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Formulation Development and Evaluation of Fast Dissolving Tablet of Olanzapine by using Superdisintegrants

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A B S T R A C T

Recent developments in the fast dissolving drug delivery system with improved patients compliance and convenience. Fast disintegrating tablets are solid dosage form which dissolves rapidly in saliva without chewing and additional water. Olanazapine is preferentially used for treatment of psychosis patients. The tablet of olanazapine was prepared by direct compression method using Cross-carmelose sodium, polyplasdone XL -10 ,sodium starch glycolate as super disintegrant and mannitol ,microcrystalline cellulose as diluents and Talcum ,magnesium stearate as lubricating agents. FT-IR study showed compatibility between drug and excipients. The pre-compression study indicated the excellent flow properties of bulk powder which is within an acceptable range of According to pharmacopeia specifications. The post-compression evaluation parameters results match the expected criteria specifications. These tablets have hardness 2.10 kg/cm^2, thickness 2.81mm, disintegration time of 28 seconds and 96.65% drug release within 40 minutes.

Keywords: Olanzapine, cross Carmellose sodium, polyplasdone XL -10, sodium starch glycolate, Microcrystalline cellulose, mannitol, magnesium stearate.

A R T I C L E I N F O

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CONTENTS

1. Introduction

Fast-dissolving drug delivery systems were developed in the alternative to tablets, capsules, and syrups for paediatric and geriatric patients who experiences difficulties in swallowing traditional oral solid dosage forms. The faster the drug dissolve into solution, quicker the absorption and onset of clinical effect. They should readily dissolve or disintegrate in the saliva generally within <40 seconds. Some drugs are absorbed from the mouth, pharynx and oesophagus as the saliva passes down into the stomach. The significance of orodispersible dosage forms are progressively being recognized in both industry and academics. [4] Olanzapine, a thienobenzodiazepine derivative, belongs to class of second generation derivative antipsychotic agents, the so-called atypical antipsychotics. They have greater affinity for serotonin 5-HT2 serotonin receptors than for dopamine D2 receptors and cause fewer extrapyramidal symptoms (EPS) in contrast with classical antipsychotics (e.g. haloperidol). The efficacy and safety of

olanzapine has been demonstrated in randomised, placebo-controlled and comparative trials in positive and negative symptoms of schizophrenia, and also as monotherapy or in combination with mood stabilizers in the treatment of acute manic or mixed episodes associated with bipolar disorder. Olanzapine, an atypical antipsychotic drug, blocks multiple neurotransmitters: serotonin, at 5H2a, 5H2c, 5H3, and 5HT6 receptors, dopamine at D1, D2, D3 and D4 brain receptor, catecholamines at alpha 1 adrenergic receptors, acetylcholine at muscarinic receptors, and histamine at H1 receptors.

2. Materials and methods

Materials: Olanzapine was received as gift sample (AR-Life Science Private Limited), Cross-carmelose sodium (Devershi enterprizes Pvt.Ltd), sodium starch glycolate (Devershi enterprizes Pvt.Ltd), polyplasdoneXL-10 (ISP. india Pvt.Ltd), microcrystalline cellulose (Amishi drugs &chemicals Pvt. Ltd), Magnesium stearate (Anusha associate), Talcum (Udaipur minerals development syndicate Pvt. Ltd) .Aerosil (Jermany kanchan rasayan)

Formulation method

Fast dissolving tablet containing olanzapine were prepared by direct compression method according to the formula given in the (table no.1) Eight different formulations were prepared. Disintergrants added to 50% before granulation and 50% after granulation By using tablet formulation. All the ingredients were sieved separately through sieve no.40 except magnesium stearate which was sieved through sieve no.60 and collected the weighed amount of drug and other ingredients were mixed first and magnesium stearate was finally added and mixed thoroughly. The tablets were compressed using 8mm punch.

Pre -compression parameters

Bulk density & tapped density

Both loose bulk density (BD) and tapped bulk density (TD) were determined. A quantity of 2 g of powder from each formula, previously lightly shaken to break any agglomerates formed, was introduced in to a 10 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight on the hard surface from the height of 2.5 cm at 2- second intervals. The tapping was continued until no further change in volume was noted. BD and TD were calculated using the following formula:

BD = weight of the powder / Volume of the packaging

TD = weight of the powder / Tapped volume of the packing

Angle of repose

Angle of repose has been defined as the maximum angle possible between the surface of pile of powder and horizontal plane. The angle of repose for the granules of each formulation can be determined by the funnel method. The granules mass is allowed to flow out of the funnel orifice on a plane paper kept on the horizontal surface. This from a pile of angle of granules on the paper. The angle of repose is calculated by substituting the values of the base radius 'R' and pile height 'H' in the following equation:

Tan θ = h/r

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

Where, θ = Angle of repose

h=Height of the cone

r= radius of the cone base

Carr's compressibility index:

An indirect method of measuring powder flow from bulk densities was developed by Carr. The percentage compressibility of a powder was a direct measure of the potential powder arch or bridge strength and stability.

Carr's index of each formulation was calculated according to equation given below:

$$\% \text{ Compressibility} = \frac{BD - TD}{BD} \times 100$$

Where,

BD = bulk density,

TD = Tapped density

Hausner ratio

The Hausner ratio is calculated by the formula

$$H = \frac{\rho_T}{\rho_B}$$

ρ_B is the freely settled bulk density of the powder,

ρ_T is the tapped bulk density of the powder.

The Hausner ratio is not an absolute property of a material; its value can vary depending on the methodology used to determine it.

Post-compression evaluation parameters

Weight variation

20 tablets were selected randomly from the lot and weighted individually to check for weight variation. Weight variation is given by the formula.

$$\% \text{ Wt. variation} = \frac{\text{Individual weight} - \text{Average weight}}{\text{Average weight}} \times 100$$

Hardness

Hardness or tablet crushing strength (fc), the force required to break a tablet in a diametric compression was measured using Monsanto tablet hardness tester. It is expressed in kg/cm^2.

Friability (F)

Friability of the tablet determined using Roche friabilator. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at a height of 6 inches in each revolution. Preweighted sample of tablets was placed in the friabilator and were subjected to the 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. The friability (F) is given by the formula.

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

***In- vitro* drug release**

Release of the drug *in vitro*, was determined by estimating the dissolution profile, USP 2 Paddle apparatus was used and paddle was allowed to rotate at 50 rpm, (900 ml) was used as a dissolution medium.

Dissolution test

Dissolution parameters:

Medium - 900 ml, 0.01M Hydrochloric acid

Apparatus - Paddle

R.P.M. - 50 rpm to 45

Temperature - 37 ± 0.5^0 C
Time - 5,10,15,20,25,30,40

Modified disintegration test

The standard procedure of performing disintegration test for these dosage forms has several limitations and they do not suffice the measurement of very short disintegration times. The disintegration time for FDTs needs to be modified as disintegration is required without water, thus the test should mimic disintegration in salivary contents. For this purpose, a petridish (10 cm diameter) was filled with 10 ml of water. The tablet was carefully put in the center of petridish and the time for the tablet to completely disintegrate into fine particles was noted.

Water absorption ratio

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

$R= 100\times (W_a/W_b)/W_b$

Where,

W_b= weight of tablet before water absorption

W_a = weight of tablet after water absorption

3. Result and Discussion

The Present study was aimed at the formulation of olanzapine fast dissolving tablets. The key advantage of this drug is its specificity of action, high safety and excellent efficacy.

Preformulation studies

Compatibility study

Standard I.R. Spectrum of olanzapine

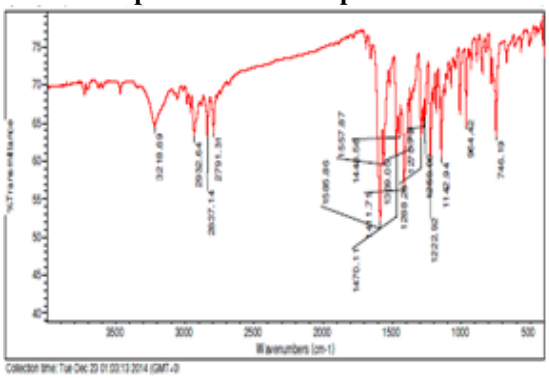

Figure 1: Standard I.R. Spectrum of olanzapine

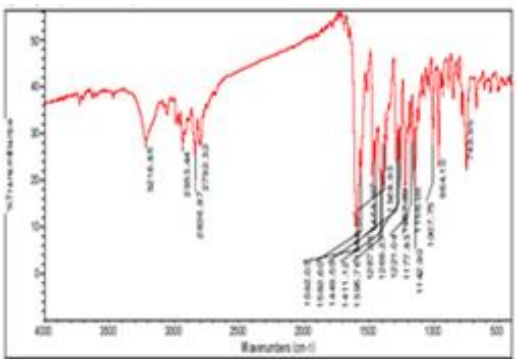

Figure 2: IR Spectrum of olanzapine Sample

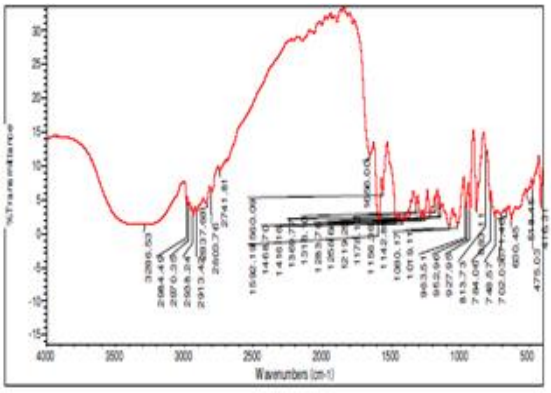

Figure 3: Olanzapine master formula

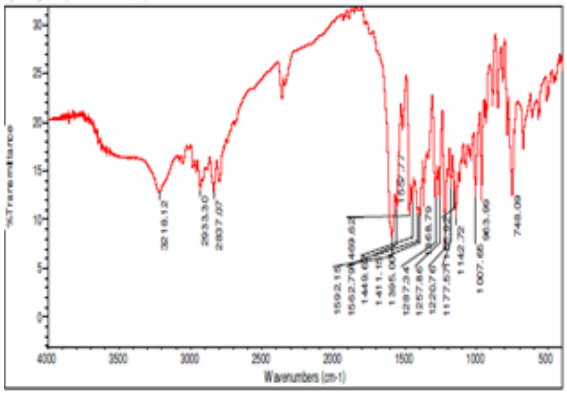

Figure 4: Olanzapine : Crosscarmellose sodium

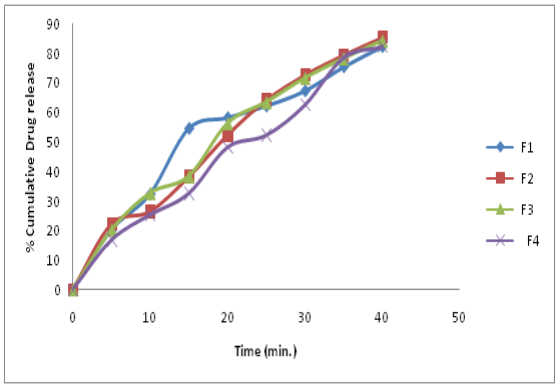

Figure 5: Dissolution study of Olanzapine (F1 to F4)

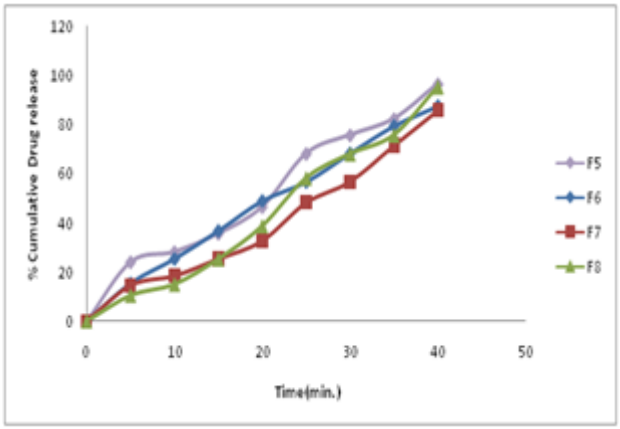

Figure 6: Dissolution study of Olanzapine (F_5 to F_8)

Table 1: Composition of fast dissolving of olanzapine tablet

Ingredient (mg per Tablet)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
Olanzapine	10	10	10	10	10	10	10	10
Cross carmelose sodium	5	4	4	5	5	5	5	5
Sodium starch glycolate	5	5	5	4	5	4	4	5
Mannitol	35	30	35	35	35	30	30	35
Microcrystalline cellulose	12	10	10	8	12	12	10	12
Colour tartrazine	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
PolyplasdoneXL-10	4	5	4	4	4	5	4	5
Aerosil	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Talcum	2	2	2	2	2	2	2	2
Mag.stearate	1	1	1	1	1	1	1	1
Total weight(mg)	75	75	75	75	75	75	75	75

Table 2: Pre-compression parameter results of olanzapine fast dissolving tablet

Formulation	**Dis-intergration Time (sec.)**	**Average Weight of 20 Tablets (mg)**	**Thickness (mm)**	**Hardness (kg/cm^2)**	**Friability (%)**	**% Drug Content**
F_1	60	74.69	2.78	2.33	0.48	96.39
F_2	80	72.42	2.45	2.40	0.54	97.56
F_3	120	75.56	2.68	2.56	0.64	99.45
F_4	58	74.92	2.70	2.50	0.58	95.18
F_5	**28**	**74.79**	**2.81**	**2.10**	**0.42**	**99.46**
F_6	55	70.36	2.85	2.35	0.45	97.64
F_7	45	76.46	2.69	2.70	0.39	98.21
F_8	32	73.89	2.54	2.24	0.43	98.78

Table 3: post-compression evaluation parameters of olanzapine fast dissolving tablet.

Formulation Batch code	**Bulk Density (gm/cm^3)**	**Tapped Density (gm/cm^3)**	**Carr's Index**	**Hausner Ratio**	**Angle of repose (θ)**
F_1	0.43	0.48	10.41	1.11	25.43
F_2	0.45	0.52	13.46	1.15	26.39
F_3	0.48	0.54	11.11	1.12	28.64
F_4	0.42	0.47	10.63	1.12	27.53
F_5	0.41	0.48	14.58	1.17	29.64
F_6	0.43	0.48	14.41	1.11	25.72
F_7	0.46	0.52	11.54	1.13	27.28
F_8	0.47	0.54	12.96	1.15	26.58

Table 4: % Cumulative Drug release

S.No.	**Time (min.)**	**% Cumulative Drug release**							
		F_1	**F_2**	**F_3**	**F_4**	**F_5**	**F_6**	**F_7**	**F_8**
1	0	0.0	0.0	0.0	0.0	**0.0**	0.0	0.0	0.0
2	5	20.23	22.20	20.25	16.82	**24.12**	15.42	14.56	10.48
3	10	32.46	26.46	32.72	25.34	**28.21**	25.32	18.41	15.02
4	15	54.64	38.20	38.42	32.63	**35.73**	36.73	25.32	25.37
5	20	58.26	52.34	56.34	48.26	**46.62**	48.91	32.67	38.75
6	25	62.21	64.12	63.53	52.34	**68.31**	56.63	48.21	58.32
7	30	67.34	72.63	71.72	62.58	**75.85**	68.21	56.75	68.12
8	35	75.46	79.35	78.31	78.62	**82.45**	79.36	71.38	75.81

Table 5: Comparison of the slope and the regression co-efficient for different models for optimized formulation F5

Time (min)	SQRT (Square root)	Log Time	%CDR	Log% CDR	%Drug Retained (100 -%CDR)	Log% Drug Retained	%Drug Retained$^{1/3}$
0	0	0	0.0	0.0	0	0	0
5	2.23	0.69	24.12	1.382	75.88	1.88	4.233
10	3.16	1	28.21	1.449	71.29	1.85	4.146
15	3.87	1.17	35.73	1.553	64.27	1.80	4.005
20	4.47	1.30	46.62	1.668	53.38	1.72	3.765
25	5	1.39	68.31	1.834	31.69	1.50	3.164
30	5.47	1.47	75.85	1.879	24.15	1.38	2.890
35	5.91	1.54	82.45	1.916	17.55	1.24	2.598
40	6.32	1.60	96.65	1.985	3.35	0.52	1.496

Table 6: Stability studies of formulation F5 at temperature 40^0c.

Parameters	Controlled	After 15 days	After 1 month
Drug content (%)	99.46	99.33	98.68
Disint.time(sec.)	28	30	32
Thickness(mm)	2.81	2.89	2.90
Hardness(kg/cm^2)	2.10	2.25	2.42
Fribility(%)	0.42	0.43	0.44

Table 7: Cumulative % Drug Release

Time (min)	Controlled	After 15 days	After 1 month
5	24.12	24.10	23.87
10	28.21	27.56	27.34
15	35.73	35.34	34.65
20	46.62	45.84	45.12
25	68.31	68.02	67.45
30	75.85	75.23	75.12
35	82.45	82.12	81.85
40	96.65	96.24	95.65

Table 8: Stability studies of formulation F8 at room temperature

Parameters	Controlled	After 15 days	After 1 month
Drug content (%)	98.78	98.65	98.23
Disint.time(sec.)	32	33	35
Thickness(mm)	2.54	2.60	2.65
Hardness(kg/cm^2)	2.24	2.35	2.42
Fribility(%)	0.43	0.44	0.45

Table No. 9. Cumulative % Drug Release

Time (min)	Controlled	After 15 days	After 1 month
5	10.48	10.23	10.02
10	15.62	15.12	14.45
15	25.37	25.23	24.87
20	38.75	38.35	37.67
25	58.35	57.45	57.32
30	68.12	67.85	67.21
35	75.81	75.24	74.85
40	95.49	95.12	94.78

4. Conclusion

The present work is aimed to Formulation and evaluation of fast dissolving tablet of olanazapine was to formulate a stable, safe and convenience dosage form, which is most suitable according all evaluation parameters. Besides, the conventional tablets also show poor patient compliance particularly by the geriatric and pediatric patients who experience difficulty in swallowing, and do not have an easy access of water.olanzapine was successfully formulated by direct compression method to improve the drug release profile. Chemical incompatibility studies confirmed that there is no interaction between drug and excipients used in the formulations. Compatibility of the drug with excipients was determined by FT-IR spectral analysis, this study was carried out to detect any changes on chemical constitution of the drug after combined it with the excipients.

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