International Journal of Pharmaceutical Development & Technology

e ISSN - 2248 - 910X

www.ijpdt.com

Print ISSN - 2248 - 9096

FORMULATION AND EVALUATION OF OLANZAPINE FAST DISINTEGRATING TABLETS USING COPROCESSED SUPERDISINTEGRANTS

Ramadevi K*, Mahalakshmi Y, Susheela V, Santhosh Kumar T, Chandra Sekhara Rao G,

Department of Pharmaceutical Technology, Yalamarty Pharmacy College, Visakhapatnam,

ABSTRACT

Fast disintegrating tablets (FDT) have emerged as an alternative to oral conventional dosage forms to target populations like pediatric, geriatric, bedridden patients. The concept of coprocessing has been developed to obtain excipients with superior properties. The aim of this study was to prepare co-processed superdisintegrants using crospovidone, sodium starch glycolate, croscarmellose sodium, and use them in the formulation of FDT of Olanzapine. Tablets were prepared by direct compression and evaluated for wetting time, water absorption ratio and *in vitro* drug release. FTIR study indicated that there was no interaction between the drug and prepared coprocessed superdisintegrants. The dissolution studies showed that the use of coprocessed superdisintegrants resulted in rapid release of drug from the tablets. It can be concluded that coprocessed superdisintegrants can be successfully used in the formulation of fast disintegrating tablets.

Keywords: Fast disintegrating tablets, Coprocessed superdisintegrants, Olanzapine.

INTRODUCTION

Despite of tremendous innovations in drug delivery, the oral route remains the preferred route for administration of therapeutic agents [1]. But the important drawback of conventional oral tablet dosage forms is 'Dysphagia' or difficulty in swallowing for many patients; almost 50% of the population is affected by such problem. Hence they do not comply with prescription, which results in high incidence of non-compliance and ineffective therapy [2].

To overcome such problems, fast disintegrating tablets or orally disintegrating tablets have emerged as an alternative dosage form [3]. The Center for Drug Evaluation and Research(CDER), US FDA defined Fast-dissolving/disintegrating tablets (FDDTs) as "A solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue". Fast disintegrating tablets are those when put on tongue disintegrate instantaneously releasing the drug which dissolve or disperses in the saliva. When faster the drug goes 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.

The basic approach in development of FDT is the use of superdisintegrants like cross linked carboxy methyl cellulose (croscarmellose), sodium starch glycolate (primogel, explotab), cross linked polyvinylpyrolidone (crospovidone) etc, which provide instantaneous disintegration of tablet after putting on tongue, there by release the drug in saliva. Types of superdisintegrants available are natural, synthetic and coprocessed [4]. Co-processing is based on the novel concept of two or more excipients interacting at the sub particle level, the objective of which is to provide a synergy of functionality improvement as well as masking the undesirable properties of individuals. Co-processing excipients lead to the formulation of excipient granules with superior properties, compared with physical mixtures of components or individual components, like improved flow properties, improved compressibility, better dilution potential, fill weight uniformity, and reduced lubricant sensitivity.

The aim of the present work was to prepare co-processed superdisintegrants using crospovidone, sodium starch glycolate, croscarmellose sodium, and use them in the formulation of FDTs. Olanzapine was used as a model drug. Olanzapine is an antipsychotic drug approved by the Food and Drug Administration (FDA), for the treatment of schizophrenia, depressive episodes associated with bipolar

Corresponding Author :- **Ramadevi K** Email:- ramakalyank@gmail.com

disorder and acute manic episodes.

MATERIALS AND METHODS

Olanzapine was obtained as a gift sample from Dr. Reddy's Laboratories, Hyd. Crospovidone, Sodium starch glycolate, Croscarmellose sodium, Avicel PH 102 from Yarrow Chem Products, Mumbai, Mannitol from Qualigens Fine Chemicals, Mumbai, Aerosil from Oxford Laboratory, Mumbai and Magnesium stearate from Qualikems Fine Chemicals Pvt. Ltd., New Delhi were purchased. All other chemicals used were of analytical grade.

Preparation of co-processed superdisintegrants

The co-processed superdisintegrants were prepared by solvent evaporation method [5]. According to the composition given in Table No. - 1, the weighed superdisintegrants were taken in a mortar and mixed thoroughly. 10 ml of ethanol was added to the mixture and stirred continuously until most of the ethanol was evaporated. The mass was dried in a hot air oven at 40^{o}C for 10 minutes. The dried mass was stored until further use.

Preparation of fast disintegrating tablets

Mouth dissolving tablets were prepared by direct compression method. All the ingredients were weighed and taken in a mortar according to the composition of formulations given in Table No. - 2. The mixture was mixed thoroughly and compressed using 9 mm flat faced punches of 10 station rotary tablet compression machine (Shakti). Mannitol improves patient compliance by imparting cool sensation and imparts mild sweet taste. It flows well and improves flow properties of other materials. MCC acts as a diluent as well as also plays a role of adsorbent. Sodium saccharin was used as a sweetener. Aerosil was used as a glidant and magnesium stearate as lubricant.

Evaluation of precompression powder blend

The flow ability of the powder blend was determined by angle of repose, Bulk Density (BD), Tapped Density (TD), Carr's Index (CI), and Hausner's ratio parameters.

EVALUATION OF TABLETS

Compatibility studies

Compatibility must be established between the drug and other excipients to produce a stable product. Compatibility was tested using Fourier Transform Infrared spectroscopy (FTIR). IR spectra of pure olanzapine and formulations containing co-processed superdisintegrants were recorded by KBr method using Bruker FTIR, Software OPUS Version. Scanning was done from 4000 – 500 cm^{-1}.

Thickness

The thickness of the tablets was determined by using Screw Gauge. Thickness of three tablets from each formulation was determined and the average value was calculated.

Limit: Tablet thickness should be controlled within a ±5 % variation of the standard value[6]

Hardness

The hardness of tablets was determined by using Monsanto hardness tester[6] (Inco, Ambala). Hardness of three tablets from each formulation was determined and the average value was calculated.

Uniformity of Weight

To study weight variation, 20 tablets per formulation were selected randomly. Each tablet was weighed individually and average weight was calculated for all the formulations [7].

IP Limit: Not more than two of the individual weights deviate from average weight by more than 7.5 % and none deviates by more than twice that percentage.

Friability

Required number of tablets were weighed (initial weight) and placed in drum (Roche friabilator). The friabilator was operated at 25 rpm for 4 minutes. The tablets were removed of any loose dust from them and weighed again (final weight). The % friability was calculated [7].

% Friability = Final weight – Initial weight / Initial weight X 100

IP Limit: A maximum loss of weight not greater than 1 % is acceptable.

Disintegration Time

The conventional disintegration test apparatus may not give correct values of disintegration time. The amount of saliva in the oral cavity is very limited (usually less than 6 ml) whereas the conventional disintegration test apparatus uses a large amount of water with rapid up and down movements. To overcome this problem, a simple method was followed. 6 ml of 0.1 N HCl was taken in a 25 ml measuring cylinder and a tablet was put into it. The time required for complete disintegration of the tablet was noted as disintegration time [8].

Wetting Time

A piece of tissue paper folded twice was placed in a petridish containing 6 ml of 0.1 N HCl. A tablet was placed on the surface of tissue paper. The time required for complete wetting of the tablet was noted as wetting time [8].

Water Absorption Ratio

A piece of tissue paper folded twice was placed in a petridish containing 6 ml of 0.1 N HCl. A preweighed tablet (initial weight) was placed on the surface of tissue paper and allowed to wet completely. The wetted tablet was reweighed (final weight) and water absorption ratio, R was determined using following equation [8].

R = Final weight – Initial weight/Initial weight X 100

Drug Content

Five tablets were weighed individually and powdered. The powder equivalent to 5 mg of olanzapine was dissolved in 10 ml of 0.1 N HCl and filtered. The drug content was determined measuring the absorbance at 258 nm after suitable dilution using UV- Visible double beam spectrophotometer (Elico, SL 159) [9].

IP Limit: Olanzapine Tablets contain not less than 90 % and not more than 110 % of the stated amount of olanzapine [10].

***In Vitro* Dissolution Studies**

The *in vitro* release of olanzapine from the formulated tablets was carried out in tablet dissolution apparatus (Electrolab TDT-08L) using 900 ml of dissolution medium maintained at 37.0±0.5 °C and a stirring rate of 50 rpm [9]. Three tablets from each formulation were tested individually in 0.1 N HCl. At every 2 minute interval, samples of 5 ml were withdrawn from the dissolution medium and replaced with fresh medium to maintain the constant volume. After filtration and appropriate dilution, the amount of olanzapine present in each sample was determined spectrophotometrically at 258 nm and cumulative percentage drug release was calculated. To compare the dissolution profiles of formulated products with a marketed formulation (MF), dissolution of OLEANZ 5 (Sun Pharma) was carried out.

To examine the drug release kinetics, the cumulative release data were fitted to models representing zero order (Q v/s t) and first order [Log(Q_0-Q) v/s t], where Q is the cumulative percentage of drug released at time tand (Q_0-Q) is the cumulative percentage of drug remaining after time t.

RESULTS

Table 1. Composition of Co-Processed Superdisintegrants

Superdisintegrants	CP1	CP2	CP3	CP4
Crospovidone (CP)	750 mg		750 mg	500 mg
Sodium Starch Glycolate (SSG)	750 mg	750 mg		500 mg
Croscarmellose Sodium (CCS)		750 mg	750 mg	500 mg

Table 2. Composition of Mouth Dissolving Tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
Olanzapine	5	5	5	5	5	5	5	5
Superdisintegrant (4%)	-	4 (CP)	4 (SSG)	4 (CCS)	4 (CP1)	4 (CP2)	4 (CP3)	4 (CP4)
Mannitol	50	50	50	50	50	50	50	50
Avicel PH 102	39	39	39	39	39	39	39	39
Sodium Saccharin	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Aerosil	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Magnesium stearate	1	1	1	1	1	1	1	1
Total Weight	100	100	100	100	100	100	100	100

Table 3. Evaluation of Pre-Compression Blend (Mean±SD, n=3)

Formulation	Angle of Repose	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's Index	Hausner Ratio
F1	36.86±0.69	0.43±0.005	0.71±0.008	39.4±0.17	1.65±0.06
F2	33.10±0.09	0.48±0.001	0.79±0.001	39.8±0.51	1.66±0.08
F3	33.02±0.11	0.50±0.002	0.69±0.005	27.0±0.68	1.37±0.19
F4	37.23±0.16	0.51±0.004	0.69±0.006	25.5±0.72	1.34±0.23
F5	32.20±0.23	0.45±0.002	0.71±0.008	36.6±0.18	1.57±0.15
F6	38.65±0.25	0.47±0.005	0.66±0.009	28.78±0.43	1.40±0.09
F7	30.11±0.16	0.43±0.006	0.71±0.01	39.40±0.65	1.65±0.22
F8	27.92±0.18	0.41±0.004	0.66±0.007	37.87±0.25	1.60±0.17

Table 4. Interpretation of FTIR Spectra

	Functional group assigned (cm^{-1})				
	NH & OH Stretching	C-H Stretching	C=C Stretching	C=N Stretching	C-N Stretching
Characteristic Peaks	3239	2929	1587	1421	1287
Olanzapine	3235.69	2926.62	1587.79	1418.66	1285.15
F8	3288.72	2911.13	1588.81	1421.58	1282.04

Table 5. Evaluation of Tablets (Mean±SD, n=3, *n=20)

Formulation	F1	F2	F3	F4	F5	F6	F7	F8
Thickness (mm)	2.19±0.023	2.25±0.034	2.26±0.013	2.16±0.56	2.26±0.035	2.23±0.065	2.22±0.067	2.27±0.053
Hardness (kg/cm^2)	2.5±0.21	2.5±0.31	2.6±0.10	2.6±0.34	2.9±0.23	2.8±0.38	2.7±0.28	2.7±0.43
Weight variation mg)*	100.01±5.98	98.34±7.13	98±7.01	96.42±7.23	96.66±6.98	97.1±6.38	100±7.26	98.28±6.4
Friability (%)	0.34	0.89	0.67	0.72	0.79	0.89	0.86	0.70
Disintegration time (seconds)	67±2.48	10±1.29	25.67±0.96	9.67±1.73	16.33±2.79	11.67±1.67	13.33±0.84	10±2.64
Wetting time (seconds)	66.67±2.39	14±.1.26	18.33±0.97	12±2.88	20.67±0.54	14±1.47	14.33±1.29	18.67±2.78
Water absorption Ratio (%)	76.53±0.98	100.33±1.6	137.5±1.01	100±0.68	127.27±1.35	148.75±1.11	110.95±0.67	129±1.26
Drug content (%)	99.86±0.01	99.89±0.05	98.72±0.04	97.60±0.09	97.64±0.02	99.82±0.98	97.60±0.68	99.83±0.53

Fig 1. FTIR Spectrum of Olanzapine

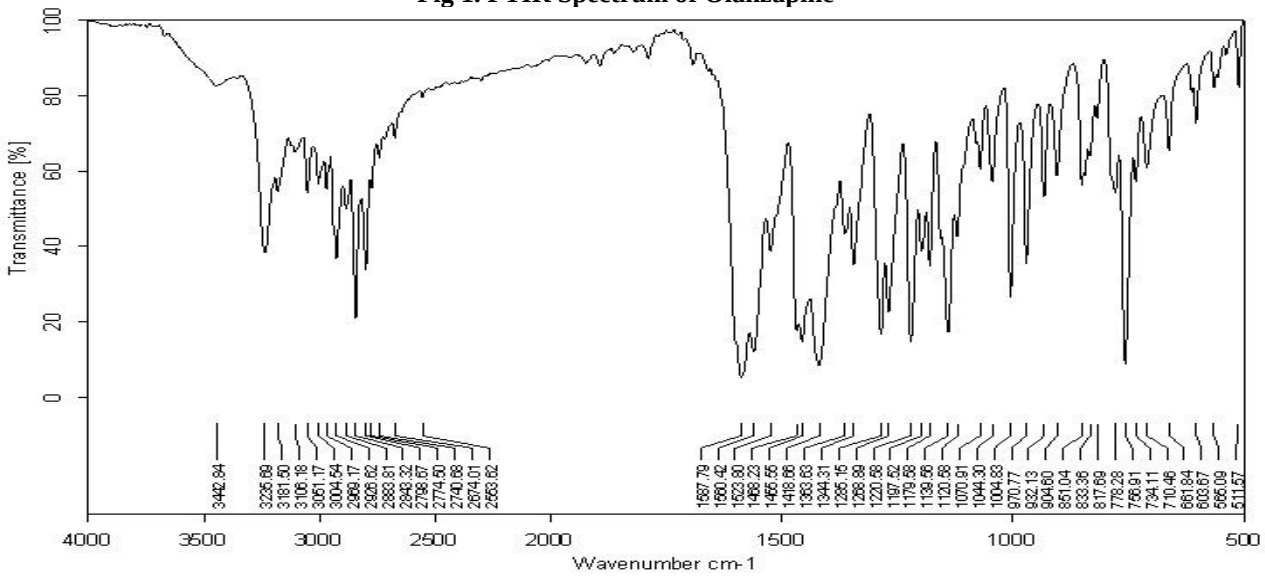


Fig 2. FTIR Spectrum of F8

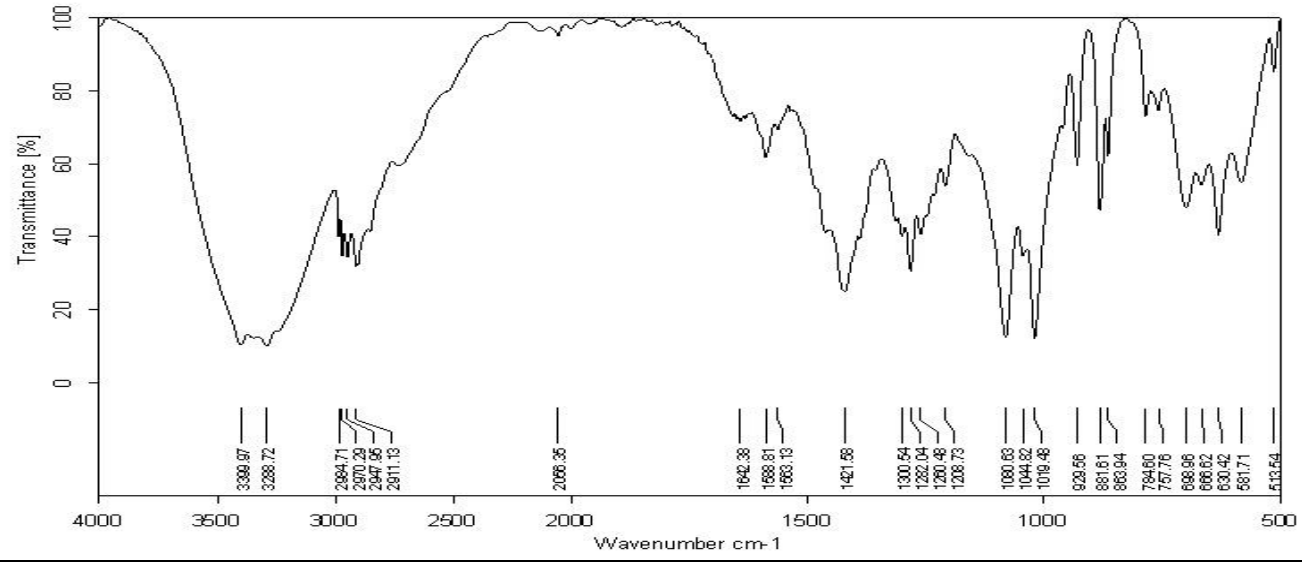


Fig 3. Dissolution Profiles of F1 – F5

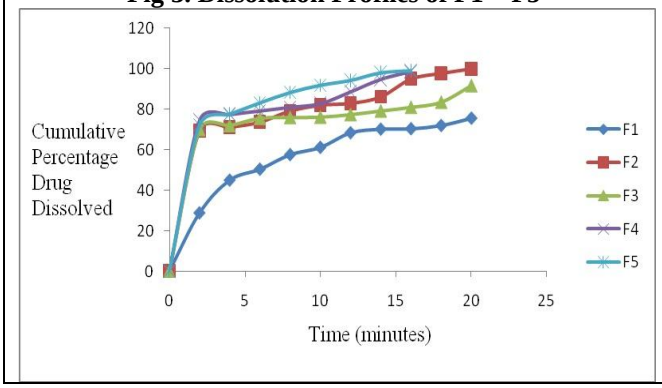
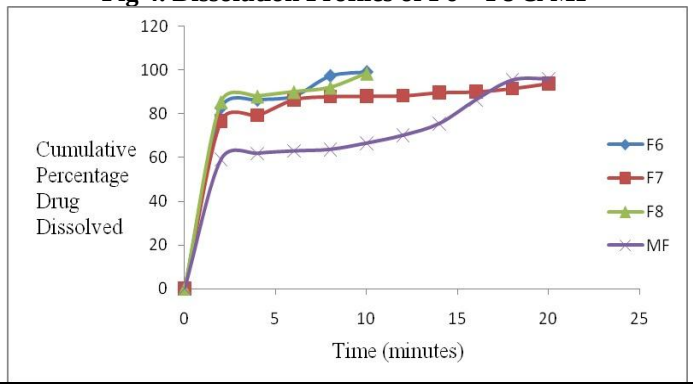


Fig 4. Dissolution Profiles of F6 – F8 & MF



DISCUSSION

Preparation of co-processed superdisintegrants

The co-processed superdisintegrants were prepared by solvent evaporation method using ethanol as solvent. When ethanol was added to the superdisintegrants mixture, clear solutions were observed in all cases except CP1. In CP1, a white dispersion was formed. After complete evaporation of solvent, the wet masses were dried. In all cases, non-sticky, amorphous powders were formed.

Evaluation of precompression powder blend

Precompression parameters of the formulations were reported in Table No. – 3. The angle of repose values were in the range of 27.92 to 38.65. The bulk density values varied from 0.41 g/ml to 0.51 g/ml and the tapped density values varied from 0.66 g/ml to 0.79 g/ml. The Carr's index values were in the range of 25.5 to 39.8 and the Hausner ratio values were in the range of 1.34 to 1.66. From the above results, it was observed that the powder blends possessed passable to poor flow properties. In formulations F7 and F8, the obtained angle of repose values showed that the flow property was improved.

EVALUATION OF TABLETS

Compatibility Studies

The IR spetcra of the drug and formulation F8 were given in Figure No. 1 & 2. From the interpretation of IR spectra (Table No. – 4), it was observed that there was a slight deviation in the values which is within acceptable limits. It concludes that there is no interaction between the drug and the prepared coprocessed superdisintegrants [11].

The thickness of tablets was from 2.16 mm to 2.27 mm. The hardness of tablets was found to be in the range of 2.5 to 2.9 kg/cm^2. According to IP, less than 7.5% weight variation is acceptable in tablets having average weight between 80 to 250. Thus, all the formulations were found to be within IP limits. Friability values of all the formulations were less than 1% which was an indication of good mechanical resistance of the tablets. Disintegration times were less than 1 minute in F2 - F8, lowest in F4 (9.67seconds). In F1, disintegration time is greater than 1minute. Wetting time depends on the ability of the superdisintegrant to swell and its capacity to absorb water. Wetting times were less than 1 minute in F2- F8, lowest in F4 (12s). In F1, wetting time is greater than 1 minute. Water absorption ratio was calculated for understanding the capacity of disintegrants to swell in the presence of a little amount of water. It was highest in F6 (148.75%) and lowest in F1(76.53%). Drug content values were from 97.6% to 99.89%. The drug content values were found within pharmacopoeial limits of 90 - 110% (Table No. – 5).

In vitro Dissolution Studies

In all the formulations containing superdisintegrants, there was a rapid drug release within 2 minutes followed by gradual increase in drug release over 20 minutes. The bursting effect of superdisintegrant showed rise in drug release. In F1, the drug release was gradual over 20 minutes. In F1, the drug dissolved was only 75.6% in 20 minutes as it did not contain any superdisintegrant. Formulations F2, F3 & F4 contained only single superdisintegrant. In F2 & F3, the drug dissolved was greater than 90% in 20 minutes and in F4, drug dissolved was 98.7% in 16 minutes. F5, F6, F7 & F8 formulations contained coprocessed superdisintegrants. In F5, drug dissolved was 99% in 16 minutes. In F6 & F8, the drug dissolved was greater than 98% within 10 minutes but in F7, drug dissolved was 93.8% in 20 minutes. F2, F3 & F7 showed similar dissolutions profiles as marketed formulation (Figure No. 3 & 4).

From the data, it was observed that, the drug release was rapid within 10 minutes in F6 & F8. In F6, the rapid drug release might be due to additive effect of swelling property of sodium starch glycolate and croscarmellose sodium. In F8, the rapid drug release might be due to combined effect of all three superdisintegrants, crospovidone, sodium starch glycolate and croscarmellose sodium, that is both swelling property and wicking action. It was observed that all the formulations followed first order drug dissolution kinetics.

CONCLUSION

In the present study, coprocessed superdisintegrants were prepared using crospovidone, sodium starch glycolate and croscarmellose sodium in 1:1 ratios. The prepared superdisintegrants were used in the

formualtion of fast disintegrating tablets of olanzapine. From the FTIR study, it was observed that the drug and coprocessed superdisintegrants were compatible. All the precompression and post compression parameters were within the acceptable range. The dissolution studies showed that the use of coprocessed superdisintegrants resulted in rapid release of drug from the tablets. So, it was concluded that coprocessed superdisintegrants can be successfully used in the formulation of fast disintegrating tablets. Coprocessing of the excipients lead to formulation of excipients with superior quality than their physical mixture.

ACKNOWLEDGEMENTS

The authors are grateful to the Chairman and the Principal of Yalamarty Pharmacy College for providing facilities to carry out the research work.

REFERENCES

1. Pahwa R, Piplani M, Sharma PC, Kaushik D, Nanda S. Orally Disintegrating Tablets - Friendly to Pediatrics and Geriatrics. *Archives of Applied Science Research*, 2(2), 2010, 35-48.
2. Divate S, Kavitha K, Sockan GN. Fast disintegrating tablets - An emerging trend. *International Journal of Pharmaceutical Sciences Review and Research*, 6(2), 2011, 18-22.
3. Corveleyn S, Remon JP. *International Journal of Pharmaceutics*, 152, 1997, 215-225.
4. Rajni B, Sushil K, Pravin P. Polymers in Fast Disintegrating Tablets – A Review. *Asian Journal of Pharmaceutical and Clinical Research*, 5(2), 2012, 8-14.
5. Mangesh MK, Rajendra PM, Rajendra MK, Mahavir HG, Giridhar RS. Design of Fast Dissolving Tablet of Atenolol using Novel Co-processed Superdisintegrant. *Asian Journal of Pharmaceutical and Clinical Research*, 6(3), 2013, 81-85.
6. Leon L *et al*., The Theory and Practice of Industrial Pharmacy. Special Indian Edition. CBS Publishers & Distributors India, 2009, 296 - 297.
7. Indian Pharmacopoeia. 1, 2007, 182-183.
8. Vinayak M, Shailesh B, Arun K, Vilas A, Sharda Z. Formulation and Evaluation of Mouth Dissolving Tablet of Olanzapine by Coprocessing Superdisintegrants. *Asian Journal of Pharmaceutical Technology & Innovations*, 1(1), 2013, 1- 20.
9. Manjunatha K, Maheswarappa, Priyankabahen DD. Design and *in vitro* evaluation of mouth dissolving tablets of olanzapine. *Asian Journal of Pharmaceutics*, 2011, 107 – 113.
10. Indian Pharmacopoeia. 3, 2007, 1471-1472.
11. Venkateskumar K**,** Suchandrasen, Verma PRP. Physicochemical characterization and *in vitro* dissolution behavior of olanzapine - mannitol solid dispersions. *Brazilian Journal of Pharmaceutical Sciences*, 48(2), 2012, 243–255.