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Formulation, Characterization and In Vivo Evaluation of Bi Layered Tablet of Olanzapine

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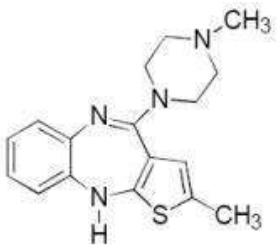
ABSTRACT
The aim of the present research work was to develop the different immediate and sustained release formulation of Olanzapine and compare their release profile, from above formulation select a best formulation for manufacturing bi-layered tablet. In the present work bi-layered tablet of Olanzapine were prepared by wet granulation method, using super disintegrants such as sodium starch glycolate and croscarmellose for immediate release layer and polymer like HPMC K4M and HPMC K100M for sustained release layer. Best formulations of each layer were selected for bi-layered tablet and bi-layered tablet were prepared. Bi-layered tablet of Olanzapine were subjected to hardness, weight variation, friability, drug content uniformity, in vitro drug release and drug polymer interaction. Based on the observations, it can be concluded that the formulated bi-layered tablets of Olanzapine using superdisintegrants, release retardant polymers and different excipients was capable of exhibiting all the properties of bi-layered tablet. They are thus reducing the dose intake, minimize dose related adverse effect, cost and ultimately improve the patient compliance and drug efficiency.

Key words:- Olanzapine tablet, Blayered tablet, Anti psychotic drug,

I. INTRODUCTION

Olanzapine, a Thienobenzodiazepine derivative, is an atypical antipsychotic agent with broad efficacy, eliciting a response in both the positive and negative symptoms of schizophrenia and bipolar disorder. The activity of olanzapine is achieved by the antagonism of multiple neuronal receptors including the dopamine
receptor D1, D2, D3 and D4 in the brain, the serotonin receptors 5HT2A, 5HT2C, 5HT3 and 5HT6, the alpha-1 adrenergic receptor, the histamine receptor H1 and multiple muscarinic receptors.



Stucture of olanzapine

II. MATERIALS :-

The following materials of Pharma grade or the best possible Laboratory Reagent (LR) were used as supplied by the manufacturer. Olanzapine Gift sample from ROAQ Chemicals Pvt. Ltd. Vadodara, Lactose S.D. Fine Chem. Ltd, Mumbai ,HPMC K4M S.D. Fine Chem. Ltd, MumbaiHPMC K100M Yarrow Chem Products, Mumbai,Microcrystalline cellulose S.D. Fine Chem. Ltd, Mumbai Magnesium stearate S.D. Fine Chem. Ltd, Mumbai, Talc S.D. Fine Chem. Ltd, Mumbai.

III. METHODS:-

Preparation of IRL:- IRL of Olanzapine (DS) was prepared by wet granulation by using different

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Super disintegrants such as SSG and Croscarmellose sodium. PVP K30 solution with containing coloring agent was used as binding solution. As DS was oily in characteristics, MCC was used as adsorbent. Manufacturing steps-Pass all the ingredients though sieve80.Mix Olanzapine with MCC geometrically and then mix with lactose. Add Superdisintegrants and mix for 10 to 15 min in mortar andpestle. Make wet mass using binding agent PVP K 30 solution containing color. Pass the cohesive mass through sieve # 16 to get uniform granules. Dry the granules at 50^0C for 15 min in hot air oven. Lubricate the granules with lubricating agent and compressed into 2.5 mg each tablet weight by adjusting hardness. The formulations are shown on table

Table 14: Formulation of immediate release layer

S. No.	Ingredients	IF1 (in mg)	IF2 (in mg)	IF3 (in mg)	IF4 (in mg)	IF5 (in mg)	IF6 (in mg)
1	Olanzapine	2.5	2.5	2.5	2.5	2.5	2.5
2	Lactose	82	79.5	82	79.5	82	79.5
3	Croscarmellose sodium	10	12.5	-	-	5	6.25
4	Sodium starch glycolate	-	-	10	12.5	5	6.25
5	Microcrystalline cellulose	25	25	25	25	25	25
6	Ponceau 4R	0.02	0.02	0.02	0.02	0.02	0.02
7	Magnesium stearate	3	3	3	3	3	3
8	Talc	5	5	5	5	5	5
	Total	127.5	127.5	127.5	127.5	127.5	127.5

Preparation of SRL:- Accurately weighed Olanzapine and polymer and others ingredients were taken in mortar and pestle and mixed well. The powder were mixed with sufficient quantity for PVP K30 solution until wet mass formed. The cohesive mass obtained was passed though sieve # 16 and the granules were dried in a hot air oven at 50^0C for 20 min. The dried granules again passed through sieve # 22 to break the large lumps. Then granules were mixed with talc and magnesium stearate and compressed into 300 mg each tablet by adjusting hardness. The formulations were shown on table no15.

Table 15: Formulation of sustained release layer (SRL)

S. no	Ingredients	Sf1 mg	Sf2 mg	Sf3 mg	Sf4 mg	Sf5 mg	Sf6 mg	Sf7 mg	Sf8 mg	Sf9 mg
1	Olanzapine	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
2	Lactose	52.75	45.25	37.75	52.75	45.25	37.75	52.75	45.25	37.75
3	HPMC K4M	45	52.5	60	-	-	-	22.5	26.25	30
4	HPMC K100M	-	-	-	45	52.5	60	22.5	26.25	30
5	Microcrystalline cellulose	20	20	20	20	20	20	20	20	20

International Journal of Pharmaceutical Research and Applications
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6	Magnesium stearate	3	3	3	3	3	3	3	3	3
7	Talc	6	6	6	6	6	6	6	6	6
	Total	129.2	129.2	129.2	129.2	129.2	129.2	129.2	129.2	129.2

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

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 (Wfinal). The percentage friability was calculated by, F= Winitial- Wfinal/ Winitial× 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 content13 in each tablet was estimated at λmax 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 37oC±0.5oC.In each test tubes one tabplaced 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

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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 variousspecifications

EVALUATION OF PRE-COMPRESSIONPARAMETERS

Table 24: Pre-compression parameters for IRL and SRL

Formulation	Bulk Density Mean ± SD	Tapped Density Mean ± SD	Car's Index Mean ± SD	Haunsers Index Mean ± SD	Angle of Repose Mean ± SD
IF1	0.557±0.002	0.637±0.005	12.610±0.217	1.145±0.030	16.596±0.356
IF2	0.556±0.005	0.655±0.004	15.084±0.226	1.174±0.020	18.360±0.275
IF3	0.523±0.004	0.626±0.003	15.773±0.109	1.164±0.022	19.421±0.173
IF4	0.585±0.003	0.684±0.003	13.899±0.177	1.163±0.013	20.147±0.156
IF5	0.612±0.010	0.682±0.007	11.767±0.206	1.133±0.009	17.913±0.039
IF6	0.666±0.004	0.755±0.006	11.148±0.157	1.142±0.025	17.101±0.077
SF1	0.592±0.005	0.694±0.003	13.779±0.206	1.154±0.009	19.604±0.279
SF2	0.591±0.008	0.699±0.002	14.494±0.328	1.169±0.017	18.480±0.063
SF3	0.605±0.004	0.681±0.003	11.223±0.186	1.133±0.009	18.201±0.088
SF4	0.623±0.005	0.703±0.002	11.531±0.127	1.132±0.010	22.548±0.280
SF5	0.596±0.004	0.710±0.004	16.144±0.249	1.200±0.028	18.331±0.077
SF6	0.591±0.004	0.727±0.002	18.716±0.397	1.256±0.029	18.168±0.104
SF7	0.615±0.003	0.728±0.004	14.825±0.673	1.174±0.028	18.467±0.091
SF8	0.512±0.001	0.623±0.002	17.564±0.436	1.243±0.024	19.347±0.072
SF9	0.620±0.002	0.693±0.001	10.754±0.181	1.124±0.017	17.396±0.021

IV. RESULT :-

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.

International Journal of Pharmaceutical Research and Applications
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POST-COMPRESSION EVALUATIONPARAMETERS:

Table: Post-compression parameters for IRL and SRL

Batch code	Weight variation Mean ± SD (in mg)	Hardness (kg/cm^2) Mean ± SD	Friability (%) Mean ± SD	Thickness Mean ± SD	Drug content (%) Mean ± SD	In vitro disintegration time (sec) Mean ± SD (in mg)
IF1	2.5±1.57	5.95±0.05	0.74±0.09	2.87±0.04	2.0±1.19	120.33±1.52
IF2	2.2±1.60	4.18±0.10	0.58±0.04	2.91±0.10	2.2±1.82	91.66±2.08
IF3	2.7±1.60	6.35±0.03	0.56±0.06	2.90±0.07	2.5±1.28	73.33±2.51
IF4	2.5±1.99	6.17±0.07	0.65±0.05	2.87±0.03	2.4±0.94	48.33±3.05
IF5	2.4±2.52	4.14±0.04	0.63±0.03	2.92±0.06	2.2±1.32	59.33±2.08
IF6	2.5±1.81	4.53±0.11	0.69±0.04	2.89±0.09	2.4±1.81	37.33±1.52
SF1	2.4±1.41	5.38±0.10	0.32±0.06	3.34±0.09	2.0±1.19	-
SF2	2.5±2.29	4.33±0.02	0.35±0.02	3.30±0.14	2.5±1.03	-
SF3	2.2±1.59	6.14±0.04	0.43±0.03	3.31±0.03	2.4±1.28	-
SF4	2.5±1.14	6.23±0.06	0.36±0.02	3.28±0.05	2.0±0.85	-
SF5	2.5±1.37	5.14±0.03	0.41±0.06	3.30±0.06	2.5±1.27	-
SF6	2.4±1.31	4.52±0.02	0.48±0.03	3.33±0.03	2.5±0.61	-
SF7	2.5±1.46	6.74±0.04	0.42±0.06	3.28±0.08	2.2±1.04	-
SF8	2.2±1.55	6.16±0.02	0.37±0.04	3.30±0.04	2.4±1.20	-
SF9	2.4±1.04	6.56±0.03	0.31±0.03	3.32±0.07	2.5±0.93	-

Table: Post-compression parameters for bi-layered tablet

Formulation	Weight variation Mean ± SD (in mg)	Hardness Mean ± SD	Friability Mean ± SD	Thickness Mean ± SD	Drug content (%) Mean ± SD (in mg)
BTF	2.5±0.46	7.05±0.15	0.38±0.01	6.28±0.14	2.5±0.53

In-vitro dissolution study

Table : In Vitro Dissolution Study Of IRL

Time in min	% CUMULATIVE DRUG RELEASE					
	IF1	**IF2**	**IF3**	**IF4**	**IF5**	**IF6**
0	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000
1	17.056±0.612	21.226±0.872	20.847±0.450	26.532±1.306	30.323±1.2.5	36.008±1.174

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 4 July-Aug 2021, pp: 1219-1228 www.ijprajournal.com ISSN: 2249-7781

3	31.805±1.075	31.908±1.280	33.738±2.620	54.965±2.391	56.561±0.778	60.653±2.255
5	53.454±2.280	56.489±2.100	56.488±1.288	68.244±0.593	64.455±2.346	68.247±1.723
10	64.837±2.481	68.251±3.001	68.2.5±1.176	81.525±0.896	77.735±1.791	83.424±2.060
15	71.106±1.634	78.121±1.913	74.141±1.523	89.829±1.107	81.543±0.873	92.918±1.314
20	80.408±1.038	83.445±1.088	82.685±0.582	94.829±0.788	87.246±1.865	98.624±0.722
25	86.676±1.427	92.366±1.472	90.280±1.281	97.497±0.931	92.376±1.325	98.827±1.427
30	91.047±2.031	94.842±1.632	93.135±0.852	98.075±1.265	96.743±1.731	99.404±1.162

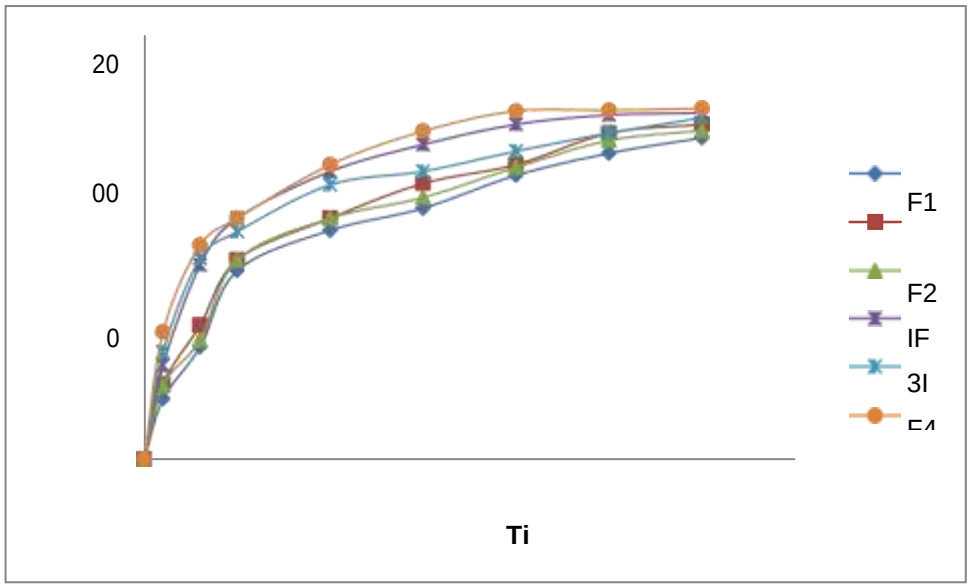

Figure 16: Release profile of immediate release layer

Table 28: In vitro dissolution study of SRL

Time in min	% CUMULATIVE DRUG RELEASE							
	SF1	SF2	SF3	SF4	SF5	SF6	SF7	SF8
0	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000
60	15.408±1.222	7.905±1.234	6.017±1.508	13.469±1.222	6.741±1.281	5.558±1.591	13.006±1.994	5.391±0.882
120	25.634±1.764	19.263±1.532	18.231±1.281	25.637±0.732	18.521±1.421	12.635±0.751	21.351±1.317	17.527±1.114
240	34.323±2.715	24.502±1.083	23.091±1.547	33.235±1.164	25.279±1.003	17.697±1.151	33.589±1.503	24.917±1.426
360	42.342±0.632	31.362±1.321	29.735±0.941	38.852±1.521	33.852±1.835	25.742±1.427	45.247±0.941	36.518±0.831
480	57.151±1.196	43.141±1.974	36.936±1.251	56.674±2.061	47.993±0.539	33.733±2.378	53.869±1.510	46.331±0.891
600	62.342±0.412	48.234±0.826	43.752±1.423	62.316±1.839	50.491±0.694	39.513±1.114	59.523±1.163	52.852±0.792

International Journal of Pharmaceutical Research and Applications
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720	76.620±1.642	56.263±2.227	54.964±2.137	70.315±2.001	65.327±1.779	47.031±1.480	68.215±0.906	64.017±0.710
960	98.183±0.352	82.430±1.267	66.957±1.402	87.123±0.645	86.182±0.467	54.439±2.565	88.053±0.676	77.498±0.918
1080	101.512±1.093	97.816±0.630	84.113±1.317	98.822±1.325	97.692±0.844	67.057±1.191	100.859±2.165	94.298±0.560

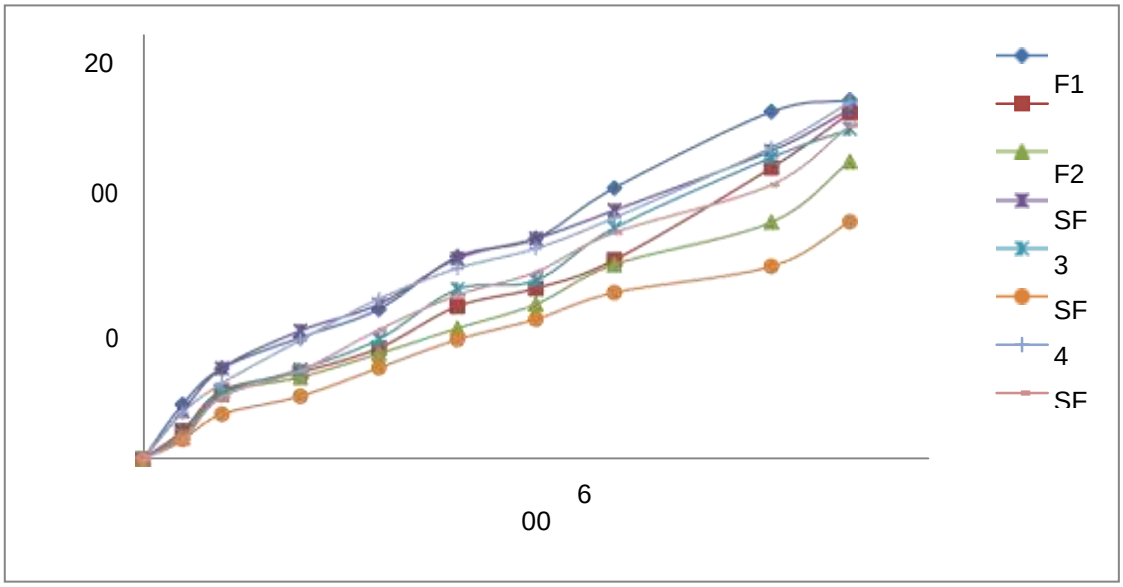
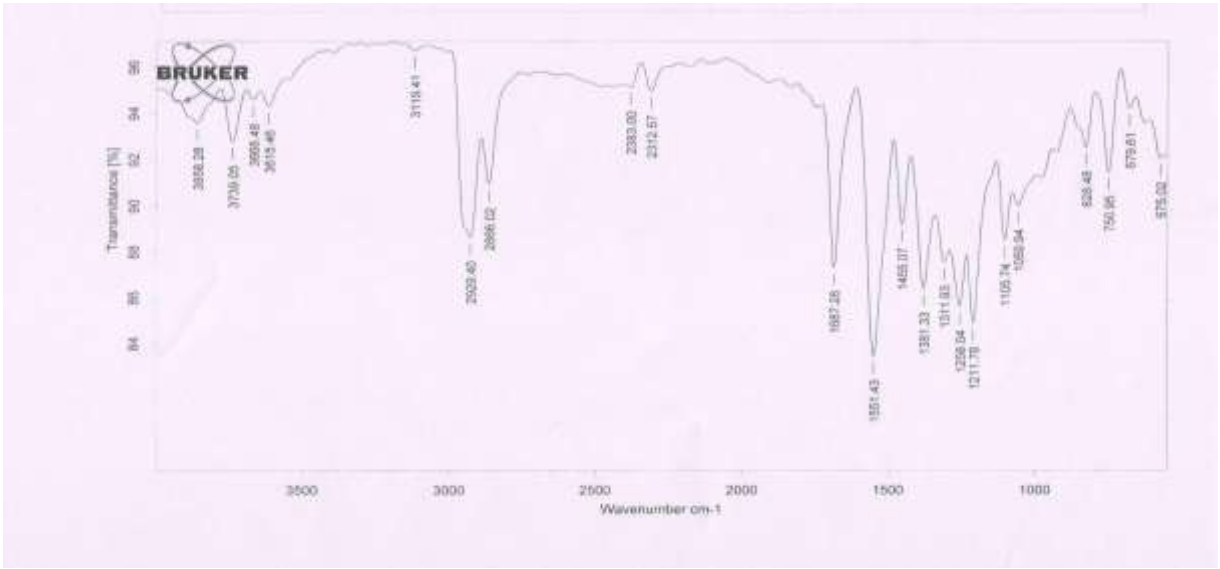


figure 17: Release profile of sustained release layer

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.



DSC Study DSC Analysis

International Journal of Pharmaceutical Research and Applications
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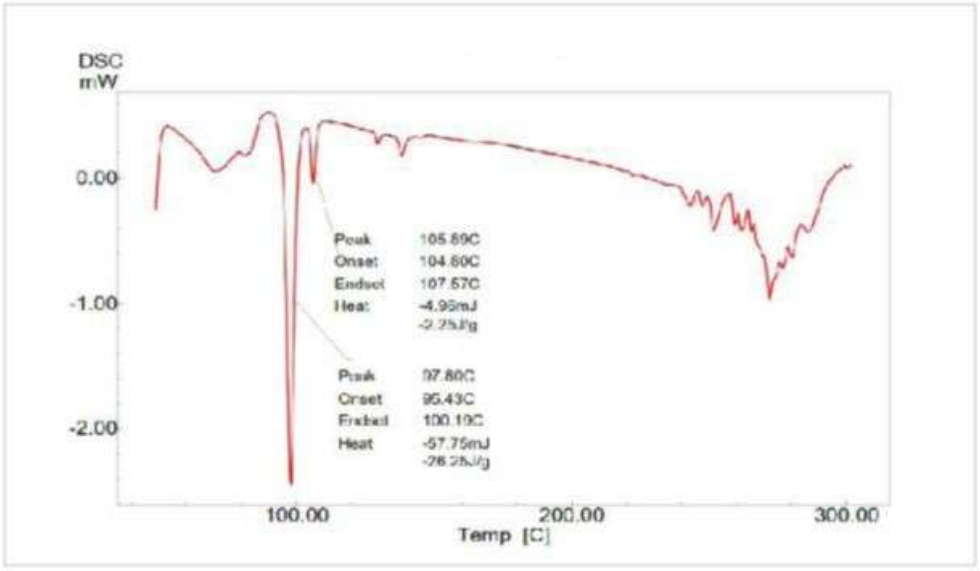

Figure 14: DSC spectrum of Olanzapine

Figure 15: DSC spectrum of Formulation

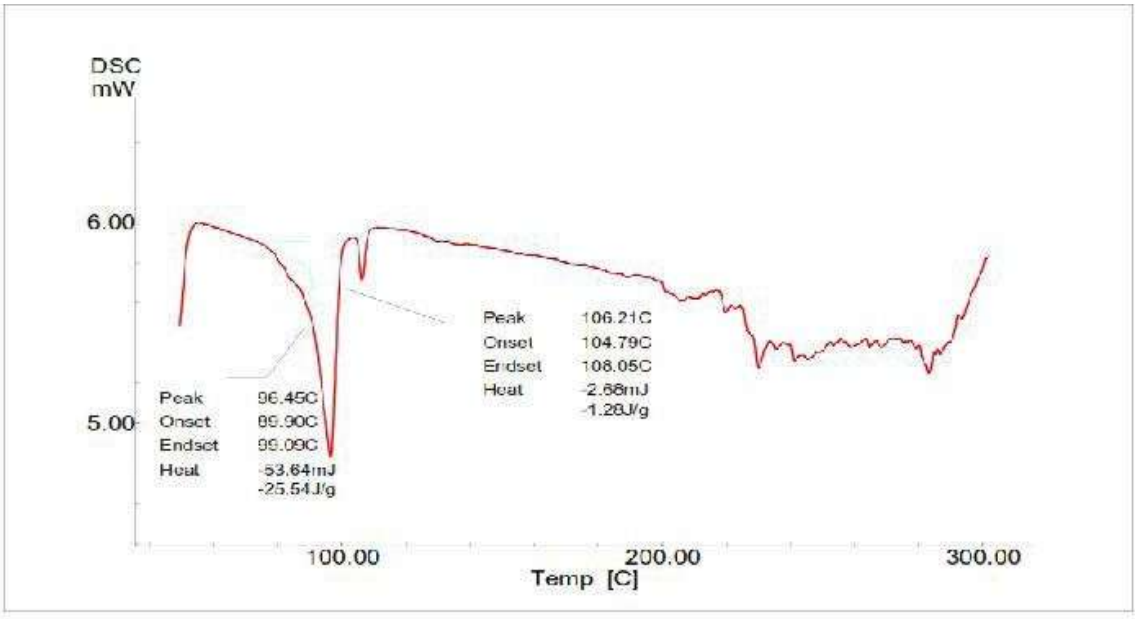

Figure 15: DSC spectrum of Formulation

V. CONCLUSION :

In the present work bi-layered tablet of Olanzapine were prepared by wet granulation method, using superdisintegrants such as sodium starch glycolate and croscarmellose for immediate release layer and polymer like HPMC K4M and HPMC K100M for sustained release layer. Best formulations of each layer were selected for bi-layered tablet and bi-layered tablet were prepared. Bi-layered tablet of Olanzapine were subjected to hardness, weight variation, friability, drug content uniformity, in vitro drug release and drug polymer interaction.The above studies lids to following conclusions: FTIR and DSC studies indicated that the drug is compatible with all the excipients.Both immediate and sustained release layer were prepared by wet granulation method and punched separately. The prepared tablets of both layers were

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evaluated for post compression parameters.According to the in vitro dissolution profile date one formulation of each layer were selected for bi-layered tablet. IF6 from immediate release formulations as they showed 98.62 % drug release within 20 minute. SF8 from sustained release formulation as they showed 94.29 % drug release within 18 hours.The bi layer tablets were prepared using the selected immediate and sustained release layer. The prepared tablets were found to be good and free from chipping and capping.The hardness of the prepared tablets was found to be in the range of 5.85 to 7.05 kg/cm^{2}The low values of the standard deviation of average weight of the prepared tablets indicate weight uniformity within the batches prepared.The friability of the prepared tablet was found to be less than1%.The percentage drug content was uniform in all the formulations of prepared bi-layered tablets.In vitro drug release pattern of the bi-layered tablets were same as individual layer tablets.The stability study showed that no significant changes in tablets after 3 monthsstudy.Based on the observations, it can be concluded that the formulated bi-layered tablets of Olanzapine using superdisintegrants, release retardant polymers and different excipients was capable of exhibiting all the properties of bi-layered tablet. They are thus reducing the dose intake, minimize dose related adverse effect, cost and ultimately improve the patient compliance and drug efficiency.

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