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FORMULATION AND IN-VITRO EVALUATION OF OLANZAPINE TABLET FOR SCHIZOPHRENIA AND BIPOLAR DISORDER

Arun Kumar Das*[1], Satyabrata Bhanja [2], T. Swetha [1] and B. Priyadarshini [1]

Department of Pharmaceutics, Malla Reddy Pharmacy College, Maisammaguda, Dhulapally, Secunderabad- 500 014, Andhra Pradesh, India

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Correspondence to Author:

Arun Kumar Das

Assistant Professor, Department of Pharmaceutics, Malla Reddy Pharmacy College, Maisammaguda, Dhulapally (Via Hakimpet Post), Secunderabad-500014, Andhra Pradesh, India

E-mail: arunkumardas07@gmail.com

ABSTRACT: Olanzapine is a thienobenzodiazepine class of drugs, which has been approved by the Food and Drug Administration (FDA), for the treatment of schizophrenia, depressive episodes associated with bipolar disorder, acute manic episodes, and maintenance treatment in bipolar disorder. Recently many formulations developed such as parenteral formulations to improve compliance in the treatment of schizophrenia and to treat agitation in patients with schizophrenia and bipolar mania. Olanzapine palmate long acting injection (depot) is a novel formulation of the atypical antipsychotic Olanzapine. The aim of the study is to prepare tablet with similar elegancy, therapeutically effective, bioequivalent formulations to that of zyprexa. Here Olanzapine tablets were prepared by wet granulation method using following ingredients: Lactose monohydrate, Mannitol, L-HPC, Microcrystalline cellulose, Crospovidone, HPC EX, HPC LF, Magnesium Stearate, HPMC, Poloxamer, pectin. The tablets were evaluated for weight variation, thickness, hardness, friability, disintegration, dissolution and stability study for the best formulation F10 which is having similar release profile as that of zyprexa. Content uniformity of F10 formulation is 99-99.6%. Total impurities for the F10 is found to be 0.257% which is less than innovator's total impurities 0.352% and the assay value of F 10 is 99.01% as in case of innovator it is 98.06. The best formulation is F10 which is having similar release profile as that of zyprexa.

INTRODUCTION: Olanzapine, a Thienobenzo-diazepine derivative, is an atypical antipsychotic agent with broad efficacy, eliciting a response in both the positive and negative symptoms of schizophrenia and bipolar disorder.

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Olanzapine (**Fig. 1**) was first introduced in 1996 as an oral formulation and is used in the treatment of schizophrenia and bipolar disorder. Olanzapine is approved in the US and Europe for the oral treatment of schizophrenia and bipolar I disorder within the dose range of 5-20 mg/day [1, 2].

The pharmacokinetics of Olanzapine is linear and dose proportional within the approved dosage range from 1 mg up to 20 mg. Olanzapine is well absorbed following oral administration in both fed and fasted states. Food does not affect the rate or the extent of Olanzapine absorption.

Time of peak concentration ranges from 2-7 hr [3, 4]. Olanzapine is extensively distributed throughout the body, binding primarily to albumin (90%) and α1 -acid glycoprotein (77%).Olanzapine is eliminated extensively (40%) of the dose by first pass metabolism. Direct glucuronidation and CYP1A2 mediated oxidation are the primary metabolic pathways for Olanzapine. Phenotypic difference for CYP1A2 between races has been reported.

The pharmacokinetics of Olanzapine is similar amongst Japanese, Chinese and Caucasians [5]. The most common adverse effects of Olanzapine in patients receiving Olanzapine in short term were weight gain, somnolence, postural hypotension, dizziness, constipation, dyspepsia, dry mouth, increased appetite, tremor, personality disorder, asthenia and akathisia [6, 7].

Schizophrenia is a group of heterogeneous, chronic psychotic disorders. Key symptoms include hallucinations, delusions and abnormal experiences, such as the perception of loss of control of one's thoughts, perhaps to some outside entity. Patients lose empathy with others, become withdrawn and demonstrate inappropriate or blunted mood.

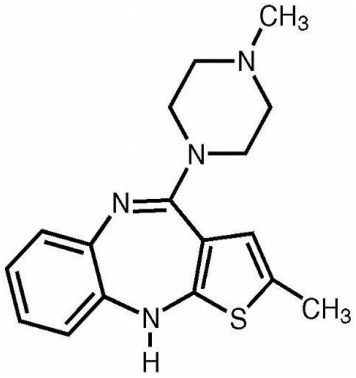

FIG. 1 OLANZAPINE STRUCTURE

MATERIALS AND METHODS:

Materials: Olanzapine was procured as a gift sample from the M/s. Orchid Chemicals, Chennai, Lactose monohydrate, Mannitol, L-HPC used as diluents got from mankind pharmaceutical limited, Microcrystalline cellulose used as disintegrant, Crospovidone, HPC EX, HPC LF as disintegrant and diluents were obtained from M/s. Colorcon Limited, India, Magnesium Stearate, HPMC Zydus Cadila, India. Poloxamer, pectin were gifted from Mankind Pharmaceutical Limited. All the chemicals and solvents used were analytical grade and purchased from Merck Ltd., India.

Methods: Olanzapine tablets are made by using wet granulation method .It involve the use of Mannitol (Pearlitol SD 200), and microcrystalline cellulose (Avicel-PH 112, PH 102) as diluents, cross povidone as binder, EX-HPC as diluents and magnesium Stearate as the lubricant. All ingredients except the lubricant were sifted through a # 40 sieve. The sifted material was mixed thoroughly in an octagonal blender for 15 minutes.

Then, the binder solution made of water and PVP was added in the mixer granulator till it form granule. Then, it is shifted to fluid bed drier and dried at 55^{o}C till the optimum amount moisture present. All the granules passed through #24 sieve and extra granular excipients added and mixed for 5minutes. Finally magnesium Stearate was sifted through a #60 sieve and mixed with the blend for two minutes. The blend was compressed with 5 mm S/C punch. Then the core tablets were coated with HPMC, pectin, Poloxamer coating solution. The different formulations of Olanzapine tablets are given in **Table 1**.

Evaluation of pre-compression parameters of powdered blend:

Loss on Drying: The moisture content of the lubricated granules was analyzed by using the Halogen Moisture Analyzer. Approximately one gram of the blend was heated at 105°C until the change in the weight was no more observed by the instrument. The % loss in weight was recorded. % LOD=100 (Initial Weight - Final Weight) / Initial Weight

Angle of Repose: The material is poured through a funnel; the tip of the funnel should be held close to the growing cone and slowly raised as the pile grows, to minimize the impact of falling particles. Stop pouring the material when the pile reaches a predetermined height or the base a predetermined width. Measure the angle [8, 9] of the resulting cone directly; divide the height by half the width of the base of the cone. The inverse tangent of this ratio is the angle of repose.

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

TABLE 1: FORMULATIONS

Ingredients Name	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Olanzapine	5	5	5	5	5	5	5	5	5	5
Lactose mono DCL15/Supertab30GR	-	-	10	-	-	-	-	156	155	147
Mannitol			-	35	30	40	40	-	-	-
L-HPC	-	-	129	-	-	40	-	8	-	-
Crospovidone			50	45	50	--	-	16	22	22
M.C.C-102/112				110	110	110	144	8	3	3
M.C.C PH102/112	156	156	-	-	-	-	-	-	8	1
Mg. Stearate	12	15	-	1	1	1	1	0.5	1	1
HPC-EX	8	8	-					-		16
HPC-LF	-	2	-	-	-	-	-	-		
D.M water	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
MCCPH 102/112(E)	16	11	-	-	-	-	6	4	4	4
Crosspovidone (E)	2	2	5.0	2.5	2.5	2.5	2.5	2	1	1
Mg. Stearate (E)	1	1	1.0	1.5	1.5	1.5	1.5	0.5	1	1
Core weight	200	200	200	200	200	200	200	200	200	200
Poloxamer 188	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%
Pectin	2%	2%	2%	2%	2%	2%	2%	2%	1%	1%
HPMC	-	-	-	-	-	-	-	-	1%	1%
DM Water/Acetone	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Total weight	208	208	208	208	208	208	208	208	208	208

Bulk Density: The bulk density [10] of a powder is the ratio of the mass of an untapped powder sample and its volume including the contribution of the interparticulate void volume. Hence, the bulk density depends on both the density of powder particles and the spatial arrangement of particles in the powder bed.

Tapped Density: The tapped density of a powder is the ratio of the mass of a tapped powder sample and volume;

- Pour (or Bulk) density = Mass / Untapped volume
- Tapped density = Mass / Tapped volume
- Hausner's ratio = Tapped density / Pour density
- Carr's Index =(Tapped density – Bulk density) /Tapped density x 100

Evaluation of Tablets: The prepared tablets were evaluated for weight variation, hardness, thickness, friability, drug content, disintegration, and dissolution and stability studies.

1. **Thickness:** Twenty tablets were randomly selected from formulations and thickness was measured individually by using Vernier's calipers. It was expressed in millimeter and average was calculated**.**

2. **Hardness:** Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness [11, 12] of the tablets was determined using Dr. Schleuniger hardness tester. It was expressed in Newton (N). Ten tablets were randomly selected from each formulation and hardness of the same were determined .The average value was also calculated**.**

3. **Friability:** The friability of tablets was determined using Roche friabilator. It is expressed in percentage (%). About 6.5 g tablets (W-initial) were transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or 100 revolutions. The tablets were dedusted and weighed again (W_{final}). The percentage friability was calculated by,

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

% Friability of tablets less than 1 % was considered acceptable.

4. **Weight Variation:** Twenty tablets were randomly selected from each formulation and weighed individually to check for weight variation. The following percentage deviation in weight variation according to USP was allowed.

5. **Drug Content Estimation:** Five uncoated tablets were selected randomly and the average weight was calculated. The tablets were crushed in a mortar and an accurately weighed amount of an average tablet was taken from the crushed blend. Then, the samples were transferred to three 100 ml volumetric flasks and diluted up to the mark using 0.1N HCl solution. The content was shaken periodically and kept for 24 hours for dissolution of the drug completely. The mixtures were filtered and appropriate dilutions were made. The drug content[13] in each tablet was estimated at λ_{max} 260.0 nm against a blank reference, and reported.

6. **Disintegration Time:** It is carried out by Electrolab Disintegration Apparatus, USP in which 900ml beaker is used and 6 test tubes are attached with 10 mesh screen at a temperature of 37^{o}C±0.5^{o}C.In each test tubes one tablet was placed and time was noted.

7. ***In vitro* Dissolution Study:** *In vitro* drug release [14, 15] studies were carried out using the USP XXIII Dissolution Apparatus II (Paddle Type) at 50 rpm. The drug release profile was studied in 900 ml of 0.1N HCl solution maintained at 37±0.5°C. Aliquots of 5 ml of dissolution medium were withdrawn at specific time intervals (5, 10, 15, 20, 30 and 45 minutes), filtered, and the amount of drug released was determined by the UV-Visible spectrophotometer (Shimadzu UV 1601PC) at 258.8nm.A multimedia dissolution study was performed for the optimized batch (F 10) in 0.1 N HCl solution, acetate buffer solution (pH 4.5), and phosphate buffer solution (pH 6.8), and a comparison of the drug release was done with the marketed product (Zyprexa) in the same three media.

8. **Comparison with Marketed Product:** The developed product was quantitatively evaluated and assessed for a tablet's properties and product quality was monitored for various specifications (given in **Table 2**).

TABLE 2: EVALUATION PARAMETERS

Evaluation Parameter		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Core Tablet	Avg. Weight (mg)	199-201	199-201	197-202	198-202	197-202	198-203	201-203.5	200-202	199-201	199-202
	Hardness (N)	70-80	80-90	60-80	70-80	68-78	50-55	88-96	180-190	85-95	50-70
	Thickness (mm)	3.76	3.76	3.60	3.83	3.86	4.25	4.30	3.53	3.70	3.75
	Disintegration Time (min.)	1½	3½	2½	5.0	5.0	6.0	2	31/2-4.0	31/2-41/2	4-41/2
	Friability (%) 400 rotation	0.42	0.42	0.07	0.35	0.34	0.37	0.22	0.081	0.08	0.173
Coated Tablet	Avg. Weight (mg)	208-209	210.5-212.0	206-209	207-209	209-211	208-212	207-209	207-210	208-210	207-209
	Hardness (N)	90-95	170-180	80-100	90-100	85-95	70-80	95-101	190-200	110-120	80-92
	Thickness (mm)	3.81	3.90	3.70	3.94	3.97	4.25-4.30	4.49-4.56	3.58-3.62	3.53	3.84
	Disintegration Time (min.)	2.0	4-4½	17	6.0	5½	9.0	31/2-51/2	31/2-4.0	31/2-4.0	5-51/2

The standards or quality control tests were carried out on marketed tablets for comparative evaluation of developed and marketed product. The observations were reported in **Tables 3, 4, 5, 6**.

TABLE 3: COMPARING DISSOLUTION PROFILE OF INNOVATOR AND F 10 IN 0.1N HCl.

Time (in min.)	% Drug Release Innovator	% Drug Release F 10
0	0	0
5	10	27
10	78	90
15	91	96
20	96	98
30	98	99
45	100	99

TABLE 4: COMPARISON OF DISSOLUTION PROFILE OF INNOVATOR AND F 10 IN pH 4.5 ACETATE BUFFER

Time (in min.)	% Drug Release Innovator	% Drug Release F 10
0	0	0
5	8	29
10	78	71
15	91	97
20	94	98
30	94	98

TABLE 5: COMPARISON OF DISSOLUTION PROFILE OF INNOVATOR AND F 10 IN pH 6.8 BUFFER

Time (in min.)	% Drug Release Innovator	% Drug Release F 10
0	0	0
5	13	16
10	49	56
15	73	79
20	82	89
30	90	97
45	93	99

TABLE 6: COMPARISON OF DISSOLUTION PROFILE OF INNOVATOR AND F 10 IN pH 7.4 PHOSPHATE BUFFER

Time (in min.)	% Drug Release Innovator	% Drug Release F 10
0	0	0
5	11.2	18.4
10	44.3	39.7
15	55.5	51.1
20	62	57
30	68.9	64
45	76	72

FTIR Studies: IR spectra for Olanzapine and formulation of tablets were recorded in a Fourier transform infrared spectrophotometer (FTIR 1615, Perkin Elmer, U.S.A.) with KBr. (given in **Fig. 2**).

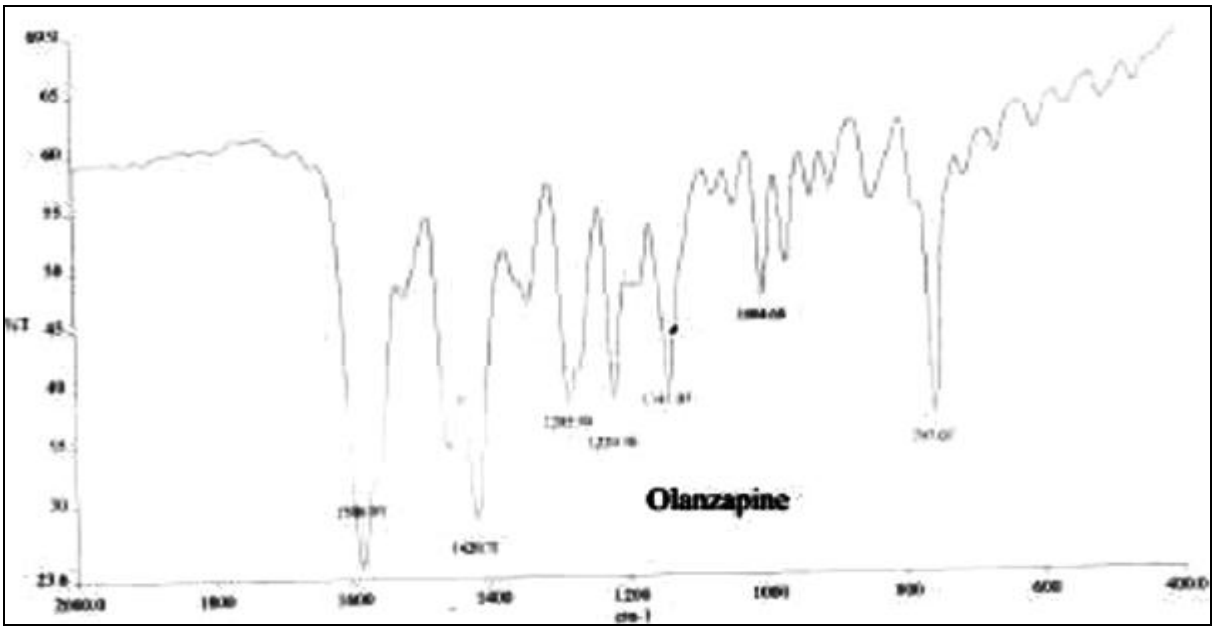

FIG. 2: FTIR OF OLANZAPINE

Differential Scanning Calorimetry (DSC) Studies: Samples of individual components as well as each drug-excipient [16, 17] were weighed (Mettler Electranic balance) directly in pierced Aluminium pans (5-10 mg) and scanned in the 50-300°Ctemperature range under static air, with heating rate of 10°C/min, using Shimadzu DSC-60 equipment. Sealed and perforated aluminium pans were used in the experiments for all the samples.

Temperature calibrations were performed using indium as standard. An empty pan sealed in the same way as the sample was used as a reference (given in **Fig. 3**):

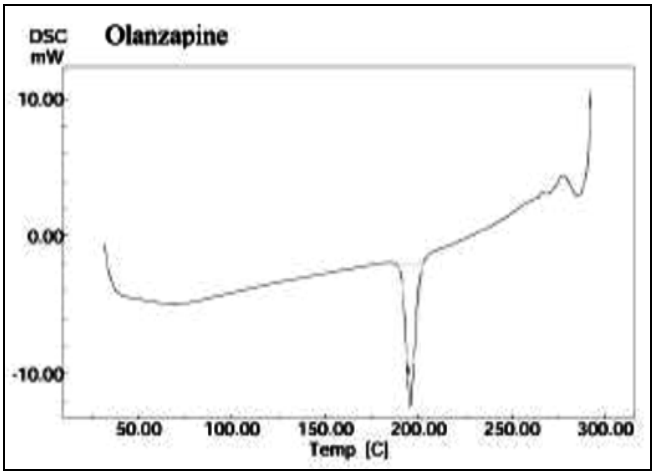

FIG. 3: DSC STUDY OF OLANZAPINE

Compatibility Study: Olanzapine with different excipient taken in different proportion in vials and were kept in accelerated stability [18, 19] condition for 2 and 4 weeks and evaluated for appearance, moisture content and assay to confirm the compatibility.

RESULT AND DISCUSSION: The present investigation was carried out to develop immediate release tablet dosage form of Class -II drug, Olanzapine. Drug-excipients compatibility study of Olanzapine with different categories of excipients was carried out. The study was carried out at different conditions of temperature and humidity like 40°C/75%RH, 2–8°C, room temperature & found their physical appearance, impurity level and water content after 2 week, 4 weeks and compare with initial value. The result shows impurity level with some drug and excipient combination increases and also slight changes in appearance but all were compatible with Olanzapine.

Excipients were considered compatible only if the total impurities do not exceed 2–times the impurities of initial. The pH dependent solubility study carried out by using different pH buffer solution ranging pH 1.2 (0.1 N HCl), pH 2.1 acid buffer, pH 4.5 acetate buffer, pH 5.5 acetate buffer and pH 6.8 phosphate buffer. Study shows solubility of Olanzapine was more in pH 1.2 (0.1 N HCl) i.e. 18.33 mg/ml. 0.1N HCl was used as dissolution medium as used by innovator. Evaluation was divided in mainly A. Pre compression parameters, B. Post compression parameters.

A. Pre Compression Parameters

a. **Loss on Drying (LOD):** As calculated, the moisture content of drug and excipient which was 2%w/w, at 80°C. LOD of dried granules maintained in that level NMT ± 1% variation by drying at 60°C and optimize drying time for achieve LOD in particular limit.

b. **Powder Flow Characteristics:** Initially some flow problem arises in direct compression method. Powder Blend shows poor flow which causes weight variation, problem in content uniformity; But Wet Granulation Method shows good flow properties of granules and final blend.

- Bulk density in the range 0.52 – 0.56gm/ml.
- Tapped density in the range 0.63-0.67gm/ml.
- Carr's Index ranging 16-22 %.
- Hausner's ratio in the range 1.2-1.3 shows the good flow characteristics.

c. **Sieve Analysis:** Sieve Analysis by mechanical shaker shows there was good blend of fines and granules which result in good flow and reduces weight variation problems.

B. Post Compression Parameters:

a. **Weight Variation:** Initially in some trails, weight variation observed, but in final trial tablet ranging 208-210 mg (Target weight – 208.0mg/Tablet) for 5 mg tablet formulation, which is less than 7.5%, indicates that the variation in the weight of the tablets is within standard official limits.

b. **Thickness Evaluation:** Thickness of tablet was observed by Vernier's Caliper. Thickness of the tablet is about 3.82± 0.02 mm which does not show any measurable deviation.

c. **Hardness Test :** Hardness of the tablet was measured in 'Newton' unit in digital harness tester The hardness of tablets found to be uniform within range 80 N to 90 N for 5mg indicates that the prepared tablets are mechanically stable.

d. **Disintegration Test:** Disintegration test was carried out in Electro lab (ED-2AL). Disintegration time for 6 tablets found to be 4.5-5.5 min for 5 mg was less than 15 min, indicating that disintegration time within the specification limit.

e. **Friability Test:** The friability was carried out by using Roche Friabilator. The percentage friability of tablet was ranging 0.03% - 0.08% for 5mg. They are less than the standard limit of 1% indicates that the prepared tablets are mechanically stable.

f. **Drug Content Uniformity:** In the initial trials drug content uniformity found outside limit but, after that each trials drug contents ranging from 99% - 99.6% which is within the range of 98 – 102% for Olanzapine. It indicates uniform distribution of drug in the tablets of each formulation.

***In vitro* Drug Release Studies:** The Olanzapine tablets were subjected to in vitro drug release studies in 0.1N HCl for 45 min. The drug release studies carried out in dissolution test apparatus using 900 ml of dissolution medium, maintained at 37°C ± 0.5°C shown in **Fig. 4**. Among all trials dissolution profile of 2 trials, i.e. F 9 and F 10 matches with innovator in 0.1N HCl medium.

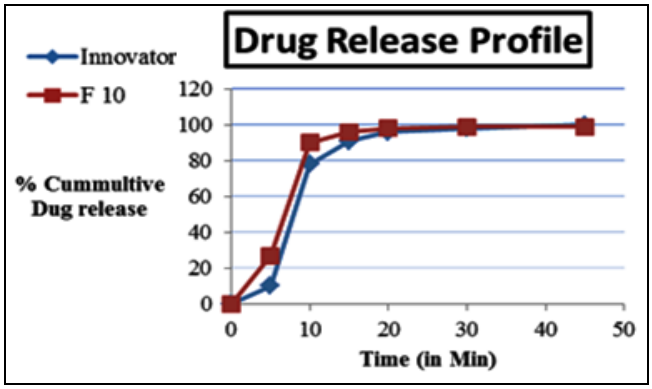

FIG. 4:

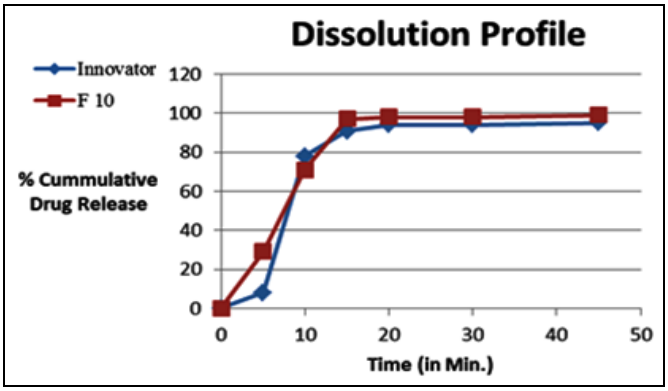

FIG. 5

Exposure Study: Exposure studies were carried out of selected formulation. In exposure study, F 10 and innovator formulation was subjected to different environmental stress [19, 20] conditions like 80° for 2 days and in autoclave at 121°C for 15 min. The result shows similar behavior between F 10 and innovator in different conditions.

Stability Study: The stability studies of F 10 were done for 6 months by packing in HDPE container in humidity chamber (40°C/75% RH).The result

Then, they were subjected to match in other two medium i.e. pH 4.5 acetate buffer and pH 6.8 phosphate buffer.

F 9 failed to match in pH 4.5 acetate buffer medium with innovator. Only F 10 matches with innovator. The dissolution study of F10 and innovator were done in pH 4.5 acetate buffer (given in **Fig. 5**) and in pH 6.8 phosphate buffer (given in **Fig. 6**). Then it was also studied for other media such as 0.001N HCl, pH 5.5 acetate buffer, pH 7.4 phosphate buffer (given in **Table 6 and Fig. 7**) and water with innovator. Thus, F 10 was finalized and taken as final formula.

Dissolution Profile:

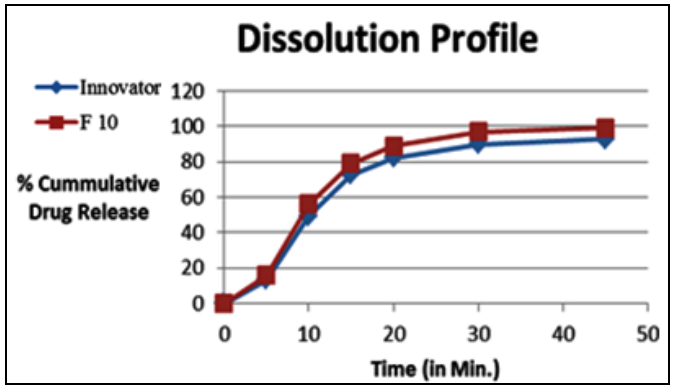

FIG. 6:

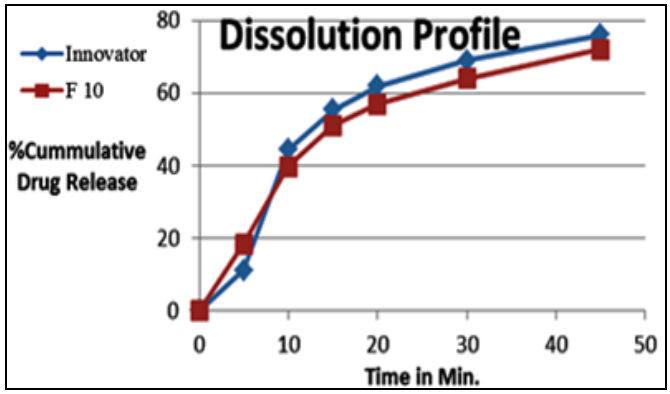

FIG. 7:

for 1 month, 2 months, 3 months and 6 months obtained. All parameters of formulation including physical parameters, impurity profile (given in **Table 7**), content uniformity or dissolution profile were determined. Total impurities for the F10 was found 0.257% as compare to innovator whose total impurities is 0.352% and the assay value of F 10 is 99.01% as in innovator its 98.06.The content uniformity physical parameter and impurities are within specification limit. So it indicates optimized formulation were stable.

TABLE 7: ACCELERATED STABILITY STUDY OF F 10 FOR IMPURITY.

Sl. No.	Impurities	Limit	Initial	1 Month	2 Month	3 Month	6 Month
1	Impurity A	0.5%	0.014%	0.007%	0.025%	0.058%	0.053%
2	Impurity B	0.5%	NA	0.009%	0.034%	0.406%	0.582%
3	Impurity C	0.5%	NA	NA	NA	0.174%	0.351%
4	Unknown Impurity	0.2%	0.106%	0.191%	0.473%	0.124%	0.16%
5	Total Impurity	-	0.257%	0.416%	1.068%	0.959%	1.411%

NA- Not Available

CONCLUSION: Here, an attempt was made to prepare a bioequivalent immediate released solid oral dosage form of Olanzapine. The present formulation has identical dissolution profile as that of innovator Zyprexa. Here the formulation F10 has less impurity in accelerated stability condition as compared to innovator.

The antipsychotics have a superior effectivity as compared with conventional agents; however, Olanzapine has an excellent tolerability profile offering high patient acceptability that in turn, may promote patient adherence to medication and an improved quality of life. As such, we consider Olanzapine to be a first choice antipsychotic for the treatment of acute exacerbations of schizophrenia and bipolar disorder.

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