec, drug content uniformity was in between 98.23 to 101.19%, water absorption ratio were found between 28 to 52% and wetting time between 54 to 107 sec. and (ZC3) Shows maximum drug release within 5 min. 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 crosspovidone (ZC1-ZC4) were faster than formulations prepared by Mannitol (ZM1-ZM4) and Polyethylene glycol (ZP9-ZP12). It may be due to the more wicking and swelling action of crospovidone than other used polymer.

CONCLUSION:

From the results it was concluded that the tablets prepared by using 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 Ziprasidone fast dissolving tablets

Ingredients (mg)	Formulations code											
	ZM_1	ZM_2	ZM_3	ZM_4	ZC_5	ZC_6	ZC_7	ZC_8	ZP_9	ZP_{10}	ZP_{11}	ZP_{12}
Solid dispersion equivalent to 20mg of drug	40.97	59.29	97.69	200.0	40.93	61.09	96.00	197.64	40.15	60.11	97.68	199.20
Crosprovidone	6	6	6	6	-	-	-	-	6	6	6	6
Sodium starch glycolate	-	-	-	-	6	6	6	6	-	-	-	-
Lactose	196.03	177.7	139.3	34.00	196.07	175.91	141.0	39.36	196.85	176.89	139.32	34.80
Kyron-T-134	5	5	5	5	5	5	5	5	5	5	5	5
Mg stearate	1	1	1	1	1	1	1	1	1	1	1	1
Talc	1	1	1	1	1	1	1	1	1	1	1	1
Total Weight	250	250	250	250	250	250	250	250	250	250	250	250

Table 2: Precompressional Parameters of Ziprasidone fast dissolving tablets.

Formulation	Bulk density (g/cc)	Tapped density (g/cc)	Angle of repose (degree)	Carr's index (%)	Hausner's ratio
ZM_1	0.392 ± 0.10	0.510 ± 0.02	24.22 ± 1.23	20.00 ± 1.58	1.275 ± 0.01
ZM_2	0.400 ± 0.02	0.500 ± 0.01	24.44 ± 1.41	21.75 ± 1.22	1.250 ± 0.09
ZM_3	0.384 ± 0.07	0.555 ± 0.01	24.22 ± 0.57	16.98 ± 0.63	1.200 ± 0.05
ZM_4	0.392 ± 0.01	0.576 ± 0.02	21.52 ± 0.69	19.73 ± 0.58	1.242 ± 0.01
ZC_5	0.401 ± 0.09	0. 425± 0.02	24.14 ± 1.20	21.66 ± 0.60	1.270 ± 0.02
ZC_6	0.401 ± 0.15	0.327 ± 0.03	24.98 ± 1.55	23.24 ± 0.75	1.311 ± 0.04
ZC_7	0.396 ± 0.02	0.556 ± 0.02	23.12 ± 1.42	16.98 ± 1.23	1.200 ± 0.01
ZC_8	0.350 ± 0.13	0.659 ± 0.01	21.56 ± 1.35	19.73 ± 0.67	1.240 ± 0.07
ZP_9	0.372 ± 0.01	0.425 ± 0.01	24.14 ± 0.13	21.66 ± 1.51	1.279 ± 0.01
ZP_{10}	0.389 ± 0.02	0.527 ± 0.02	24.98 ± 1.21	23.25± 1.59	1.311 ± 0.02
ZP_{11}	0.461 ± 0.03	0.551 ± 0.02	23.11 ± 1.07	17.97 ± 1.19	1.200 ± 0.03
ZP_{12}	0.376 ± 0.04	0.558 ± 0.02	20.10 ± 1.26	19.20 ± 1.08	1.242 ± 0.01

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

Parameters	Formulations code											
	ZM_1	**ZM_2**	**ZM_3**	**ZM_4**	**ZC_5**	**ZC_6**	**ZC_7**	**ZC_8**	**ZP_9**	**ZP_{10}**	**ZP_{11}**	**ZP_{12}**
Hardness ($kg/cm^{2)}$ ± SD	3.0 ± 0.11	3.5 ± 0.10	3.0 ± 0.15	3.5 ± 0.20	3.0 ± 0.10	3.0 ± 0.21	3.0 ± 0.05	3.0 ± 0.18	3.0 ± 0.12	3.0 ± 0.14	3.0 ± 0.10	3.0 ± 0.10
Friability (%)	0.55	0.65	0.61	0.42	0.61	0.52	0.42	0.47	0.59	0.77	0.59	0.73
Thickness* (mm) ± SD	4.61 ± 0.09	4.63 ± 0.10	4.62 ± 0.20	4.57 ± 0.21	4.54 ± 0.28	4.62 ± 0.12	4.58 ± 0.17	4.54 ± 0.10	4.54 ± 0.15	4.62 ± 0.13	4.63 ± 0.25	4.56 ± 0.20
Weight variation* (mg) ± SD	249 ± 0.61	248 ± 0.13	250 ± 0.47	248 ± 0.25	251 ± 0.37	249 ± 0.61	248 ± 0.42	249 ± 0.49	250 ± 0.05	249 ± 0.60	251 ± 0.50	250 ± 0.43
In vitro disintegration time* (sec) ± SD	89 ±1.50	76 ± 1.00	65 ± 1.70	51 ± 1.00	56 ± 1.45	48 ± 1.28	36 ± 2.15	13 ± 1.55	85 ± 1.21	81 ± 1.10	75 ± 1.00	65 ± 1.11
Wetting time* (sec)± SD	92 ± 1.0	87 ± 1.42	69 ± 1.89	61 ± 2.10	92 ± 1.12	73 ± 1.35	64 ± 1.79	54 ± 1.41	107 ± 1.25	98 ± 1.21	87 ± 1.15	81 ± 1.48
Water absorption ratio* ± S.D	51 ± 1.24	52 ± 1.09	33 ± 1.12	28 ± 1.34	51 ± 1.31	49 ± 1.73	33 ± 1.54	42 ± 1.37	50 ± 1.34	42 ± 1.55	34 ± 1.14	42 ± 1.12
Drug Content* (%) ± SD	98.23 ± 0.22	101.19 ± 0.34	100.80± 1.63	100.48 ± 1.21	99.98 ± 1.41	99.99 ± 0.55	99.99 ± 1.53	100.48 ± 1.51	99.99 ± 0.73	100.01 ± 0.57	98.91 ± 1.16	99.93 ± 1.42

Table 4: Release profile of the Ziprasidone fast dissolving tablets

Formulation Code	$t_{50\%}$ (min)	$t_{90\%}$ (min)
ZM_1	5.60 ±1.42	10.08 ±0.65
ZM_2	5.57 ± 1.08	10.03±1.11
ZM_3	4.02 ±0.67	9.95 ±1.84
ZM_4	3.53 ±0.54	6.35±0.56
ZC_5	4.00 ± 1.97	7.20 ±0.75
ZC_6	3.00 ± 0.89	5.40 ±0.71
ZC_7	2.44 ±1.08	4.47 ±1.21
ZC_8	2.50 ± 0.65	4.50 ±1.08
ZP_9	6.05 ± 0.21	10.89 ±1.46
ZP_{10}	5.54 ± 0.42	9.97±1.69
ZP_{11}	5.04 ± 0.57	9.07 ±1.03
ZP_{12}	4.50 ± 1.02	8.01 ±0.42

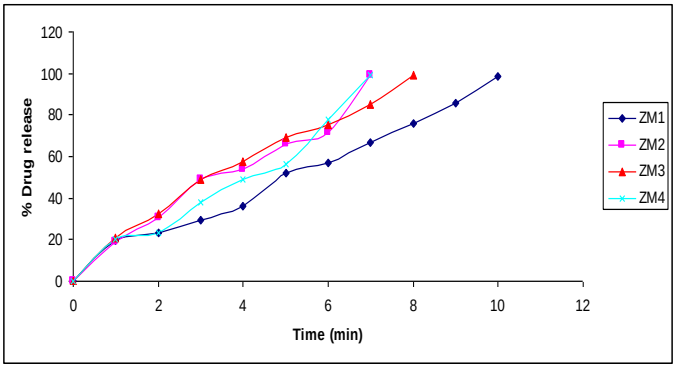


Figure 1: Release profile of Ziprasidone FDT's prepared solid dispersion using mannitol

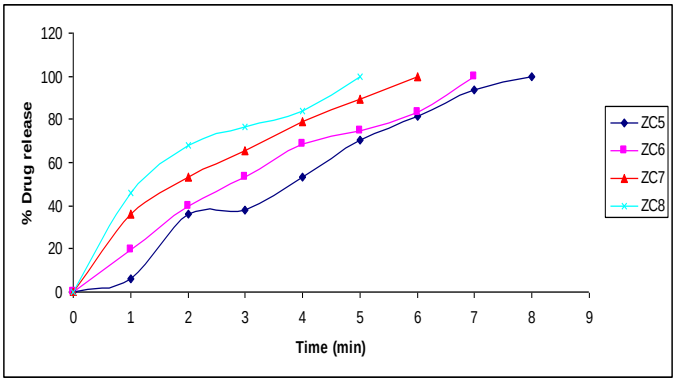


Figure 2: Release profile of Ziprasidone FDT's prepared solid dispersion using crosspovidone

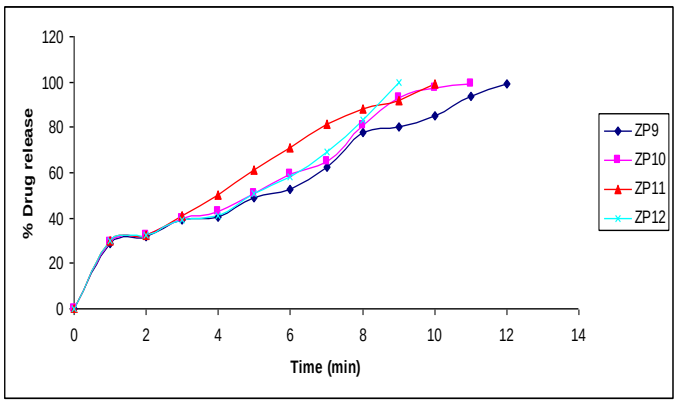
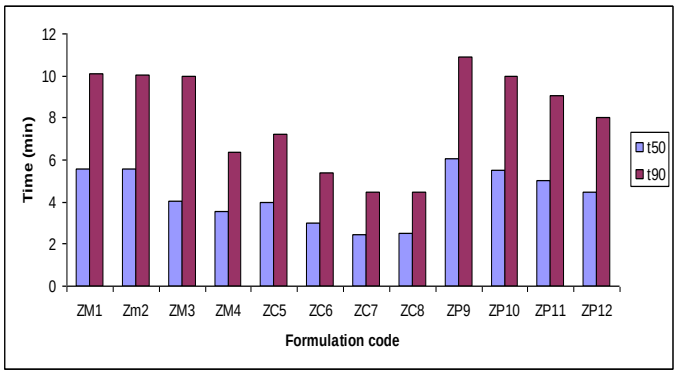


Figure 3: Release profile of Ziprasidone FDT's prepared solid dispersion using polyethylene glycol



Figgure 4: Comparison of release profile (t_{50}min and t_{90}min) formulations of Solid dispersion method

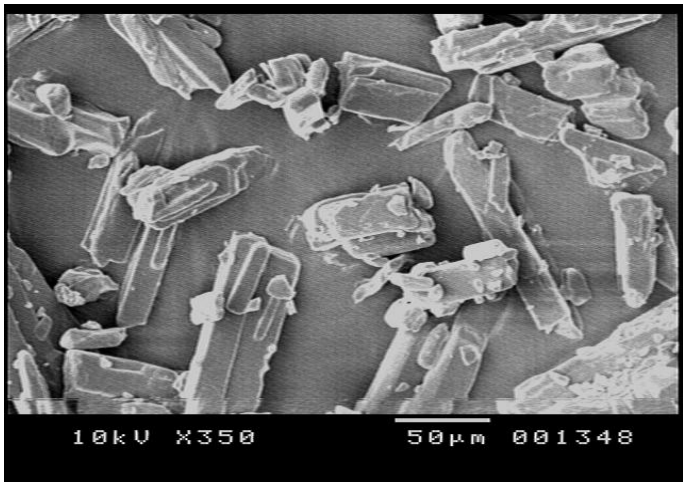


Figure 5: SEM of pure drug Ziprasidone

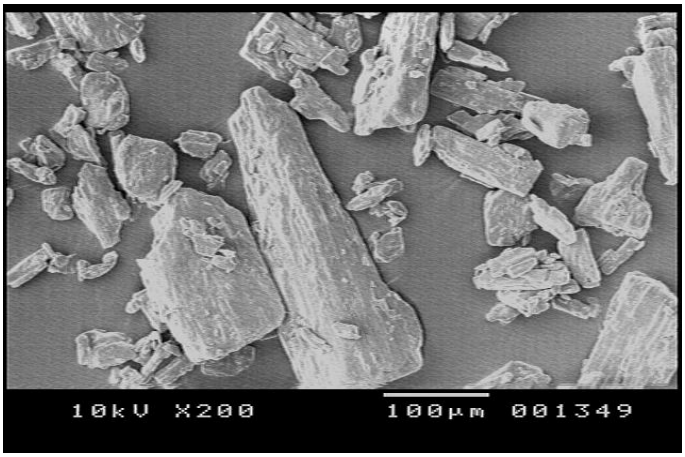


Figure 6: SEM of the DM Mannitol

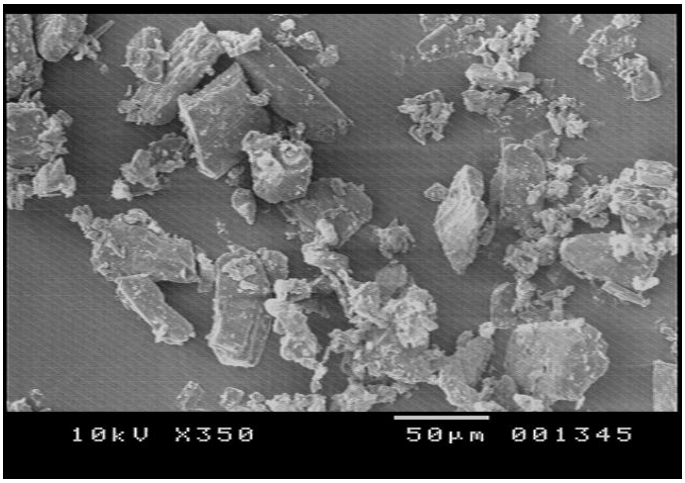


Figure 7: SEM of the Ziprasidone Mannitol solid dispersion

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