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Formulation and Evaluation of Mouth Dissolving Tablet of Olanzapine by Coproducting Superdisintegrants

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ABSTRACT

The scenario present in this article is to focus on areas of research in cancer and its therapy. An outline is explained here related to cancer and its therapeutics. It is possible to design and construct targeted with least side effects system by application of nanotechnology. At Nano scale, novel properties are present with nanoparticle making them magic bullets to kill various diseases. Here it is explored that nanoparticles have so much potential to be used as carriers, selective, targeted system. In the recent years, due to lots of changes and advancement in technique, facility etc. scope for dosage form design has been widened.

Key-words:

Mouth dissolving tablets, direct compression, co-processed superdisintegrants, croscarmellose sodium, crospovidone

INTRODUCTION

The desired therapeutic level may be achieved through administration of a variety of dosage forms in a particular dose and at a particular frequency. Drugs are more frequently taken by oral administration. As compared with the other routes, the oral route is the most convenient and popular among all populations for drug delivery. Although a few drugs taken orally are intended to be dissolved within the mouth, the vast majority of drugs taken orally are swallowed. Geriatric patients may have difficulty in swallowing and chewing the tablets, resulting in patient noncompliance and ineffective therapy¹. To overcome these problems, Mouth Dissolving Tablets are designed. For poorly soluble orally administered drugs, the rate of absorption is often controlled by the rate of dissolution. The rate of dissolution can be increased by increasing the surface area of available drug by various methods (micronization, complexation, solid dispersion etc). Another prerequisite for the mouth dissolution may be the disintegration time of tablets, as rapid disintegration of tablets delivers a fine suspension of drug particles and thus, greater dissolution of the drug².

Major challenge for tablet manufacturing comes from the flow properties of the materials to be compressed. Most of the formulations (> 70%) contain excipients at higher concentration than active drug. Single component excipients do not always provide a requisite performance of the active component in the formulation, so there is a need to develop a multicomponent excipients system such as Co-processing of the excipients, to improve the performance level of the formulation³.

A co-processed excipient is a combination of two or more compendial or noncompendial excipients designed to physically modify their properties in a manner not achievable by simple physical mixing, and without significant chemical change. However, in some instances, formation of necessary components may occur, such as *in-situ* salt formation. Coprocessing of the excipients could lead to formation of excipients with superior quality than their physical mixture containing individual excipients⁴.

Olanzapine or 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno [2,3-b][1,5] benzodiazepine belonging to Antipsychotics agents which was approved by the Food and Drug Administration (FDA). It is used in the treatment of schizophrenia, depressive episodes associated with bipolar disorder, acute manic episodes, and maintenance treatment in bipolar disorder. Furthermore, on account of the low aqueous solubility it is well-absorbed after oral administration. The absolute bioavailability is only approximately 31.5% due to extensive hepatic metabolism.

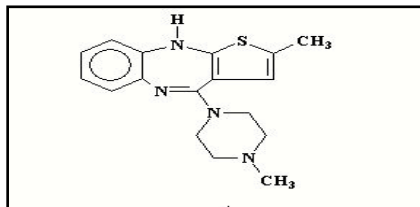


Figure 1: Chemical Structure of Olanzapine

The present research involves the preparation and evaluation of fast dissolving tablets of Olanzapine by using co-processed superdisintegrants containing crospovidone and croscarmellose sodium was studied.

MATERIALS AND METHODS

A. Materials

Olanzapine was kindly supplied by Ipca Laboratories Ltd. (Mumbai, M.S, India). Mannitol was obtained from Indoco Remedies (Aurangabad, M.S. India) Croscarmellose Sodium (Ac-Di-Sol), Crospovidone (Polyplasdone XL), Microcrystalline Cellulose (Avicel PH), Colloidal Silicon Dioxide (Aerosil), Magnesium Stearate and Sodium Saccharin were obtained from MG Biopharm. (Mumbai, M.S, India). All other chemicals used were of analytical grade and were used without further purification.

B. Methods

1. Compatibility Studies

A proper design and formulation of a dosage form requires considerations of the physical, chemical and biological characteristics of both the drug and the excipients used in fabrication of the product. Compatibility must be established between the active ingredient and other excipients to produce a stable, efficacious, attractive and safe product. If the excipients are new and if no previous literature regarding the use of those particular excipients with an active ingredient is available, then compatibility studies are of supreme importance. Hence, before producing the actual formulation, compatibility of Olanzapine with different polymers and other excipients was tested using the Fourier Transform Infrared Spectroscopy (FT-IR) technique and Differential Scanning Calorimetry (DSC) ¹⁰.

➤ **Fourier Transform Infra Red Spectroscopy (FTIR)**

FTIR spectra of pure Olanzapine, co-processed mixture and physical mixture of drug and excipients were recorded on FTIR 4100 (Jasco). The IR spectrum of all the samples was obtained using KBr pellet technique. All samples were mixed with IR grade potassium bromide separately and scanned in the range of 4000-400 cm⁻¹ (FTIR-4100, Jasco).

➤ **Differential Scanning Calorimetry (DSC)**

Thermal properties of the pure drug, co-processed mixture and the physical mixture of drug and excipients were analyzed by Shimadzu DSC- 60, Shimadzu Ltd. Japan. The samples were heated in hermetically sealed aluminum pans. Heat runs for each sample were set from 0°C to 300°C at a heating rate of 10°C/ min, using nitrogen as blanket gas.

2. Preparation of co-processed superdisintegrants

The co-processed superdisintegrants were prepared by solvent evaporation method. A blend of crospovidone and croscarmellose sodium in the ratio (1:1, 1:2, & 1:3) was added to 10ml of ethanol. The contents of the beaker (250 ml capacity) were mixed thoroughly and stirring was continued till most of ethanol evaporated. The wet coherent mass was granulated through # 44-mesh sieve. The wet granules were dried in a hot air oven at 60°C for 20 minutes. The dried granules were sifted through # 44-mesh sieve and stored in airtight container till further use.

3. Preparation of mouth dissolving tablets by using direct compression method:

Mouth dissolving tablets of Olanzapine were prepared by direct compression method. Composition of various formulations is shown in figure 1. All the excipients were passed through #60 mesh separately. Then the ingredient weighed and mixed properly and compressed into tablet of 75 mg using 6 mm flat punches using karnavati (Remik) tablet press machine. The total weight of the individual tablet was maintained at 75 mg.

Table 1: Formulation of Mouth dissolving tablets of Olanzapine

Tablet Ingredient(mg)	Formulation Batches						
	C0	PM1	PM2	PM3	CP1	CP2	CP3
Olanzapine	5	5	5	5	5	5	5
CSP + CCS	-	3	3	3	3	3	3
Pearlitol SD-200	51	50	50	50	50	50	50
Avicel PH 102	17	15	15	15	15	15	15
Aerosil	0.50	0.50	0.50	0.50	0.50	0.50	0.50
Sodium Saccharine	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Peppermint Flavor	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Magnesium Stearate	1	1	1	1	1	1	1
Total Weight	75	75	75	75	75	75	75

Where = C0-Control release formulation (without superdisintegrants), CSP-Crospovidone, CSS-Croscarmellose sodium, PM1, PM2, PM3 are Physical mixture of superdisintegrants in different ratio (1:1, 1:2, 1:3), CP1 CP2, CP3, are the Co-processed superdisintegrants in different ratio (1:1,1:2, 1:3) respectively.

4. Evaluation of Precompression Parameters

Weighed quantity of powder blend was taken in a graduated cylinder and the bulk volume (V_b) was measured, and weight of the blend (M) was determined. The measuring cylinder containing known mass of powder blend was tapped for a fixed time and the tapped volume (V_t) occupied in the cylinder and the weight of the blend (M) was measured. From that bulk density, tapped density, Hausner's ratio and Compressibility index were calculated.

Bulk Density (D_b)

It is the ratio of total mass of powder to the bulk volume of powder. An accurately weighed quantity of powder, which was previously passed through sieve # 40 [USP] and carefully poured into graduated cylinder. Then after pouring the powder into the graduated cylinder the powder bed was made uniform without disturbing. Then the volume was measured directly from the graduation marks on the cylinder as ml ¹¹. The volume measure was called as the bulk volume and the bulk density is calculated by following formula;

$$D_b = M / V_b$$

Where, M is the mass of powder

V_b is the bulk volume of the powder.

Tapped Density (D_t)

It is the ratio of total mass of powder to the tapped volume of powder. Volume was measured by tapping the powder for 100 times and the tapped volume was noted if the difference between these two volumes is less than 2%. If it is more than 2%, tapping is continued for some times and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2% (in a bulk density apparatus) ¹¹. It is expressed in g/ml and is given by,

$$D_t = M / V_t$$

Whereas, M is the mass of powder & V_t is the tapped volume of the powder.

Carr's Index

The simplest method of measurement of free flow of powder is compressibility, an indication of the ease with which material can be induced to flow is given by compressibility index (I) (Bhowmik D et al.,2009) which is calculated as follows,

$$\text{Carr's Index} = D_t - D_b / D_t \times 100$$

Where, D_t is the tapped density of the powder and D_b is the bulk density of the powder.

Hausner's ratio

Hausner's ratio is an indirect index of ease of powder flow¹². It is calculated by the following formula,

$$\text{Hausner's ratio} = D_t / D_b$$

Where, D_t is the tapped density. & D_b is the bulk density.

Lower Hausner's ratio (<1.25) indicates better flow properties than higher once (>1.25).

Angle of Repose (θ)

The angle of repose of powder was determined by the funnel method. The accurately weighed powder was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the powder. The powder was allowed to flow through the funnel freely onto the surface¹³. The diameter of the powder cone was measured and angle of repose was calculated using the following equation,

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

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

Where, θ is the angle of repose, h is the Height, r is the radius.

5. Evaluation of Post Compression Parameters¹⁵

a. General Appearance

The general appearance of a tablet, its visual identification and over all 'elegance' is essential for consumer acceptance. Therefore tablets were evaluated for its organoleptic properties.

b. Thickness

Tablet thickness is an important characteristic in reproducing appearance and also in counting by using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Ten tablets were taken and their thickness was recorded using Vernier caliper.

c. Weight Variation

Weight variation was calculated as per method described in Indian Pharmacopoeia (I.P. 2007). 20 tablets were weighed individually and the average weight is calculated. The requirements are met if the weights of not more than 2 of tablets differ by more than the percentage listed in table no tablets differ in weight by more than double that percentage.

d. Hardness

Tablets were selected at randomly from each formulation and hardness was checked by using Monsanto Hardness Tester.

e. Friability Test

Pre-weighed sample of tablets was placed in the Roche Friability tester, which was then operated for 100 revolutions. Tablets were de dusted and reweighed; tablets should not lose more than 1% of their initial weight.

$$\% \text{ Friability} = \text{loss in weight} / \text{Initial weight} \times 100$$

f. Disintegration Test (time) ¹⁵

Many reports suggest that conventional DT apparatus may not give correct values of DT for MDTs. The amount of saliva available in the oral cavity is very limited (usually less than 6 ml) whereas the conventional DT apparatus uses a large amount of water with very rapid up and down movements. MDT is required to disintegrate in such small amount of saliva within a minute without chewing the tablet. In a simplest method to overcome this problem, 6 ml of 0.1 N HCl was taken in a 25 ml measuring cylinder. Temperature was maintained at $37 \pm 2^\circ\text{C}$. A MDT was put into it and time required for complete disintegration of the tablet was noted.

g. Wetting time

A piece of tissue paper (12cmx10.75cm) folded twice was placed in a Petri dish (6.5 cm internal diameter) containing 6 ml of 0.1 N HCl. A tablet was carefully placed on the surface of the tissue paper and allowed to wet completely. The time required for complete wetting of the tablet was measured as a wetting time ¹⁸.

h. Water Absorption Ratio

A piece of tissue paper folded twice was placed in a small Petri dish (10 cm diameter) containing 6 ml of 0.1 N HCl. A tablet was put on the tissue paper and allowed to wet completely. The wetted tablet was then reweighed ¹⁸. Water absorption ratio, R was determined using following equation.

$$R = 100 (W_a - W_b) / W_b$$

Where, W_a = weight of tablet after absorption

W_b = weight of tablet before absorption.

i. Content uniformity

20 tablets from each batch were weighed accurately and powdered powder equivalent to 100 mg Olanzapine was shaken with 100 ml of 0.1N HCl in 100 ml amber colored volumetric flask and from this 10 ml was pipette out and then dilute up to 100 ml. From standard solution again 10 ml pipette out and diluted up to 100 ml in 100 ml amber colored volumetric flask. Resulting solution was filtered and

assayed at 258 nm, using a UV- visible beam spectrophotometer (UV-1800, Lab India) and content of Olanzapine was calculated.

j. In vitro dissolution Study

In vitro release rate study of mouth dissolving tablet of Olanzapine was carried out using the Type II (Paddle apparatus) method. The dissolution test was carried out using 900 ml of 0.1 N HCl, at $37 \pm 0.5^\circ\text{C}$ and 50 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus at 2 min interval upto 30 min and withdrawn volume was replaced with fresh dissolution media. The withdrawn samples diluted with dissolution medium and then filter it with watmann filter paper and assayed at 258 nm, using UV-visible spectrophotometer (UV-1800) Cumulative percent drug release was then calculated.

RESULT AND DISSCUSION

1. Compatibility Studies

Fourier Transform Infra Red Spectroscopy (FTIR)

Drug polymer compatibility studies were carried out using Fourier Transform Infra Red spectroscopy to establish or rule out any possible interaction of Olanzapine with the polymers used in the formulation. The FT-IR spectra of the formulations were compared with the FT-IR spectra of the pure drug. The results are shown in fig 2-5, indicating that the characteristic absorption peaks due to pure Olanzapine have appeared in the formulated tablets, without any significant change in their position after successful formulation, indicating the absence of any chemical interaction between Olanzapine and Polymers.

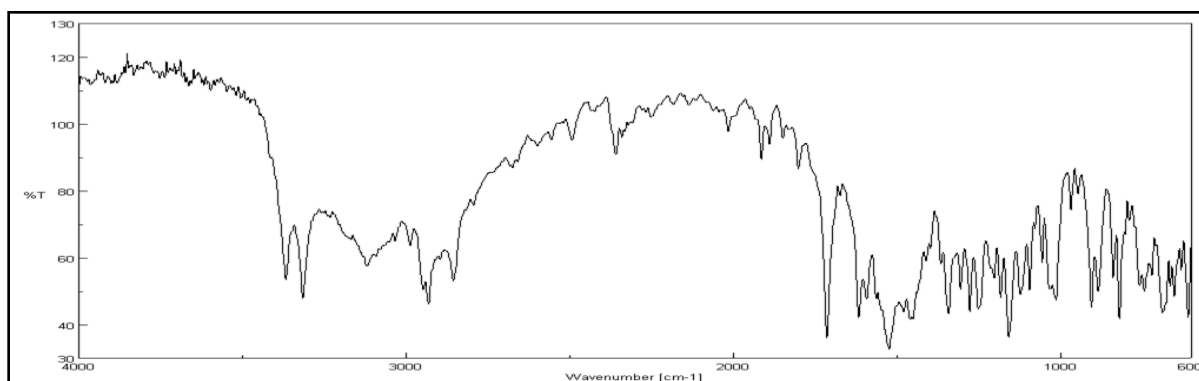


Figure 2: IR spectrum of Olanzapine

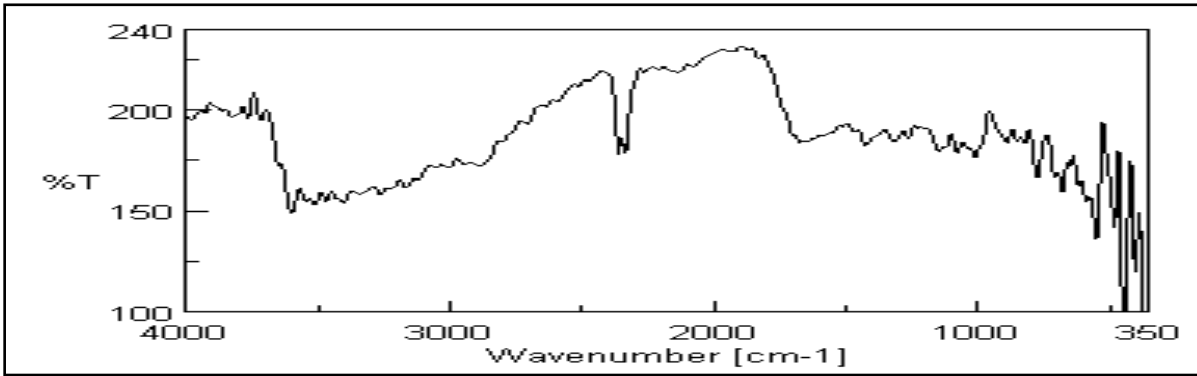


Figure 3: IR of Drug + Co-processed superdisintegrants

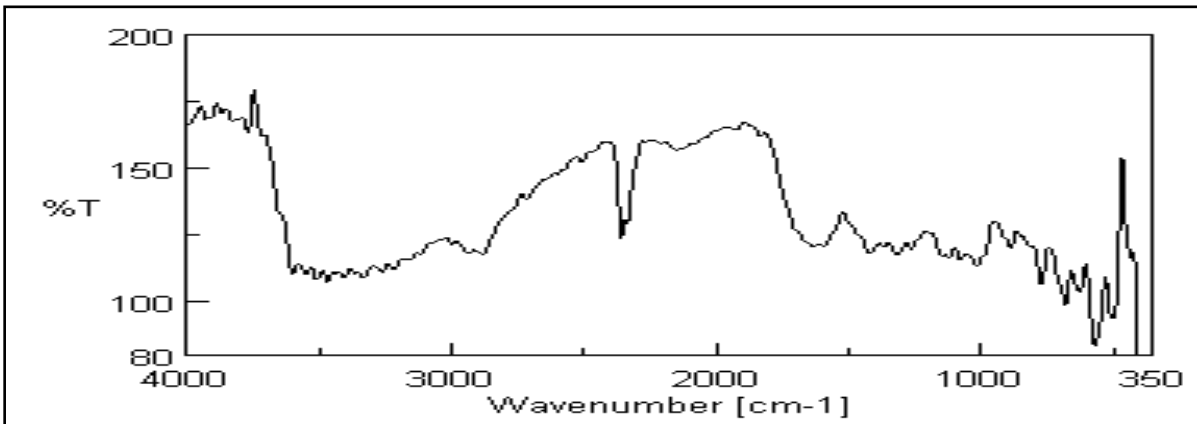


Figure 4: IR of drug+ Physical Mixture.

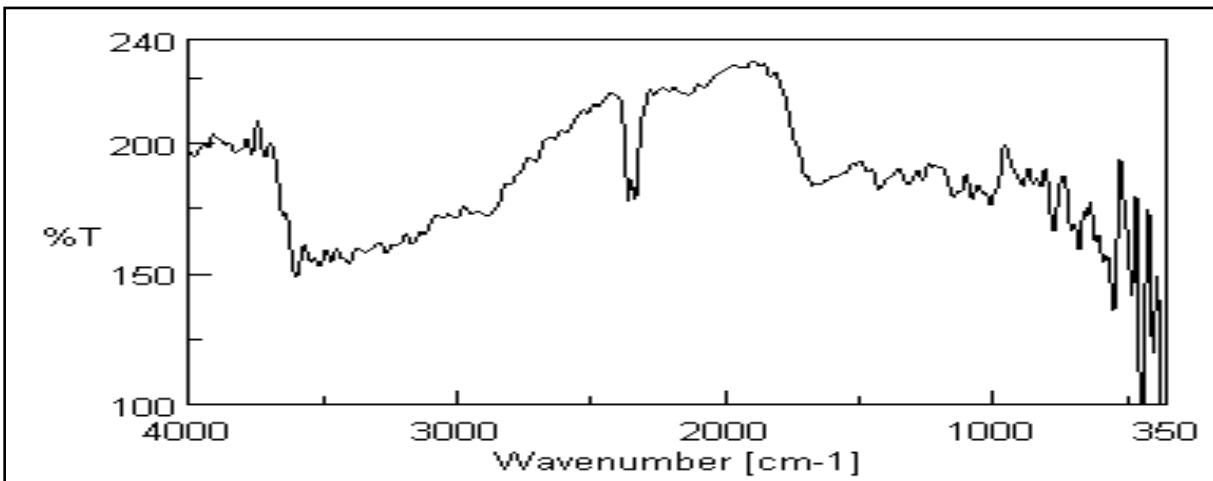


Figure 5: FTIR of Optimized Batch

Differential Scanning Calorimetry (DSC)

DSC is useful in the investigation of solid-state interactions. The DSC analysis of pure ENM showed a sharp endothermic peak at 208°C corresponding to its melting point (Figure 6). The thermograms were

generated for pure drug and drug excipients mixtures. The DSC analysis of physical mixture of the drug and excipients revealed negligible change in the melting point of Olanzapine in the presence of other excipients. Thermograms are shown in figure 7 and figure 8 respectively.

Mouth dissolving tablets of Olanzapine were prepared using above co-processed superdisintegrants and physical mixtures of superdisintegrants. Directly compressible mannitol was used as a diluent to enhance mouth feel. A total of six formulations and control formulation CP0 (without superdisintegrant) were designed.

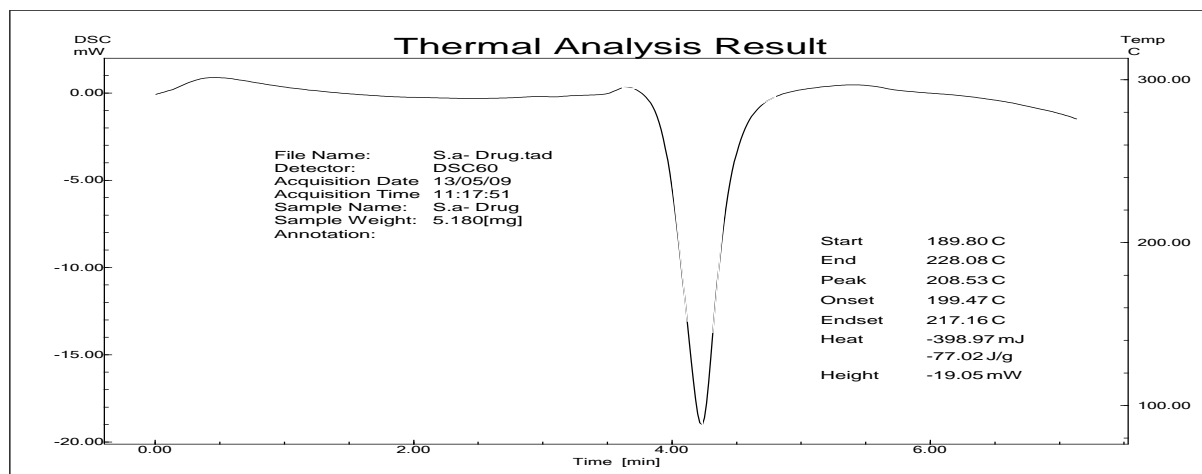


Figure 6:

DSC Thermogram of Olanzapine

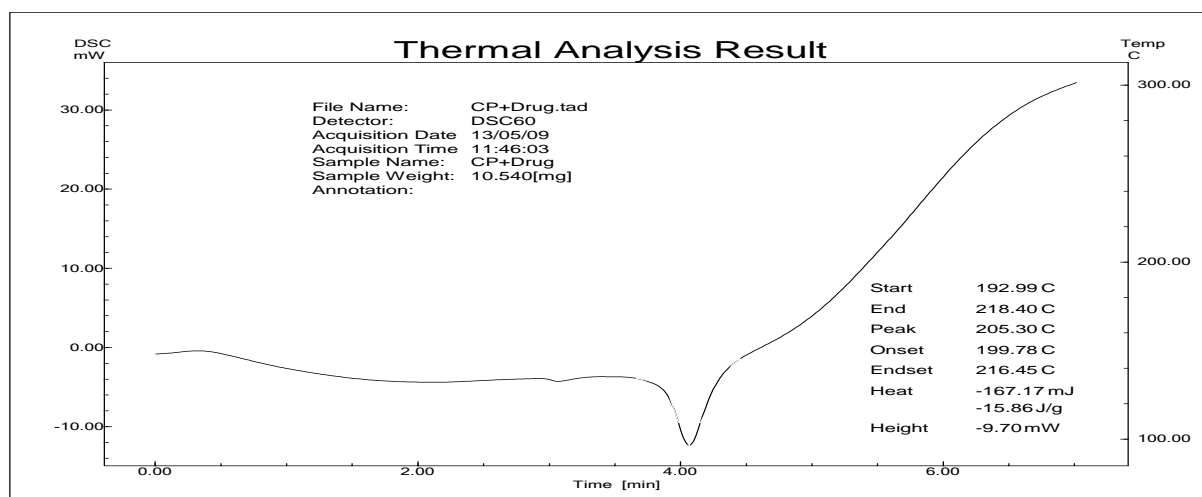


Figure 7:

DSC of Drug + Co-processed superdisintegrants (CSP+CSS) in 1:1 ratio

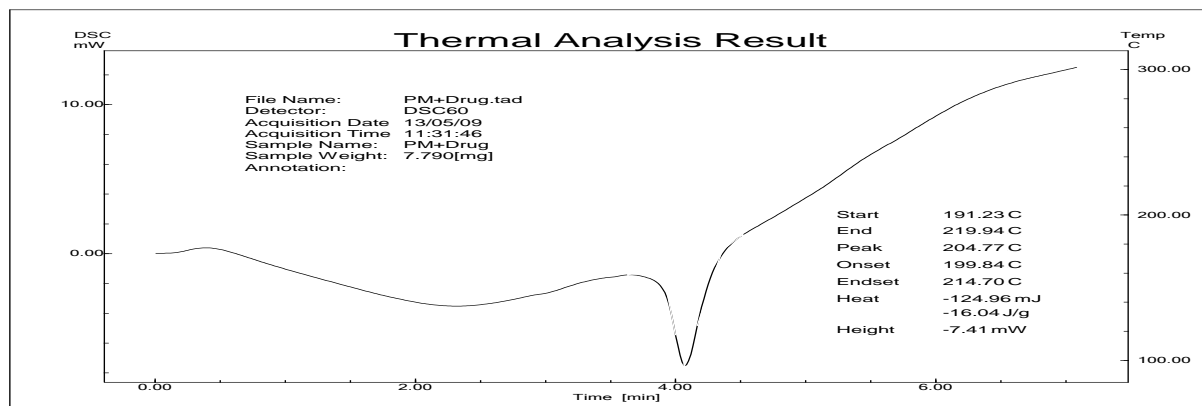


Figure 8:

DSC of Drug + Physical Mixture in 1:1 ratio

2. Pre-Compression Parameters of Powder Blend

Pre-compression parameter for the formulations prepared by direct compression technique is shown in Table 6. The bulk density for all the formulations batches varied from 0.379 gm/cm³ to 0.502 gm/cm³. The tapped density for all the formulations batches varied from 0.434 gm/cm³ to 0.6 gm/cm³. The angle of repose of co-processed superdisintegrants was found to be <25° which indicate excellent flow in comparison to physical mixture of superdisintegrants >30° due to granule formation, Carr's index in the range of 12.21-28.75% and Hausner's ratio in the range of 1.13-1.40. The results (table 2) showed that all the parameter of Superdisintegrants is within limit and were used for further studies.

Table 2: Characterization of powder blends of superdisintegrants

Formulation batches	Evaluation of parameter					
	Angle Of repose	Bulk Density (g/cm ³)	Tapped Density (g/cm ³)	Compressibility Index (%)	Hausner's Ratio	Flowability
CP1	25.27±0.11	0.263±0.005	0.308±0.008	12.26±0.098	1.134±0.046	Good
CP2	25.67±0.15	0.262±0.001	0.309±0.01	13.26±0.18	1.142±0.019	Good
CP3	25.89±0.12	0.264±0.002	0.316±0.006	15.54±0.51	1.130±0.2	Good
PM1	28.13±0.69	0.354±0.004	0.464±0.02	24.89±0.17	1.368±0.063	Good
PM2	28.77±0.19	0.380±0.002	0.522±0.006	27.04±0.09	1.366±0.005	Good
PM3	29.28±0.11	0.280±0.008	0.398±0.002	28.08±0.08	1.45±0.098	Good

3. Evaluation of Post Compression Parameters of Olanzapine Tablets.

All batches of tablets were subjected for post compression parameters evaluation, such as hardness, friability, thickness, drug content, weight variation, wetting time, and *in-vitro* disintegration time were studied shown in table 3.

In all the formulations, the hardness test indicates good mechanical strength. The results were in the range 3.10 to 3.60 kg/cm². Friability was observed in the range 0.40 to 0.65 i.e. less than 1% which indicates that the tablets had a good mechanical resistance. Thickness of all formulations was observed in the range from 2.12 to 2.21 mm. Drug content was found to be in the range of 97.75 to 99.36 %, which is within acceptable limits. Weight variation was found within the specifications of I.P'96. The wetting time experiment mimics the action of saliva in contact with the tablet to illustrate the water uptake and subsequent wetting of tablet. Wetting time is closely related to the inner structure of the tablet which showed that wetting process was very rapid in almost all formulations. The wetting time is an important criteria for understanding the capacity of disintegrants to swell in presence of little amount of water were found to be in the range of 25.55 to 114 sec. Among all the designed formulations, formulation CP1 was found to be promising and was displayed an *in-vitro* disintegration time of 27 sec, which facilitates its faster disintegration in the mouth.

Amongst all the formulations CP1 containing 4% w/w of co-processed superdisintegrant (1:1 mixture of crospovidone and sodium croscarmellose sodium) was found to be promising and has shown an *in-vitro* disintegration time of 27 sec, wetting time of 25.55 sec when compared to the formulation PM1 containing 4% w/w of physical mixture of superdisintegrants (1:1 mixture of crospovidone and croscarmellose sodium) which shows *in-vitro* disintegration time of 53 sec, wetting time of 38 sec and control formulation (CPO) which shows 105 sec, 114 sec. values respectively for the above parameters.

The percent cumulative drug release of all formulated batches is shown in figure 9 and Table 3. % cumulative drug release for 10 min for all formulation batches i.e. CP1 to CP3, PM1 to PM3 and C0 showed wide variation in the range of 66.99 and 99.96 %. % CDR for formulation batch C0 was found 79.48. The formulation batches i.e. CP1, CP2, CP3, PM1, PM2, PM3 showed drug release in 10 min as 99.96, 97.29, 90.37, 96, 95.45 and 94.76 % respectively. The wide variation in the % CDR at 10th min was observed because of change in amount of proportion of superdisintegrants taken for study. Hence it was evident that selected Superdisintegrants taken for study played vital role in dissolution behaviour. This data reveals that among all the formulation CP1 shows faster drug release i.e. 99.96 %.

Table 3: Evaluation of compressed tablet for formulation batches

Evaluation Parameters	Formulation batches						
	C0	CP1	CP2	CP3	PM1	PM2	PM3
Weight Variation (Kg/cm ²)	74.45±0.04	75.3±0.72	74.66±1.98	74.66±1.52	75±0.57	74 ±1	74.25±1
Thickness (mm)	2.15±0.017	2.21±0.025	2.13±0.040	2.29±0.05	2.25±0.055	2.30±0.065	2.12±0.025
Hardness (Kg/cm ²)	3.60±0.04	3.60±0.004	3.10±0.05	3.36±0.03	3.50±0.04	3.28±0.01	3.19±0.02
Friability (%)	0.40±0.11	0.67±0.05	0.53±0.12	0.50±0.4	0.66±1	0.65±0.15	0.59±0.01
Water Absorption Ratio (%)	51.44±0.98	93.46±0.08	91.20±1	87.89±0.55	75.26±0.015	78.59±0.24	80.64±0.047
Wetting time (seconds)	114±2.54	25.55±0.07	29.68±0.067	34.44±2.54	38±0.5	42±1.19	57±1.9
<i>In vitro</i> DT (seconds)	105±1.19	27±1.73	34±2.64	39±0.23	53±1	59±1.79	61±2.64
Drug Content (%)	99.36±0.02	99.65±0.03	99.45±0.02	98.06±0.05	98.55±0.03	98.06±0.05	97.75±0.02

Table 4: Dissolution profile of formulation batches (Comparative study).

Time (min)	Cumulative % drug release							
	C0	CP1	CP2	CP3	PM1	PM2	PM3	MF
2	27.54±0.45	82.62±1.2	73.26±0.45	70.56±0.65	75.42±0.28	71.10 ±0.58	69.66±0.36	33.9±0.3
4	33.74±0.52	90.62±0.75	81.76±0.34	77.79±0.62	80.15±0.75	80.67 ±0.39	77.2±0.72	41.28±0.26
6	41.94±0.5	98.31±0.58	92.20±0.59	70.97±0.55	87.98±0.48	90.48 ±0.42	84.15±0.58	46.59±2.54
8	57.81±0.21	99.21±0.65	95.40±0.72	80.87±0.5	91.72±0.56	93.00 ±0.48	90.00±0.45	52.08±1.88
10	66.99±0.64	99.96±0.84	97.2± 0.29	90.37±0.74	96.00±0.25	95.45 ±0.63	94.76±0.38	64.36±0.02
12	71.82±0.37	-	98.59±0.38	98.42±0.74	97.59±0.62	95.99 ±0.7	97.69±0.6	69.76±0.36
14	79.48±0.47	-	99.02±0.02	98.67±0.55	98.2±0.46	97.60 ±0.58	96.89±0.38	73.21±0.86
16	81.32±0.15	-	-	-	-	-	-	78.92±0.12
18	84.68 ±0.17	-	-	-	-	-	-	85.3 ±0.4

20	90.22 ±0.19	-	-	-	-	-	-	89.73±0.22
22	93.56 ±0.02	-	-	-	-	-	-	91.06±0.32
24	96.87 ±0.27	-	-	-	-	-	-	93.44±0.07
26	97.32 ±0.44	-	-	-	-	-	-	98.9 ±0.12

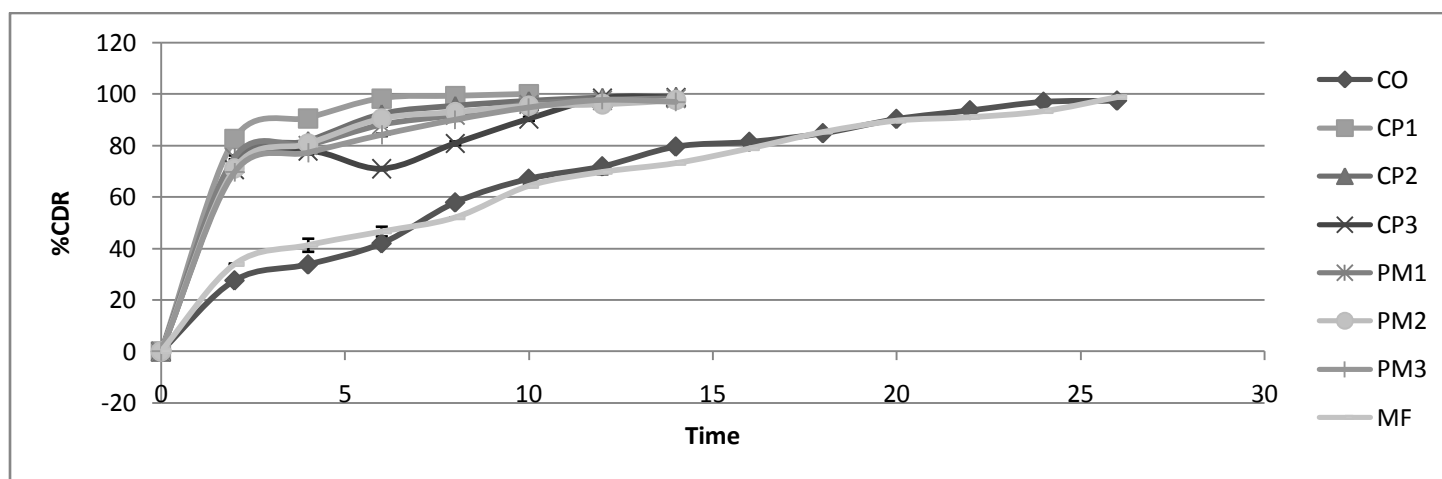


Figure 9: Comparative dissolution profiles for PM and CP batches in 10 min.

In vitro dissolution study was carried out for conventional marketed Olanzapine tablet (Zeprex) and compared with formulation CP1, PM1 and CO. CP1 had taken 10 minutes for 99.96% drug release; PM1 had taken 14 minutes for 98.67%, CO release 97.32 % drug in 26 min. While marketed formulation was taken 20 minutes for 89.73 % drug release.

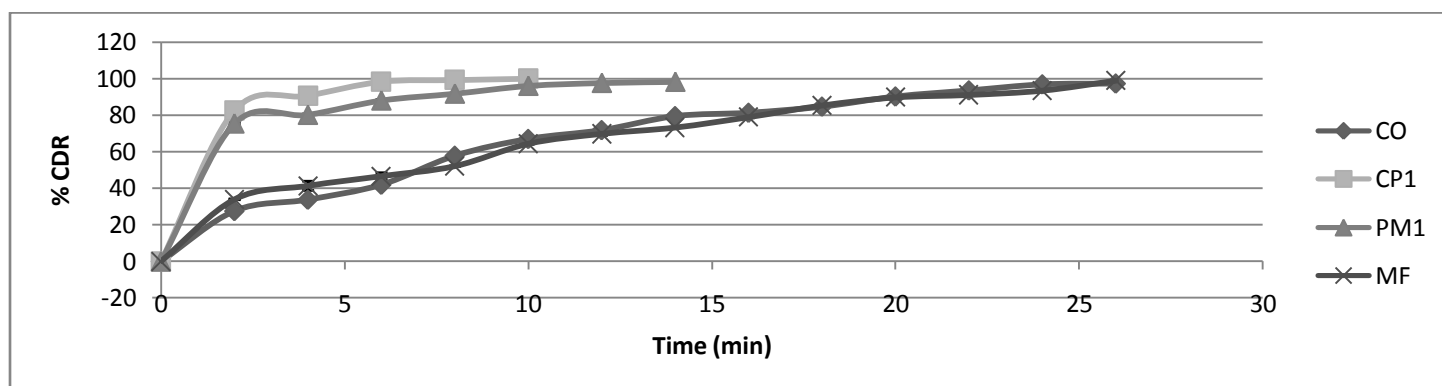


Figure 10: Comparative dissolution profiles for CO, CP1, PM1 and MF batches.

MF- marketed formulation, Co- control release formulation, CP- Co-processed of 1:1 formulation and PM –physical Mixture of 1:1 formulation.

CONCLUSION

From the FT-IR spectroscopic study it was observed that there is no significant shift in the IR values. Hence it may be concluded that there is no chemical interaction between the drug and the polymers. All the preformulation parameters viz., Carr's index, Hausner's ratio and Angle of repose values are within the acceptable range and hence the tablets comply with requirement. Post-compression parameters such as hardness, friability, weight variation, thickness measurement, disintegration time and drug content determination have indicated that the values are within the acceptable range. Overall, the results suggest that MDTs of Olanzapine containing co-processed superdisintegrating agent could be successfully formulated. Thus the present study has demonstrated the potential of MDTs of Olanzapine for rapid absorption, leading to enhanced bioavailability, resulting in efficacious therapy and improved patient compliance.

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