Research Article

Comparitive Evaluation of Olanzapine Immediate Release Tablets by Using Natural Super Disintegrants

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ABSTRACT

In the present study, natural gums (*Locust bean gum* and Modified gum karaya) were investigated as superdisintegrants for use in immediate release tablet formulations containing olanzapine. Prepared tablets were evaluated for thickness, hardness, friability, uniformity of weight, disintegration time, wetting time and dissolution study. The formulated tablets had good appearance and better drug release properties. Modified gum karaya showed shorter disintegration time and showed 100% release is selected as optimized formulation. Immediate release tablet formulations containing modified gum karaya showed better dissolution efficiency property than the most widely used synthetic superdisintegrants. . The dissolution rate followed first-order kinetics as the graphs drawn between log % drug unreleased vs time were found to be linear. The dissolution rate of Olanzapine was found to be effected by the concentration of the superdisintegrant used in the preparation of tablets. The formulation (F_4) prepared with 5%w/w of modified gum karaya was offered relatively rapid release of Olanzapine when compared with other concentrations employed in this investigation. The difference factor (F_1) and similarity factor (F2) were calculated for marketed formulation and for formulations prepared with modified gum karaya. The difference factor (F_1) and similarity factor (F2) were found to be 11 and 72 respectively. Similarity factor (F2) is more than 50 and difference factor (f1) is less than 15, hence dissolution profiles are found to be similar.

Keywords: Crosspovidone, locust bean gum, modified gum karaya, olanzapine

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INTRODUCTION

The proper choice of superdisintegrants and its consistency of performance are of importance to the formulation of a rapidly disintegrating dosage form or immediate releasing dosage forms. The choice of super disintegrant for a tablet formulation depends largely on the nature of drug being used.

For example, the solubility of the drug component could affect the rate and mechanism of tablet disintegration. Water soluble materials tend to dissolve rather than disintegrate, while soluble materials generally tend to disintegrate if an appropriate amount of super disintegrant is included in the formulation [1]. Furthermore the ionic nature of the drug and superdisintegrants and their potential interactions have been reported to affect the dissolution of tablet formulations [2]. Disintegrant are an essentials component to tablet formulations. The ability to interact strongly with water is essential to disintegrant function. Combinations of swelling and /or wicking and/or deformation are the mechanisms of disintegrant action.

For centuries man has made effective use of materials of nature origin in the medical and pharmaceutical field. Today, the whole world is increasingly interested in natural drugs and excipients. Natural materials have advantages over synthetic materials because they are nontoxic, less expensive and freely available.

Furthermore they can be modified to obtain tailor made materials for drug delivery systems allowing them to complete with the

synthetic products that are commercially available [3]. Plants products nowadays are widely used as an alternative to synthetic products due to ease of local accessibility, lower prices as compared to synthetic products, biocompatible, biodegradable nature and environment friendly nature. Extensive swelling, porosity and wicking action of the natural material in the tablet formulation were found to be contributing its super disintegrant. Immediate release tablets are those which disintegrate rapidly and get dissolved to release the medicaments. Immediate release may be provided for by way of an appropriate pharmaceutically acceptable diluents or carrier, which diluents or carrier does not prolong, to an appreciable extent, the rate of drug release and/or absorption [4].

MATERIALS AND METHODS

Olanzapine was obtained as gift sample from orchid pharmaceuticals, Hyd. Crosspovidone were obtained as gift sample from Natco Pharma Ltd, Hyderabad. Micro crystalline cellulose, Mannitol, Magnesium stereate and Talc were purchased from S.D. Fine chem. Ltd, Mumbai. Locust bean gum was obtained from Sipra labs Ltd, Hyd. Gum karaya was obtained from Loba fine chernei, Mumbai.

Preformulation studies:

Influence of pH of solvent on solubility of Olanzapine:

0.1N Hydrochloric acid, pH4.5 acetate buffers, pH 6.8 phosphate buffers and distilled water were prepared. Five ml quantity of buffer was taken into test tube. Excess quantity of buffer was added to the test tube. Then kept aside for 24 hrs and filtered through 0.23µm membrane filter. Finally, sample was suitably diluted and analyzed at 259nm by using UV-Visible spectrophotometer.

Influence of particle size on solubility of Olanzapine:

Sieve analysis of the drug sample was carried out using sieves numbered as 16, 22, 44, 60, 80, and 120. The fractions retained on 16/22, 22/44, 44/60, 60/80, 80/100, 100/120 were collected and transferred into different test tubes containing 0.1N Hydrochloric acid. All the test tubes were kept aside for about 24 hrs and filtered through 0.23µm membrane filter. Then the collected filtrates were analyzed at 259 nm by using UV-Visible spectrophotometer.

Preparation of Modified Gum Karaya [5]:

Powdered gum was taken in a bowl and subjected of heating using sand bath for different time periods at different temperatures. The results of swelling capacity and viscosity were decreased as a function of temperature and time period of heating. However, it was observed that Gum Karaya samples were charred, when heated at 140ºC. In the preparation of modified form of Gum Karaya, no further change in viscosity of Gum Karaya was observed by heating it at 120ºC for 2 h were selected to prepare modified form of Gum Karaya. The prepared modified form of Gum Karaya was finally re-sieved (100 mesh) and stored in airtight container at 25ºC.

Extraction of locust bean gum [6]:

The seeds are dehusked by treating the kernels with dilute sulfuric acid or with thermal mechanical treatment, elimination of the germ followed by milling and screening of the endosperm (native carob bean gum). The gum may be washed with ethanol or isopropanol to control the microbiological load (washed carob bean gum). It may also be further clarified (purified, extracted) by dispersing in hot water, recovery with isopropanol or ethanol, filtering, drying and milling, which is called as clarified (purified, extracted) carob bean gum.

Preparation of Olanzapine tablets:

Tablets containing 10mg of Olanzapine were prepared by direct compression method. Drug was passed through sieve no 100 . Olanzapine along with other excipients were mixed in a mortor. The resulting blend was lubricated with magnesium stereate and compressed into tablets using the cadmach single punch (round shaped, 9mm thick) machine. The composition of the different tablets formulated was shown in the following (**Tables 1-3**).

Measurement of Micrometric properties

The flow properties of powder blend of tablets were investigated by measuring the bulk density, tapped density, Carr's index and angle of repose.

EVALUATION OF OLANZAPINE TABLETS

Thickness: Thickness was measured by using vernier calipers.

Hardness: The hardness of tablet was measured by Monsanto hardness tester. The hardness was measured in terms of kg/cm.

Drug content: Twenty tablets were powdered, and 10 mg equivalent weight of Olanzapine in tablet powder was accurately weighed and transferred into a 100 ml volumetric flask. Initially, 5 ml methanol was added and shaken for 10 min. Then, the volume was made up to 100 ml with 0.1N HCL buffer. The solution in the volumetric flask was filtered, diluted suitably and analyzed spectrophotometrically at 361 nm [7].

Uniformity of weight: Twenty tablets were randomly selected from each formulation, individually weighed, the average weight and standard deviation was calculated [8].

Friability: Roche friabilator was used to determine the friability. Pre weighed tablets were placed in friabilator and rotated at a speed of 25 rpm for 4 minutes or up to 100 revolutions. The tablets are dropped from a distance of 6 inches in each revolution. The tablets were then reweighed after removal of fines and the percentage of weight loss was calculated [9]. $\%\text{FRIABILITY} = \frac{\text{INITIAL WEIGHT} - \text{FINAL WEIGHT}}{\text{INITIAL WEIGHT}} \times 100$

In vitro disintegration test:

The disintegration time was measured using disintegration test apparatus. One tablet was placed in each tube of the basket. The basket with the bottom surface made of a stainless-steel screen (mesh no.10) was immersed in water bah a 37 ± 2° C. The time required for complete disintegration of the tablet in each tube was determined using a stop watch. To be complied with the pharmacological standards, dispersible tablets must disintegrate within 3min when examined by the disintegration test for tablets [10].

In-vitro Dissolution Study:

The release rate Olanzapine from immediate release tablets is determined using United State Pharmacopoeia (USP) XXIV dissolution testing apparatus II (paddle method). The dissolution test was performed using 900 ml of 0.1N HCL buffer, at 37± 0.50C and 50 rpm. A sample (5 ml) of the solution is withdrawn from the dissolution apparatus at regular intervals for 5 min. The samples are replaced with fresh dissolution medium of same quantity. The samples are filtered through a 0.45ì membrane filter. Absorbance of these solutions is measured at 259 nm using a Shimadzu UV/Vis double beam spectrophotometer [11].

Comparison of dissolution profile by model independent methods [12]:

Model independent approaches includes difference factor (F_1) and a similarity factor (F_2) were used to compare dissolution profiles. The difference factor (f_1) calculates the percent (%) difference between the two curves at each time point and is a measurement of the relative error between the two dissolution curves.

$f_1 = \{[\sum_{t=1}^{n} | R_t - T_t |]/ [\sum_{t=1}^{n} R_t]\} x100$

Where n is the number of time points,

R is the dissolution value of the reference at time t

T is the dissolution value of the test at time t.

The similarity factor (f_2) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) dissolution between the two dissolution curves.

$f_2 = 50 \text{ x } \log \{[1+ (1/n) \sum_{t=1}^{n} (R_t - T_t)^2]^{-0.5} x100\}$

Where n is the number of time points,

R is the dissolution value of the reference at time t

T is the dissolution value of the test at time t.

RESULTS AND DISCUSSION

Influence of pH on solubility of Olanzapine was studied in four different solvents viz 0.1 N Hcl (pH1.2), pH 4.5 acetate buffer, pH 6.8 phosphate buffer and distilled water. Olanzapine was more soluble in pH 1.2 buffer than compared to other medias. As the principle peaks observed were identical in the spectra of drug and spectra of Drug and gum mixtures, it was confirmed that no chemical or physical interaction exists between the drug and the excipients employed in this investigation.

To study the influence of concentration of the modified gum karaya on the

performance of Olanzapine, a set of four formulations (F_1, F_2, F_3, F_4) were prepared using four different concentrations of modified gum karaya (2%, 3%, 4% & 5%w/w) respectively. The formulated tablets were subjected to various quality control tests. All the tablets complied with the pharmacopoeial standards, but F_1 failed to meet the fineness of dispersion requirements. The dissolution rate followed first-order kinetics as the graphs drawn between log % drug unreleased vs time were found to be linear. The dissolution rate of Olanzapine was found to be effected by the concentration of the superdisintegrant (Modified gum karaya) used in the preparation of tablets. Based on the dissolution rate, the order of drug release from the four formulations were F_4> F_3> F_2> F_1. The formulation (F_4) prepared with 5%w/w of modified gum karaya was offered relatively rapid release of Olanzapine when compared with other concentrations employed in this investigation.

A statistically significant difference between dissolution efficiencies (DE_{12}) of Olanzapine tablets formulated with different concentrations of modified gum karaya was calculated using a one-way analysis of variance (ANOVA). The P value was found to be less than 0.05, which indicates that there was a significant difference between F_1, F_2, F_3, F_4 with respect to dissolution efficiencies (DE_{12}).

To study the influence of concentration of the locust bean gum on the performance of Olanzapine, a set of four formulations (F_5, F_6, F_7, F_8) were prepared using four different concentrations of Locust bean gum (2%, 3%, 4% & 5%w/w) respectively. The formulated tablets were subjected to various quality control tests and the results were shown in (**Table 5**). All the tablets complied with the pharmacopoeial standards, but F_5 failed to meet the fineness of dispersion requirements. The dissolution rate followed first-order kinetics as the graphs drawn between log % drug unreleased vs. time were found to be linear.

The dissolution rate of Olanzapine was found to be effected by the concentration of the superdisintegrant (Locust bean gum) used in the preparation of tablets. Based on the dissolution rate, the order of drug release from the four formulations was F_8> F_7> F_6> F_5. The formulation (F_8) prepared with 5%w/w of locust bean gum was offered relatively rapid release of olanzapine when compared with other concentrations employed in this investigation.

A statistically significant difference between dissolution efficiencies (DE_{12}) of Olanzapine tablets formulated with different concentrations of locust bean gum was calculated using a one-way analysis of variance (ANOVA). The P value was found to be less than 0.05, which indicates that there was a significant difference between F_5, F_6, F_7, F_8 with respect to dissolution efficiencies (DE_{12}).

To study the influence of concentration of the crosprovidine on the performance of Olanzapine, a set of four formulations (F_9, F_{10}, F_{11}, F_{12}) were prepared using four different concentrations of crosprovidine (2%, 3%, 4% & 5%w/w) respectively. All the tablets complied with the pharmacopoeial standards, but F_9 failed to meet the fineness of dispersion requirements. The dissolution rate followed first-order kinetics as the graphs drawn between log % drug unreleased vs time were found to be linear. The dissolution rate of Olanzapine was found to be effected by the concentration of the superdisintegrant (Crosprovidine) used in the preparation of tablets. Based on the dissolution rate, the order of drug release from the four formulations was F_{12}> F_{11}> F_{10}> F_9. The formulation (F_{12}) prepared with 5%w/w of crosprovidine was offered relatively rapid release of Olanzapine when compared with other concentrations employed in this investigation.

A statistically significant difference between dissolution efficiencies (DE_{12}) of Olanzapine tablets formulated with different concentrations of crosprovidine was calculated using a one-way analysis of variance (ANOVA). The P value was found to be less than 0.05, which indicates that there was a significant difference between F_{12}, F_{11}, F_{10}, F_9 with respect to dissolution efficiencies (DE_{12}).

The difference factor (f_1) and similarity factor (f2) were calculated for marketed

formulation and for formulations prepared with modified gum karaya. The difference factor (f_1) and similarity factor (f2) were found to be 11 and 72 respectively. Similarity factor (f2) is more than 50 and difference factor (f1) is less than 15, hence dissolution profiles are found to be similar.

CONCLUSION

To study the influence of pharmaceutical excipients on performance of olanzapine, natural superdisintegrants and cross povidone at different concentrations were used to prepare olanzapine immediate release tablets. Among all the tablets, tablets formulated with modified gum karaya were found to be best for Olanzapine to formulate as immediate release tablets.

Table 1: Composition of Olanzapine immediate release tablets formulated with Gum karaya

S.No.	Ingredients	F5	F6	F7	F8
1	Olanzapine	10	10	10	10
2	Gum Karaya	4	6	8	10
3	Mannitol	84.5	82.5	80.5	78.5
4	MCC	100	100	100	100
5	Talc	2	2	2	2
6	Mg stearate	1.5	1.5	1.5	1.5

Table 2: Composition of Olanzapine immediate release tablets formulated with Carob bean gum (locust bean gum)

S.No.	Ingredients	F1	F2	F3	F4
1	Olanzapine	10	10	10	10
2	Carob bean gum	4	6	8	10
3	Mannitol	82.5	80.5	78.5	76.5
4	MCC	100	100	100	100
5	Talc	2	2	2	2
6	Mg stearate	1.5	1.5	1.5	1.5

Table 3: Composition of Olanzapine immediate release tablets formulated with Cross povidine

S.No.	Ingredients	F21	F22	F23	F24
1	Olanzapine	10	10	10	10
2	Cross Povidone	4	6	8	10
3	Mannitol	84.5	82.5	80.5	78.5
4	MCC	100	100	100	100
5	Talc	2	2	2	2
6	Mg stearate	1.5	1.5	1.5	1.5

Table 4: *In-vitro* dissolution kinetics of Olanzapine immediate release tablets formulated with different concentrations of Modified gumkaraya, locust bean gum, Crosspovidone

S.No.	Formulation	T_{50} (min)	T_{90} (min)	DE_{12} (%)	K (min^{-1})	Correlation coefficient values		
						Zero Order	First Order	Hixson-Crowell cube root
1	F_1	10.04	33.37	26.38	0.069	0.986	0.988	0.981
2	F_2	8.17	27.15	37.22	0.084	0.950	0.982	0.974
3	F_3	6.72	22.35	44.73	0.103	0.940	0.98	0.971
4	F_4	2.41	8.02	63.26	0.287	0.942	0.979	0.988
5	F_5	10.82	35.98	28.28	0.064	0.975	0.991	0.974
6	F_6	10.79	35.87	32.69	0.064	0.975	0.987	0.963
7	F_7	8089	29.56	39.98	0.077	0.960	0.986	0.977

8	F_8	7.87	26.17	44.30	0.088	0.946	0.986	0.981
9	F_9	11.94	39.7	36.89	0.058	0.918	0.954	0.961
10	F_{10}	9.9	32.9	42.13	0.070	0.912	0.952	0.972
11	F_{11}	8.598	28.57	47.13	0.080	0.890	0.937	0.964
12	F_{12}	5.007	16.64	58.89	0.138	0.911	0.967	0.988

Table 5: Physical parameters of Olanzapine immediate release tablets formulated with different concentrations of Modified Gum karaya, Locust bean gum, Crosspovidone

S. No.	Formulations	Average weight(mg)	Drug content (%)	Disintegration time(min)	Friability	Hardness (kg/sqcm)
1	F1	199 ± 0.41	98.76 ±0.34	3.2 ± 0.12	0.67 ± 0.23	3.3 ± 0.45
2	F2	199 ± 0.41	99.3 ± 0.13	2.6 ± 0.14	0.74 ± 0.21	3 ± 0.32
3	F3	201 ± 0.17	99.43 ±0.28	1.6 ± 0.21	0.65 ± 0.12	2.8 ± 0.45
4	F4	200 ± 0.14	98.29 ±0.32	0.90± 0.17	0.89 ± 0.11	2.5 ± 0.34
5	F5	201±0.17	96.3±0.23	1.6± 0.36	0.78± 0.27	2.83±0.26
6	F6	200±0.31	99±0.16	1.2± 0.21	0.88±0.31	3.2±0.21
7	F7	202+0.26	99.4±0.36	1±0.17	0.79±0.19	2.95±0.38
8	F8	200+0.36	99.3±0.13	0.79+0.19	0.77±0.22	2.8±0.21
9	F9	198±0.53	97.6±0.16	1.5±0.10	0.74±0.02	3±0.4
10	F10	199+0.18	98±0.31	1.2+0.19	0.6±0.08	2.6±0.16
11	F11	201+0.13	98.5±0.42	0.82±0.23	0.64±0.12	2.3±0.12
12	F12	199+0.28	99.3±0.21	0.66±0.43	0.59±0.32	3.1±0.32

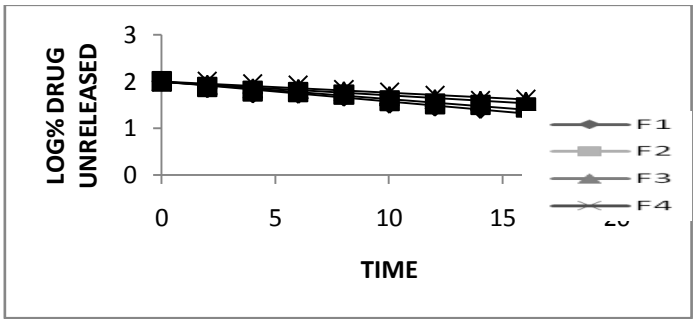

Figure 1: *In-vitro* dissolution profile of Olanzapine immediate release tablets formulated with different concentrations of Gum karaya (F_1, F_2, F_3, F_4)

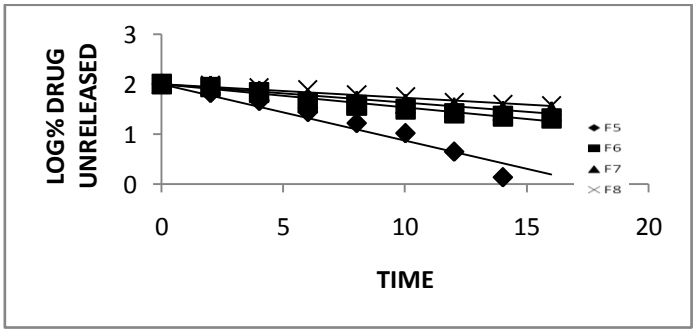

Figure 2: *In-vitro* dissolution profile of Olanzapine immediate release formulated with different concentrations of Carob bean gum (F_5, F_6, F_7, F_8)

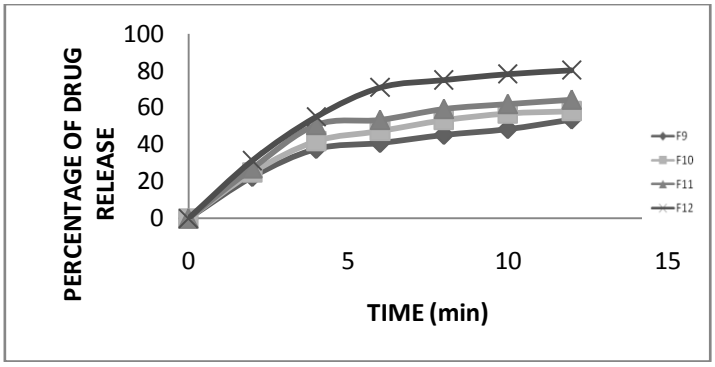

Figure 3: *In-vitro* dissolution profile of olanzapine immediate release tablets formulated with different concentrations of crosprovidine (F9, F10, F11, F12)

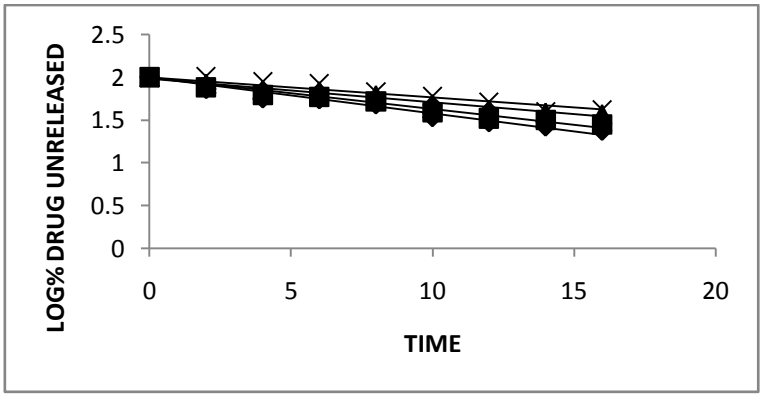

Figure 4: First order plots of Olanzapine immediate release tablets formulated with different concentrations of Gum karaya (F_1, F_2, F_3, F_4)

REFERENCES

1. Johnson J. R, Wang L. H, Gordon M. S, Chowhan Z. T. Effect of formulation solubility and hygroscopicity on disintegrating efficiency in tablets prepared by wet granulation. Journal of Pharmaceutical Sciences. 1991; 80:469 –471.
2. Chien Y. W, Van Nostrand P, and Hurwitz A. R, Shami E. G. Drug– disintegrant interactions: binding of oxymorphone derivatives. Journal of Pharmaceutical Sciences. 1981;90: 709–710.
3. Girish K jani, Dhiren P Shah. Gums and mucilages: versatile excipients for pharmaceutical formulations. Asian journal of pharmaceutical sciences. 2009;4 (5):309-323.
4. Vijay Sharma, Anil K. Philip, and Kamla Pathak. Modified Polysaccharides as Fast Disintegrating Excipients for Orodispersible Tablets of Roxithromycin. AAPS PharmSciTech. March 2008; Vol. 9, No. 1:DOI: 10.1208/s12249-0079026-4.
5. www.fda.gov.<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM0702.
6. Murali Mohan Babu G.V, Prasad Ch. D.S, Ramana Murthy K.V. Evaluation of Modified Gum Karaya as Carrier for the Dissolution Enhancement of Poorly Water-Soluble Drug Nimodipine. International journal of Pharmaceutics. 2002; 234:1-17.
7. A.Martin and J.Swarbrick, Physical pharmacy, 3rd edition, Mumbai: Varghese publishing house, 1993, Pg. No. 444-7.
8. Indian pharmacopoeia 2007, Vol 3, Monographs on dosage forms, The Indian pharmacopoeia commission, Ghaziabad, 2007.
9. USP 27/NF 22, Asian edition, General test procedures, U.S. Pharmacopoeial convention, Rockville MD, 2000.
10. C.P.Jain and P.S. Naruka. "Formulation and evaluation of immediate release tablets of Valsartan". International Journal of Pharmacy and Pharmaceutical Sciences,2009; Vol. 1, Issue 1, July-Sep:219-227.
11. G.Rajalakshmi, N. Damodharan, Abhinav chaudhary, D.Maheswara Reddy, Formulation and evaluation of orodispersible tablets of pheniramine maleate, International Journal of PharmTech Research,2010;2(1):310-318.
12. RamaRao N, Chowdary KP. Improvement of dissolution rate and bioavailability of Piroxicam with pre-gelatinized starch. Indian J Pharm Sci. 2001; 63:36-40.