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Formulation and evaluation of intraorally rapid disintegrating tablets of olanzapine

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ABSTRACT

Olanzapine is an atypical antipsychotic, FDA for the treatment of schizophrenia and bipolar disorder. Olanzapine is structurally similar to clozapine and quetiapine. The present research work is aimed at developing a Formulate and Evaluated of a Rapid disintegrating tablet dosage form of Olanzapine. Who have little or no access to water are also good candidates for Rapid disintegrating tablets of Direct Compression method was employed for blending of drug with polymers in the given ratio as a nine formulations. The prepared powder blends were then compressed into tablets using the necessary Superdisintegrants like CCS, CP, and SSG and Excipients. The tablets were evaluated for Weight variation, thickness, hardness, friability, Drug Content and Disintegrating Time (Sec) were subjected to a 40 minutes in vitro drug release studies (USP dissolution rate test apparatus II, 50 rpm, 37^{0}C ±0.5^{0}C) using phosphate buffer, pH 6.8 as a dissolution medium (900ml). The amount of Olanzapine released from the tablet formulations at different time intervals was estimated using a UV spectroscopy method. The formulations that showed a considerable retardation of the drug release are considered promising. Among the nine formulations, F5 formulation containing Drug to Crospovidone (CP) in ratio 1:0.25 is optimized based on its ability to till 40 mins of invitro dissolution time, and its % Cumulative Drug Release Of The 96.09% of dissolution study.

Key words: Olanzapine, schizophrenia, direct compression, Crospovidone

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INTRODUCTION

Rapid dissolving tablets are those when put on tongue disintegrate instantaneously releasing the drug which dissolve or disperses in the saliva. The faster the drug into solution, quicker the absorption and onset of clinical effect. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablets dosage form[1].

The major advantage of the ODT formulation is that it combines the advantages of both liquid and conventional tablet formulations, and also offering advantages over both traditional dosage forms. It provides the convenience of a tablet formulation, and also allowing the ease of swallowing provided by the liquid formulation. Good mouth feel property helps to change the perception of medication as bitter pill particularly in pediatric patient

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage forms. The reason that the oral route achieved such popularity may be in part attributed to its ease of administration as well as the traditional belief that by oral administration the drug is as well absorbed as the food stuffs that are ingested daily[2].

MATERIALS AND METHODS

Olanzapine was a gift sample from MSN Laboratories Pvt Ltd, Hyderabad, Sodium Starch Glycolate, Crospovidone, Croscarmellose Sodium was supplied by Signet Chem Mumbai and Magnesium Stearate, Talc, and Microcrystalline Cellulose was supplied by Yarrow Chem Products Mumbai.

Preformulation Studies:

Standardization of Olanzapine by UV-Visible spectrophotometry:

Standard calibration of Olanzapine in 6.8 Phosphate buffer: 100mg of Olanzapine was accurately weighed and dissolved in100ml of 6.8 phosphate buffer to obtain a concentration of 1000µg/ml. From the above 10ml was withdrawn and diluted to 100ml to obtain a concentration of 100µg/ml. From this stock solution aliquots of 0.5ml, 1ml, 1.5ml, 2ml and 2.5ml were diluted in 10ml volumetric flask with phosphate buffer to give concentrations in range of 5µg/ml to 25µg/ml respectively, absorbancewas measured at 257 nm as shown in fig 1and table 1.

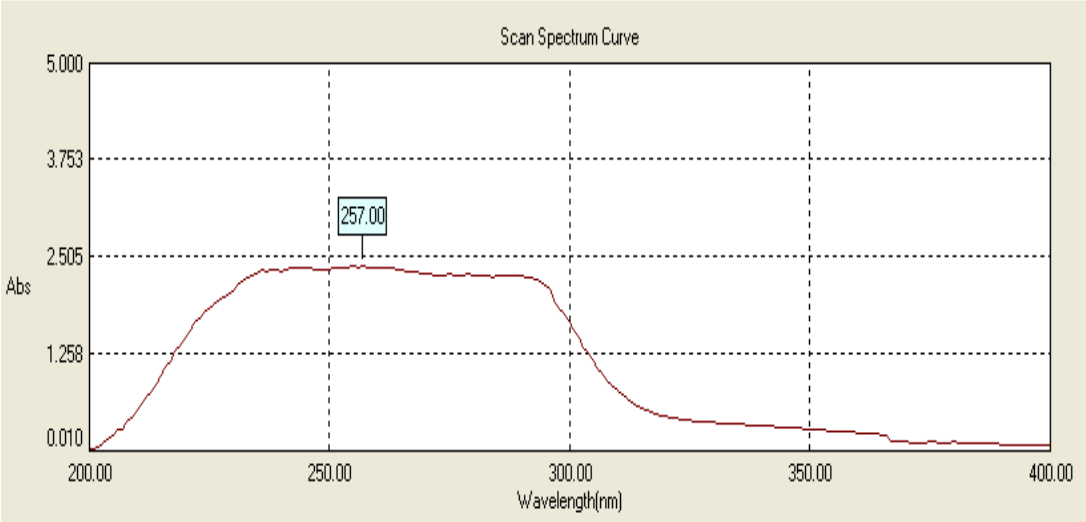

Figure 1: λmax of Olanzapine in pH 6.8 Phosphate buffer (257 nm)

Table 1:Standard graph of Olanzapine in pH 6.8 Buffer

S. No	Concentration	Absorbance
1	0	0
2	4	0.278
3	8	0.578
4	12	0.806
5	16	1.118
6	20	1.370

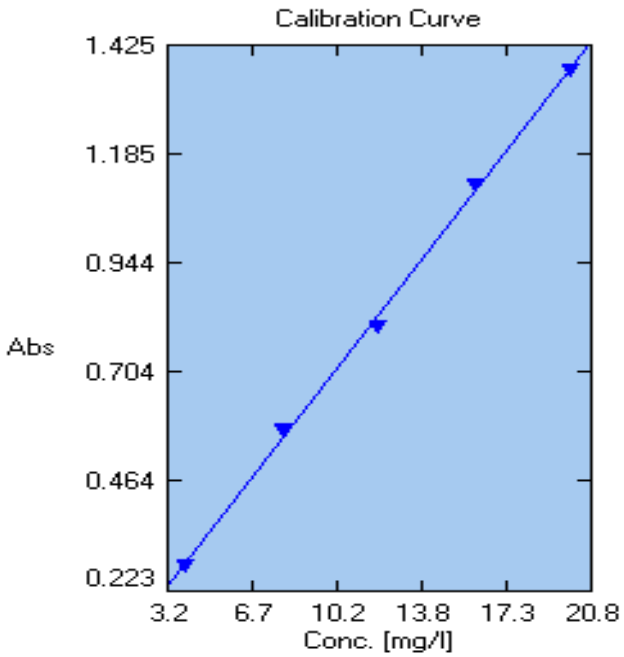

Figure 2: Standard graph of Olanzapine in pH 6.8 Buffer

Drug- Excipient Compatibility by FTIR studies:

In the preparation of Rapid disintegrating tablet, drug and polymer may interact as they are in close contact with each other, which could lead to instability of drug. Preformulation studies regarding drug-polymer interactions are therefore very critical in selecting appropriate polymers. FT-IR spectroscopy (Agilent Technologies) was employed to ascertain the compatibility between Olanzapine and selected polymers. The individual drug and drug with excipients were scanned separately.

Procedure: Potassium bromide was mixed with drug and polymer in the ratio of 100:1 and pellet was prepared using KBr pellet press and spectrum was taken using FTIR (Agilent Technologies). FT-IR spectrum of Olanzapine was compared with spectrum of Olanzapine and polymer. Disappearance of Olanzapine peaks or shifting of peak in any of the spectra was studied[3,4]

FTIR Studies:

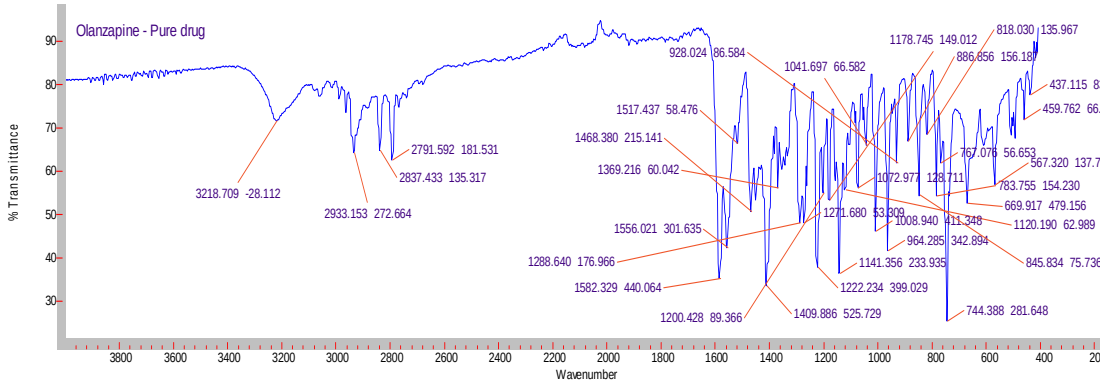

Figure 3: FTIR Graph of Pure Drug (Olanzapine)

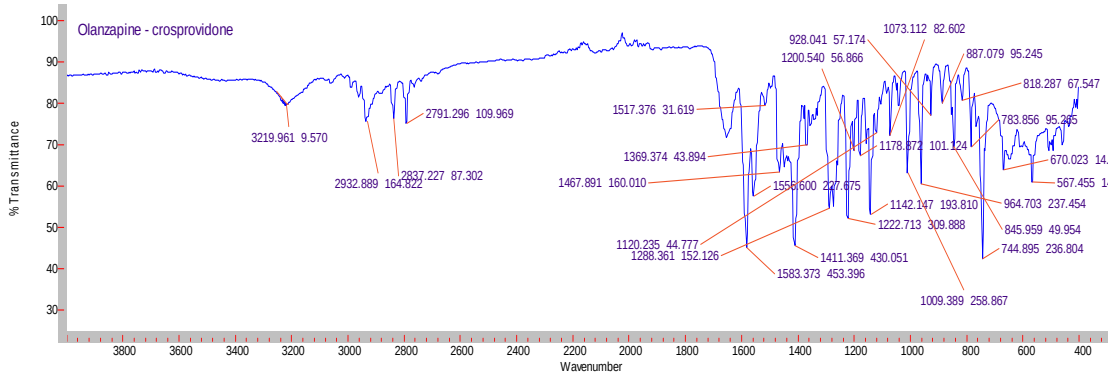

Figure 4: FTIR Graph of Olanzapine+Crospovidone

PRECOMPRESSION PARAMETERS:

1. Angle of Repose (Θ):

The friction forces in a loose powder can be measured by the angle of repose (q). It is an indicative of the flow properties of the powder. It is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane

$\tan(\Theta) = h / r$

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

Where,
Θ is the angle of repose.
h is the height in cm
r is the radius in cm

The powder mixture was allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of powder formed. Care was taken to see that the powder particles slip and roll over each other through the sides of the funnel. Relationship between angle of repose and powder flow property.

2. Bulk Density (D_b):

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weight powder (passed through standard sieve # 20) into a measuring cylinder and initial weight was noted. This initial volume is called the bulk volume. From this the bulk density is calculated according to the formula mentioned below. It is expressed in g/ml and is given by,

$D_b = M / V_b$

Where,
M is the mass of powder
V_b is the bulk volume of the powder.

3. Tapped Density (D_t):

It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 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 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2 % (in a bulk density apparatus). It is expressed in g/ml and is given by,

$D_t = M / V_t$

Where,
M is the mass of powder
V_t is the tapped volume of the powder.

4. Carr's compressibility index:
The Carr's compressibility Index was calculated from Bulk density and tapped density of the blend. A quantity of 2g of blend from each formulation, filled into a 10mL of measuring cylinder. Initial bulk volume was measured, and cylinder was allowed to tap from the height of 2.5cm. The tapped frequency was 25±2 per min to measure the tapped volume of the blend. The bulk density and tapped density were calculated by using the bulk volume and tapped volume[5,6,7].

Carr's compressibility index was calculated by using following formula:

Carr's compressibility index (%) = [(Tapped density-Bulk density) X100]/Tapped density

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

Hausner ratio=D_t/D_b

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

Table 2 : Precompression Parameters

Formulation code	Angle of Repose (θ)	Bulk Density(g/ml)	Tapped Bulk Density(g/ml)	Carr's Index (%)	Hausner's Ratio
F1	22.81	0.467	0.592	14.10	1.15
F2	26.28	0.498	0.536	12.68	1.13
F3	20.45	0.416	0.554	12.33	1.12
F4	23.14	0.482	0.592	13.41	1.15
F5	24.90	0.434	0.547	12.73	1.13
F6	22.20	0.466	0.556	13.86	1.16
F7	21.11	0.482	0.517	14.09	1.17
F8	23.34	0.411	0.519	13.72	1.19
F9	25.36	0.568	0.528	14.11	1.13

Preparation of tablets:
Different tablets formulations were prepared by direct compression technique. All powders were passed through 60 mesh. Required quantities of drug and polymers were mixed thoroughly Magnesium stearate was added as lubricant. Talc was used as glidant. Micro crystalline cellulose was used as diluent. Finally the powder mix was subjected to compression after mixing uniformly in a polybag. Prior to compression, the blends were evaluated for several tests. In all formulations, the amount of the active ingredient is equivalent to 75mg of Olanzapine[8,9] (Table 3)

Table 3: Composition of Olanzapine Tablets

S. No	Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Olanzapine	20	20	20	20	20	20	20	20	20
2	Sodium Starch Glycollate(SSG)	5	10	----	----	----	----	15	----	----
3	Cross Caramellose Sodium(CCS)	----	----	5	10	----	----	----	15	----
4	Crospovidone(CP)	----	----	----	----	5	10	----	----	15
5	Magnesium stearate	2	2	2	2	2	2	2	2	2
6	Talc	2	2	2	2	2	2	2	2	2
7	Microcrystalline Cellulose(MCC)	46	41	46	41	46	41	36	36	36
	Total weight	75	75	75	75	75	75	75	75	75

All ingredients are expressed in mg only

EVALUATION OF TABLETS:

A) Weight Variation Test:

From each batch twenty tablets were selected at a random and average weight was determined. Then individual tablets were weighed and the individual weight was compared with an average weight, the variation in the weight was expressed in terms of % deviation.

B) Hardness and Friability Test:

For each formulation the hardness was determined by using Monsanto hardness tester and Friability of the tablets was checked by using Roche Friabilator. This device subjects tablets to the combined effect of abrasion and shock by utilizing plastic chamber which revolves at 25 rpm dropping the tablets at a distance of 6 inches with an each revolution. Preweighed sample of tablets was placed in the friabilator, which was then operated for 100 revolutions. Tablets were dusted and reweighed and then % Friability was calculated.

C) Water Absorption Ratio and Wetting Time:

A piece of tissue paper folded twice was placed in a small Petridish containing 6 ml of water. A tablet of known weight was put on the paper and the time required for complete wetting of tablet was measured. The wetted tablet was then weighed; water absorption ratio R was determined using t

$$\mathbf{R = W_b - Wa/W_b \times 100}$$

Where;

W_b is weight of tablet before water absorption.

W_a is weight of tablet after water absorption.

D) Drug Content Uniformity Study:

Five tablets were weighed individually and powdered. The powder equivalent to 75 mg of Olanzapine was weighed and extracted in 6.8 phosphate buffer (100 ml) and the concentration of drug was determined by measuring absorbance at 257 nm by spectrophotometer.

Table 4: Postcompression parameters

S.No	Formulation	Weight variation	Thickness (mm)	Hardness (Kg/Cm^2)	Friability %	Disintegrating Time (sec)
1	F1	0.201	2.5	2.5	0.34	47
2	F2	0.213	2.6	3	0.25	51
3	F3	0.198	2.7	3	0.46	62
4	F4	0.198	2.7	3	0.48	68
5	F5	0.200	2.1	2.5	0.41	54
6	F6	0.213	2.4	3	0.39	55
7	F7	0.215	2.5	2.5	0.36	53
8	F8	0.213	2.4	2.5	0.33	59
9	F9	0.215	2.5	3.5	0.39	45

Table 5: In vitro dissolution studies

% Cumulative Drug Release of the Formulations (f1-f9)

Time(mins)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0.00	0.00	0.00	0.00	**0.00**	0.00	0.00	0.00	0.00
5	18.49	16.43	17.83	19.71	**24.13**	8.76	8.76	17.91	10.49
10	37.39	28.71	33.95	30.35	**25.93**	14.15	14.15	25.03	27.49
15	53.67	37.24	58.74	50.15	**40.25**	24.21	24.21	40.90	46.87
20	56.82	52.43	62.04	68.88	**59.63**	36.77	36.77	57.01	65.06
25	59.24	65.43	68.72	72.5	**72.07**	42.13	42.13	75.59	81.34
30	65.87	71.44	73.90	76.4	**79.19**	58.21	58.21	79.02	81.59
35	72.43	78.93	79.42	80.99	**89.17**	66.13	66.13	79.84	84.50
40	79.82	84.66	83.83	84.22	**96.09**	73.45	73.45	81.02	90.32

***In-Vitro* Drug Release Study:**

Dissolution rate was studied 6.8 phosphate buffer as dissolution medium. Temperature of the dissolution medium was maintained at 37±0.5ºC; aliquot of dissolution medium was withdrawn at every 5 minute interval and filtered. The absorbance of filtered solution was checked by UV spectrophotometric method at 257 nm and concentration of

the drug was determined from standard calibration curve. Dissolution rate was studied for all designed formulations[10-12].

Dissolution release profiles of Formulations:

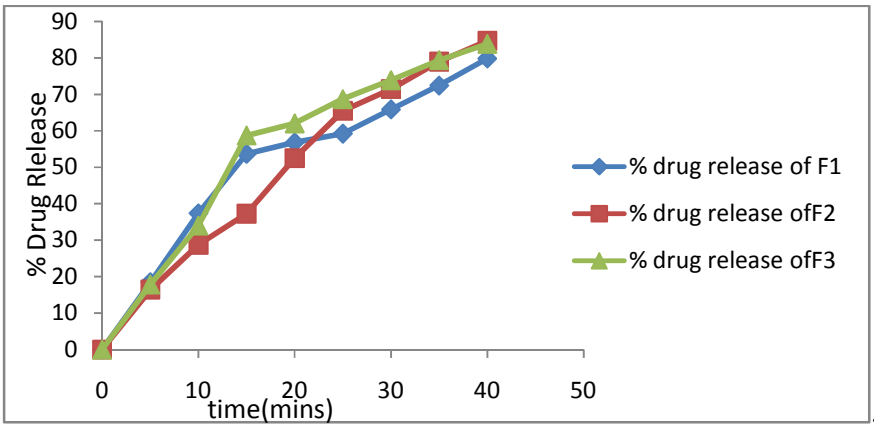

Figure 5: Dissolution profiles of Formulations F1-F3

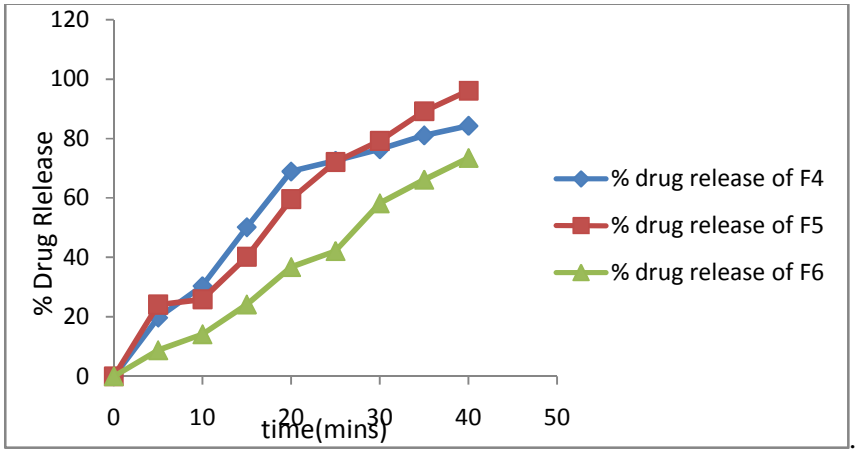

Figure 6: Dissolution profiles of Formulations F4-F6

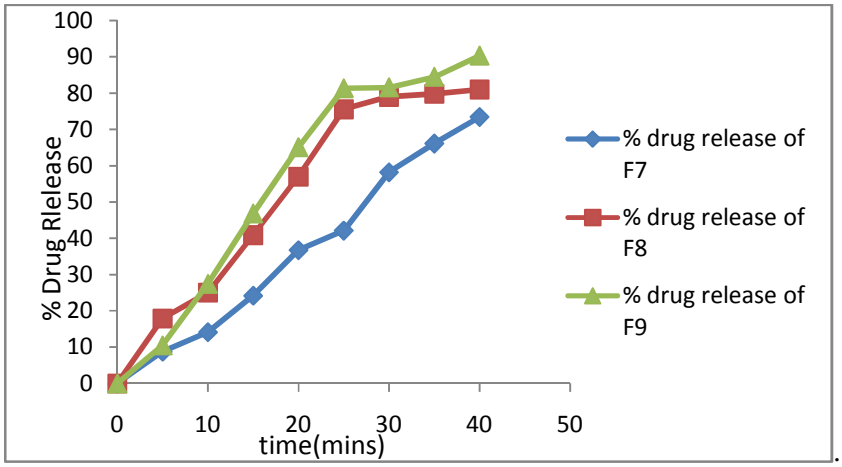

Figure 7: Dissolution profiles of Formulations F7-F9

RESULTS AND DISCUSSION

Olanzapine has an UV absorbance of 257nm. Solutions ranging from 4 to 20 µg/ml were prepared using 6.8 Phosphate buffers separately, absorbance was measured for each solution at λ max of 257 nm using LABINDIA 3000^{+} Double beam UV/ visible spectrophotometer, and graph was plotted for absorbance versus concentration of olanzapine. Standard graph of olanzapine in 6.8 pH Buffer at λ max 257nm. The drug exipient compatability studies were done by using FTIR and there is no interference to the drug and exipients. Precompression Parameters and post compression parameters were done and they were within the range.

CONCLUSION

The Rapid dissolving tablets of olanzapine were prepared successfully using Polymers in different ratios of by using Superdisintegrants. We can conclude Out of nine formulations formulated using various Superdisintegrants like CCS, CP, and SSG among these Formulation F5 containing 0.25 % Crospovidone (CP) showed maximum drug release within 40 minutes of dissolution study. These formulations showed disintegrating times of 54 seconds respectively. Thus based on Disintegrating times and dissolution profiles, F5 is optimized to be the best among all the nine Formulations.

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