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FORMULATION AND IN VITRO EVALUATION OF RABEPRAZOLE SODIUM DELAYED RELEASE TABLETS

Bhavani K.* and Matsyagiri L.

Swami Vivekananda Institute of Pharmaceutical Sciences, Vangapally, Yadagirigutta, Yadadri- Bhuvanagiri-508286, Telangana, India.

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***Corresponding Author**
Bhavani K.
Swami Vivekananda Institute of Pharmaceutical Sciences, Vangapally, Yadagirigutta, Yadadri-Bhuvanagiri-508286, Telangana, India.

ABSTRACT

The main objective of this research work was to formulate and evaluate the delayed release tablets of rabeprazole sodium, an anti ulcer drug like peptic ulcer and duodenal ulcer. Rabeprazole was class-I proton pump inhibitor to gain FDA approval. Rabeprazole sodium delayed release tablets were prepared by direct compression technique and dry granulation method. All the Excipients are tested for compatibility with drug, which revealed that there was no physical and chemical interaction occurred. During film coating Appearance, average weight, hardness, thickness, disintegration and during film coating appearance of film coating, Average weight of film coating tablet, disintegration time and during enteric coating appearance and average weight of enteric coated tablets acid resistance this parameters were performed like wt variation test, hardness, friability, disintegration time. Among all formulations, formulation F12 was found to be best of all the formulations showing drug release matching the innovator product so to that formulation all the quality control tests were done for conformation. Stability study is carried out for 3 months at 25°C; 60% RH: and 40°C; 75% RH, according to ICH guidelines. The effect of these variables on drug release also studied. The *in vitro* drug release studied was performed in the disintegration apparatus.

Key Words: Anti ulcer drug, Delayed release, Rabeprazole sodium.

INTRODUCTION

Dosage forms can be designed to modify the release of the drug over a given time or after the dosage form reaches the required location. Drug release only occurs some time after the administration or for a prolonged period of time or to a specific target in the body.[1]

Modifications in drug release are often desirable to increase the stability, safety and efficacy of the drug, to improve the therapeutic outcome of the drug treatment and/or to increase patient compliance and convenience of administration.[2] Enteric coating is those which remain intact in the stomach, but will dissolve and release the contents once it reaches the small intestine. Their prime intension is to delay the release of drugs which are inactivated by the stomach contents or may cause nausea or bleeding by irritation of gastric mucosa.[3]

Important Reasons for Enteric Coating are as follows

- To protect acid-liable drugs from the gastric fluid
- To protect gastric distress or nausea due to irritation from drug
- To deliver drugs intended for local action in the intestines
- To deliver drug that are optimally absorbed in the small intestine to their primary absorption site in their most concentrated form
- To provide a delayed release component to repeat actions
- Protect the drugs from harmful effect of the gastric contents; some of the drugs are prone to be hydrolyzed in acid media-example Pantoprazole.[4]

A peptic ulcer is a hole in the gut lining of the stomach, duodenum, or oesophagus. a peptic ulcer of the stomach is called a gastric ulcer; of the duodenum, a duodenal ulcer; and of the oesophagus, an oesophageal ulcer respectively. An ulcer occurs when the lining of these organs is corroded by the acidic digestive juices which are secreted by the parietal cells of the stomach. Rabeprazole belongs to class I drugs of the BCS, characterized by high solubility and high permeability. It belongs to a class of compounds called proton pump inhibitors substituted benzimidazoles, which inhibit the final common step in gastric acid secretion. The key action mechanism is inhibition of H+/K+- adenosine triphosphate (also known as acid pump or proton pump), an enzyme present in the gastric parietal cells. This effect on the final step of the gastric acid formation thereby reducing gastric acid output both during basal conditions and stimulated acid secretion, irrespective of stimulus.[5]

The aim and objectives of the present study is to develop a pharmaceutically stable, cost effective and quality improved formulation of Rabeprazole sodium delayed release tablets. To achieve this goal various prototype formulation trials will be taken and evaluated with respect to the various quality controls such as dissolution, assay, acid resistance. The formula will be finalized by comparing the *in vitro* dissolution profile with that of the innovator.

MATERIALS AND METHODS

Rabeprazole sodium was a gift from Dr Reddy's Lab., India: cross povidone, Sodium stearyl fumarate, Ethyl cellulose, Hypromellose phthalate Diacetylated monoglycerides obtained as a gift sample from Natco Pharma, India. Mannitol, Sodium carbonate anhydrous, dehydrated alcohol by Elvina pharmaceuticals. All other reagents used were of analytical grade.

Estimation of Rabeprazole sodium

Two different solutions of Rabeprazole sodium were prepared in 0.1 N HCl and 6.8 pH phosphate buffer respectively. The UV spectra were taken using spectrophotometer. The UV maxima of Rabeprazole sodium in 0.1 N HCl and 6.8 pH phosphate buffer were found to be 260 nm and 284 nm respectively.[6]

Method of preparation of tablet

Co-sift Rabeprazole Sodium, Sodium Carbonate anhydrous, and Cros povidone through sieve # 30. Sift Mannitol through sieve # 30. Sift the Step 1 and Step 2 materials through # 30 mesh. Load the step 3 materials into blender and mix for 30 mins. Sift Sodium stearyl fumarate through sieve # 40 along with a portion of prelubricated blend. Load the step 5 material to the blender and mix for 5 mins. Compress the lubricated blend of step no. 6 into tablets. Disperse ethyl cellulose in dehydrated ethanol under stirring to prepare clear solution add Water insoluble polymer and stir well. Divide the core tablets of step no. 7 into 2 equal lots and coat tablets in a coating machine with step no. 8 dispersion to achieve a target weight gain of 4.0 ± 0.5% w/w and 6.0 ± 0.5% w/w each. Warm the Seal-coated tablets in coating pan at 50°C ± 5°C for 20 -30 mins. Disperse Hypromellose phthalate (HP-55) in mixture of dehydrated ethanol and purified water (80:20) under stirring to prepare clear solution. Add diacetylated monoglycerides to the step no. 11 solution. Prepare dispersion of pigment blend yellow with purified water using homogenizer and add to the step no. 12 solution and stir well. Coat the seal coated tablets of step no.10 (4% w/w and 6% w/w) in a coating machine with step no. 13 dispersion to achieve a target weight gain of 10.0 ± 0.5% w/w. Warm the enteric-coated tablets in coating pan at 50 ± 5°C for 20 -30 mins.[7, 8]

Table 1: Compilation of Rabeprazole Enteric Coated Tablets (F1-F6).

Ingredients	F 1	F 2	F 3	F 4	F 5	F 6
Rabeprazole sodium	20	20	20	20	20	20
Mannitol	59.80	59.80	72.30	72.30	47.30	47.30
Sodium Carbonate Anhydrous	10	10	10	10	10	10
Crospovidone	40	40	30	30	50	50
Hydroxy propyl cellulose	2.50	2.50	-	-	5.00	5.00
Sodium starch Fumarate	2.70	2.70	2.70	2.70	2.70	2.70
Seal coating stage						
Ethyl cellulose	1.62	2.16	2.7	4.05	2.7	4.05
Water insoluble polymer (compound A)	-	-	2.7	4.05	2.7	4.05
Water soluble polymer (compound B)	6.48	8.64	-	-	-	-
Enteric coating stage						
HPMCP 55	17.17	17.50	16.85	17.17	16.85	17.17
Myvacet	1.72	1.75	1.69	1.72	1.69	1.72
Pigment blend Yellow	2.58	2.62	2.52	2.58	2.52	2.58

Table 2: Compilation of Rabeprazole Enteric Coated Tablets (F7-F12).

Ingredients	F7	F8	F9	F10	F11	F12
Rabeprazole sodium	20	20	20	20	20	20
Mannitol	67.30	67.30	59.80	59.80	52.30	52.30
Sodium Carbonate Anhydrous	10	10	10	10	10	10
Cros povidone	30	30	40	40	50	50
Hydroxy propyl cellulose	5.00	5.00	2.50	2.50	-	-
Sodium starch Fumarate	2.70	2.70	2.70	2.70	2.70	2.70
Seal coating stage						
Ethyl Cellulose	2.7	4.05	2.7	4.05	2.7	4.05
Water Insoluble Polymer (Compound A)	2.7	4.05	2.7	4.05	2.7	4.05
Water soluble polymer (compound B)	-	-	-	-	-	-
Enteric coating stage						
HPMCP 55	16.85	17.17	16.85	17.17	16.85	17.17
Myvacet	1.69	1.72	1.69	1.72	1.69	1.72
Pigment blend Yellow	2.52	2.58	2.52	2.58	2.52	2.58

Pre-compression parameters[9]

Angle of repose

Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and horizontal plane. The frictional force in a loose powder or granules can be measured by angle of repose.

$$\Theta = \tan^{-1}(h/r) \quad \ldots\ldots\ldots\ldots\ldots\ldots (1)$$

Where, Θ is the angle of repose, h is height of pile, r is radius of the base of pile.

From the cone formed on a graph sheet was taken to measure the area of pile, thereby evaluating the flowability of the granules. Height of the pile was also measured.

Bulk density

A quantity of accurately weighed powder from each formula, previously shaken to break any agglomerates formed was introduced into a 25 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 seconds interval. The taping was continued until no further change in volume was noted. L.B.D and T.B.D were calculated using following formula;

$$L.B.D = \frac{\text{Weight of the powder}}{\text{Volume of the packing}} \text{ --------- (2)}$$

$$T.B.D = \frac{\text{Weight of the powder}}{\text{Tapped volume of packing}} \text{ ---------- (3)}$$

Carr's index

The compressibility index of the granules was determined by carr's or compressibility index. Grading of the powders for their flow properties according to carr's index was given by (%) Carr's Index can be calculated by using the following formula

$$(\%) \text{ Carr's Index} = \frac{T.B.D - L.B.D}{T.B.D} \times 100 \text{ ----- (4)}$$

Hausener's ratio

Hausener's ratio can be calculated by using the following formula

$$\text{Hausener's ratio} = \frac{T.B.D}{L.B.D} \text{ ----- (5)}$$

Post-compression parameters[10]

Hardness test

The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in Kg/cm^2. Three tablets were randomly picked from each formulation and the mean and standard deviation values were calculated.

Weight variation test

The tablets were selected randomly from each formulation and weighed individually to check for weight variation. The U.S Pharmacopoeia allows a little variation in the weight of a tablet.

Friability study

Twenty (20) tablets were selected from each batch and weighed. Each group of tablets was rotated at 25 rpm for 4 minutes (100 rotations) in the Roche friabilator. The tablets were then dusted and re-weighed to determine the loss in weight. Friability was then calculated as percent weight loss from the original tablets.

$$\text{Friability} = \frac{\text{Initial weight of tablet} - \text{Final weight of tablet}}{\text{Initial weight of tablet}} \times 100 \quad \ldots\ldots (6)$$

Thickness

Thickness of the tablets was measured by screw gauge by picking tablets randomly from all the batches.

***In vitro* disintegration time**

The process of breakdown of a tablet into smaller particles is called as disintegration. *In-vitro* disintegration time of a tablet was determined using disintegration apparatus as per I.P. specifications. Place one tablet in each of the 6 tubes of the basket and run the apparatus using pH 6.8 (simulated saliva fluid) maintained at 37 ± 2°C as the immersion liquid. The assembly should be raised and lowered between 100 cycles per minute. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded.

***In vitro* dissolution tests**

Drug release profile was evaluated *in vitro* using a dissolution test apparatus (Electro Lab, TDT-08L, Mumbai, India). The USP XIII Type II (paddle type) method was selected to perform the dissolution profile of rabeprazole sodium. The dissolution for all the formulations was carried out according to US Pharmacopoeia for 2 h in 0.1N HCl and then media was changed into phosphate buffer pH 6.8. The temperature was maintained at 37±0.5°C and a constant paddle rotation speed of 100 rpm. Samples (10 ml) were withdrawn at regular intervals and filtered through membrane filter (pore size 0.22 µm). The samples were analyzed by UV Visible Spectroscopy.[11]

Similarity factor and dissimilarity factor calculation

The similarity factor (f_2) was defined by CDER, FDA, and EMEA as the "logarithmic reciprocal square root transformation of one plus the mean squared difference in percent dissolved between the test and reference release profiles". Dissimilarity or difference factor (f_1) describes the relative error between two dissolution profiles. It approximates the percent

error between the curves. The percent error is zero when the test and reference release profiles are identical and increases proportionally with dissimilarity between the two profiles. f_2 is the simplest among those methods. Moore & Flanner proposed a model independent mathematical approach to compare the dissolution profile using two factors f_1 & f_2.

$$f_1 = \{ [\sum_{t=1}^{n} | R_t - T_t |] / [\sum_{t=1}^{n} R_t] \} . 100$$

$$f_2 = 50. \text{Log} \{ [1 + (1/n) \sum_{t=1}^{n} (R_t - T_t)^2]^{-0.5} . 100\}$$

Where 'R_t' and 'T_t' are the cumulative percentage dissolved at each of the selected n time point of the reference & test product respectively. The factor f_1 is proportional to the average difference between the two profiles, where as factor f_2 is inversely proportional to the averaged squared difference between the two profiles, with emphasis on the larger difference among all the time points.[12]

Accelerated Stability Studies Rabeprazole sodium tablets 20 mg were evaluated for accelerated stability studies at 400C /75 % RH condition carried out for a period of 3 months.[13]

RESULTS AND DISCUSSION

The present study was undertaken to formulate Rabeprazole enteric coated tablets. The study involves preformulation studies of drug and excipients, formulation and processing development along with evaluation of tablets made with the optimized formulation. Finally delayed release tablets were evaluated by *in vitro* methods. Results and discussion of the above studies are presented below:

Table 3: Blend properties of different formulations.

Batch	Blend Property				
	B.D (gm/ml)	T.D (gm/ml)	C.I (%)	H.R	property
F1	0.710	0.873	19.714	1.251	Fair
F2	0.710	0.873	19.714	1.251	Fair
F3	0.483	0.681	29.03	1.409	Passable
F4	0.483	0.681	29.03	1.409	Passable
F5	0.461	0.714	35.385	1.548	Fair
F6	0.461	0.714	35.385	1.548	Fair
F7	0.500	0.600	23.22	1.295	Passable
F8	0.500	0.600	23.22	1.295	Passable
F9	0.541	0.691	21.62	1.276	Passable
F10	0.541	0.691	21.62	1.276	Passable
F11	0.501	0.605	17.19	1.207	Fair
F12	0.501	0.605	17.19	1.207	Fair

Table 4: Physical Evaluation (Core tablet).

Physical parameter	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F 8	F 9	F 10	F 11	F 12
Weight variation	1.65	1.57	1.42	1.54	1.18	1.35	1.44	1.23	1.48	1.54	1.63	1.38
Hardness	7.8	7.4	7.2	7.4	7.1	6.8	7.4	7.8	7.5	7.8	8.0	7.6
Thickness	3.97	3.99	3.97	3.99	3.97	3.95	3.99	3.94	4.00	3.98	3.92	3.94
Friability	0.45	0.52	0.21	0.18	0.38	0.57	0.46	0.48	0.55	0.49	0.42	0.48
Disintegration time	2.44	2.50	1.50	1.44	3. 10	3. 18	2. 50	2. 44	2. 15	2. 22	2	2. 10

Table 5: Physical Evaluation (After Sub Coating and Enteric Coating).

		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Seal coated Tablet	Hardness (Kg/cm^2)	8.2	8.0	8.2	8.4	8.3	8.1	8.5	8.8	8.6	9.0	9.2	8.8
	Thickness (mm)	4.01	4.03	4.00	4.04	4.01	4.00	4.06	4.00	4.02	4.04	3.99	4.00
Enteric coated Tablet	Hardness (Kg/cm^2)	8.6	8.4	8.6	8.8	8.7	8.5	9.0	9.4	9.2	9.6	9.6	9.4
	Thickness (mm)	4.05	4.07	4.04	4.08	4.05	4.04	4.10	4.04	4.06	4.08	4.04	4.05

Table 6: Stability Data for F12.

Batch number and stability condition	Description	Assay (%)	Acid release in 0.1N HCl (%)	Dissolution study in pH 6.8 PBS
Room temperature (Initial)	Light yellow colored enteric coated tablets.	99.72	1.28	97.38
40°C / 75% RH (1 month)	Light yellow colored enteric coated tablets.	99.43	1.54	93.23
40°C / 75% RH (2 months)	Light yellow colored enteric coated tablets.	99.30	2.26	92.14
25°C/60% RH (1 month)	Light yellow colored enteric coated tablets.	99.47	1.32	95.98
25°C/60% RH (2 months)	Light yellow colored enteric coated tablets.	99.35	2.00	94.92

Assay

Assay is an indicative of the amount of the drug present in the dosage form. Here it gives the insight information about the substances of the process and about effect of changes. In Formulation11 the assay of the tablets was found to be 99.30% initially, after 1 month it was decreased to 98.29% and 99.05%, later it was found to be 97.30% and 98.69% after 2 months at 40^0C/75% RH and 25^0C/75% RH respectively. In Formulation 12 the assay of the tablets was found to be 99.72% initially, after 1 month it was decreased to 99.43% and 99.47%, later

it was found to be 99.30% and 99.35% after 2 months at 40^0C/75% RH and 25^0C/75% RH respectively.

Acid release

This indicates that the dosage form is resistance to acid media after 2 hours. In Formulation11 the acid release of the drug from tablets was found to be 1.90% initially, after 1 month it raises to 2.09% and 2.04%, later it was found to be 2.20 and 2.12% after 2 months at 40^0C/75% RH and 25^0C/75% RH respectively. This indicates that there is little change in the acid resistance of Rabeprazole delayed release tablets for batch 11. In Formulation 12 the acid release of the drug from tablets was found to be 1.28% initially, after 1 month it raises to 1.54% and 1.32%, later it was found to be 2.26% and 2.00% after 2 months at 40^0C/75% RH and 25^0C/75% RH respectively. This indicates that there is little change in the acid resistance of Rabeprazole delayed release tablets for batch 12.

DISSOLUTION STUDIES

The dissolution was carried out for different experimental trials and also for the innovator. The various results that are obtained are tabulated below. Dissolution studies are carried out in the following media.

Table 7: Data of dissolution Profile of Formulation F1-F12.

Formulations	*Percentage drug release*				
	Up to 2 hrs	2 hr 10 min	2 hr 20 min	2 hr 30 min	2 hr 45 min
F1	0	1	96	97	83
F2	0	0	57	98	85
F3	0	14	99	98	89
F4	0	0	64	96	87
F5	0	1	64	83	98
F6	0	0	55	87	97
F7	0	0	58	94	91
F8	0	0	3	91	89
F9	0	37	89	97	96
F10	0	1	84	97	94
F11	0	57	84	84	96
F12	0	27	93	97	90
Innovator	0	29	94	97	92.3

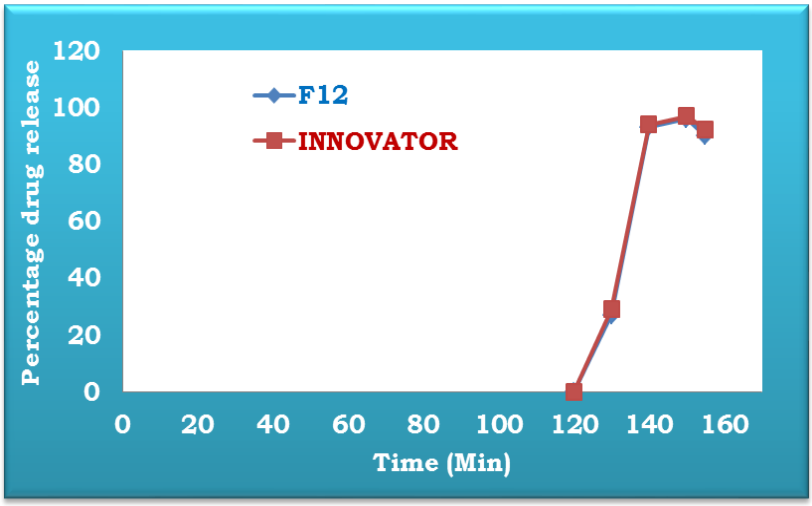

Figure: 1 *In vitro* drug release of optimized formulation (F12) and Innovator.

Similarity factor and dissimilarity factor calculation[36]

The similarity factor f_2 and its significance is shown in the following table.

Table 8: Similarity factor f_2 and its significance.

Similarity factor (f2)	Significance
<50	Test and reference profiles are dissimilar.
50 -100	Test and reference profiles are similar.
100	Test and reference profiles are identical.
>100	The equation yields a negative value.

Table 9: f_2 value calculation.

Dissolution profile comparison					
Time (mins)	**Innovator (R)**	**F12 (T)**	**(R-T)**	**$(R-T)^2$**	**f_2 value**
0	0	0	0	0	**89**
10	29	27	2	4	
20	94	93	1	1	
30	97	97	0	0	
45	92.3	90	2.3	5.29	
Total	**220**	**217**	**3**	**10.29**	

Since the f_2 value of formulation 12 is 89, which is very close to 100, the formulation is said to be more similar to that of the reference product of Rabeprazole Sodium (Pariet).

DISCUSSION

The objective of the study is to formulate and evaluate Rabeprazole sodium Delayed Release tablets compared to the innovator product. Twelve formulations of enteric coated tablets of Rabeprazole were developed by preparing core tablets using mannitol as diluent and crospovidone as super disintegrant and Stabilizer in different proportions and varying the

compositions of sub coating and enteric coating using Pigment yellow, Myvacet and HPMC Phthalate. The core tablets were prepared by Direct compression method. The results indicated that the finished product formulation F12 fulfilled all the specifications of the physical properties and *in vitro* release and is comparable to the innovator product. Formulation F1 to F11 was failed due to various reasons like less acid resistance compared innovator or increased impurities profiles during the course of stability or less *in vitro* drug release compared to innovator. Even though all the formulations are releasing the drug but those are not comparable to innovator product. Formulation F12 fulfilled all the specifications prescribed for Rabeprazole delayed release tablets and comparable to the innovator product.

CONCLUSION

The Rabeprazole sodium is a proton pump-inhibitor which is used in the treatment of peptic ulcer. In this study Rabeprazole enteric coated tablets were prepared by using HPMC Phthalate 55 as enteric coating polymer. Twelve formulations of enteric coated tablets of Rabeprazole were developed by preparing core tablets using mannitol as diluent and Cros povidone as super disintegrant and Stabilizer as in different proportions and varying the compositions of sub coating and enteric coating using Pigment yellow, Myvacet and HPMC Phthalate 55 .The core tablets were prepared by direct compression method. F12 was found to be best of all the formulations showing drug release matching the innovator product so to that formulation all the quality control tests were done for conformation. Stability study is carried out for 3 months at 25°C; 60% RH: and 40°C; 75% RH, according to ICH guidelines. The tablets were tested for acid release during the stability period and confirmed that results were found within the limits. The identified formula shall be utilized for the formulation development and other studies for successful launching of the product.

REFERENCES

1. Jain NK., Advances in controlled and Novel Drug Delivery, 2000; 268-269. CBS publications, New Delhi.
2. Rama. B, Shalem Raju Talluri, Grace Rathnam, Formulation Development and Evaluation of Enteric Coated Tablets of Rabeprazole Sodium, Journal of Pharmacy and Biological Sciences, 2014; 9(5): 14-20.

3. Rakesh T, Prashant P, Rabiprazole sodium delayed release multi particulates: Effect of enteric coating layer on product performance. Journal of Advance Pharmaceutical Technology & Research, 2011; 2(3): 184-191.
4. Gobinath T, Kamalakkannan V, Sambath kumar R, Formulation and evaluation of enteric coated tablets of Pantoprazole, Journal of Chemical and Pharmaceutical Sciences, 2014; 7(3): 176-184.
5. Brunton LL, Lazo JS, Parker KL, eds. Goodman and Gilman's The Pharmacological Basis of Therapeutics, New York, Mc Graw Hill, 2006.
6. Matsyagiri. L, Jagadeesh. P, Mounika. B, Srinivas. V, Theja. V, Madhiha Jabeen and Dr. K. Hemamalini, effect of solvents on Spectrophotometric Estimation of Tinidazole in bulk and dosage forms, World Journal of Pharmaceutical Research, 2018; 7(9): 1742-1754.
7. Aulton ME, Well Tl. Pharmaceutics: The science of dosage form design. London, England, Churchill livington, 1998; 247.
8. Liberman H, Lachman L, The Theory and Practice of Industrial Pharmacy. 3rd Ed., Bombay: Verghese Publication House, 1991; 171-193.
9. Martin A. Micromeritics In: Martin A. Physical pharmacy, Batimores. MD: Lippincott Williams and Wilkins, 2001; 423-454.
10. Matsyagiri. L, Gowri Shankar. N. L, Santoshi. T, Bhuvanesh. S, Sumathi. CH, Hemalatha. T, Mustafa Rahaman. MD, Effect of dissolution medium on mouth dissolving tablets of aceclofenac, International Journal of Pharmaceutical Sciences and letters, 2012; 2(3): 82-91.
11. USP XXIV, 17th Ed., Rockville, 1947, MD, 2000.
12. Costa P. An alternative method to the evaluation of similarity factor in dissolution testing. International Journal of Pharmaceutics, 2000; 5: 77-83.
13. International conference on harmonization (ICH) harmonized tripartite guideline for stability testing of new drugs substances and products Q1A (R2), Mar 2004; aug-2003. Q1A (R2).