INTERNATIONAL JOURNAL OF ADVANCES IN PHARMACY, BIOLOGY AND CHEMISTRY
Research Article

Formulation and Evaluation of Rabeprazole Sodium Enteric Coated Pellets

KL. Senthilkumar*, M. Muthukumaran and B. Chenchuratnam

Padmavathi College of Pharmacy & Research Institute, Dharmapuri, Tamilnadu, India.

ABSTRACT

The aim of the present investigation was to prepare delayed release i.e., enteric coated pellets of Rabeprazole sodium by using hydroxyproply methyl cellulose based sub coating and methacrylic acid copolymer based enteric coating. The different batches of pellets were prepared by drug suspension layering method. Comparatrive study of dissolution profile of final batch with market preparations was conducted and it was concluded that final batch shown good similarity with market products. The results of the accelerated stability of final formulation revealed that storage conditions were excellent.

Keywords: Rabeprazole sodium, sub coating, enteric coating.

INTRODUCTION

Proton Pump Inhibitors (PPIs) are used in the treatment of acid – related gastro – duodenal disorders by reducing gastric acid secretion. Proton pump inhibitors are substituted benzimidazoles and all share a similar core structure and mode of action, but differ in substituent groups. The type of substituents affects the chemical properties of the compounds that directly influence their rates of reactions and therefore their stability in different media. The stability of PPIs in aqueous media is a function of P^H with an increased rate of degradation as the P^H decreases. Degradation of the Rabeprazole leads to a yellow or purple discoloration of the pellets, film layer or dissolution medium. Stability of Rabeprazole sodium also decreases under moisture conditions. Exposure of Rabeprazole sodium to the acidic content of the stomach would lead to significant degradation of the drug and hence, reduced bioavailability.[2]

Delayed release dosage form is best formulations which are used for drugs that are destroyed in the gastric fluids, or cause gastric irritation or are absorbed preferentially in the intestine. Such preparations contain an alkaline core material comprising the active substance, a separating layer and enteric coating layer.[3,4]

The first aim of present work was to prepare Delayed release i.e., enteric coated pellets of Rabeprazole sodium by using Methacrylic acid copolymer in Fluid bed processor to prevent degradation in the stomach due to the acidic environment or gastric enzymes and compare with the market sample

MATERIALS

Rabeprazole Sodium (I.H.S) Mannitol (Pearlitol SD200), Sodium Carbonate (I.P), Polyplasdone XL, XL-10 (ISP), Talc (I.P), Opadry clears (Colorcon), Eudragit L30D-55, Triethyl citrate

EXPERIMENTAL

Preformulation studies

Preformulation studies were carried out for appropriate selection of excipients in view of Rabeprazole Sodium modified release pellets.

Micromeritic properties of Rabeprazole Sodium

1. Angle of repose

The angle of repose of Rabeprazoe powder were determined by the funnel method. The accurately weight powder blend were taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. The

diameter of the powder cone was measured and angle of repose was calculated using the following equation.

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

Where h and r are the height and radius of the powder cone.

2. Bulk Density and tapped Density

Both Bulk density (BD) and tapped density (TD) was determined. A quantity of 2 gm of Rabeprazole sodium powder from each formula, previously shaken to break any agglomerates formed, was introduced in to 10 ml measuring cylinder. After that the initial volume was noted and the cylinder was allowed to fall under its own weight on to a hard surface from the height of 2.5cm at second intervals. Tapping was continued until no further change in volume was noted. Bulk density and Tapped density were calculated using the following equations.

Bulk density = weight of the powder blend/untapped volume of the packing

Tapped density = weight of the blend/Tapped volume of the packing

3. Compressibility Index

The compressibility Index of the powder blend was determined by Carr's compressibility index. The formula for Carr's Index is as below;

$$\text{Carr's Index (\%)} = \{(TD - BD) \times 100\} / TD$$

4. Hausner's ratio

Hausner's ratio is a number that is correlated to the flowability of a powder or granular material. The ratio of tapped density to bulk density of the powders is called the Hausner's ratio. It is calculated by the following equation.

$$\text{Hausner's ratio (H)} = TD / BD$$

Where TD = tapped density, BD = bulk density.

Drug excipients compatibility study

Drug excipients compatibility studies were carried out by mixing the drug with various excipients in different proportions. Studies were carried out in flint vials at Accelerated conditions, 40±2°C /75%RH±5% RH. The studies were conducted for 4 weeks and compared with control at 2 - 8 °C. Physical observations of the blend were recorded at regular interval of one week.

Table 1: Compatibility study of Rabeprazole sodium with excipients

Diluents	Drug-Excipients Ratio	40±2°C /75%RH±5% RH
Rabeprazole Sodium (API)	----	4 weeks
A.P.I + Mannitol	1:10	4 weeks
A.P.I + Sodium carbonate	1:10	4 weeks
A.P.I + Opadry clear	1:1	4 weeks
A.P.I +L-HPC-LH 21	1:1	4 weeks
A.P.I + Talc	1:0.5	4 weeks
A.P.I + Crospovidone	1:1	4 weeks
A.P.I + Hydroxy Propyl Cellulose	1:1	4 weeks
A.P.I + Eudragit L100-55	1:1	4 weeks

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 spectras 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.

Formulation development of core pellets of Rabeprazole sodium

The drug suspension was prepared by mixing Rabeprazole sodium, sodium carbonate, crosspovidone and Hydroxypropylmethyl cellulose in purified water. The suspension was then placed into the spray gun system of Glatt fluid bed processor machine and sprayed onto the sugar core pellets while the Glatt machine was set in running condition. This would allow the drug to be evenly coated onto the core pellets to form drug – coated spherical pellets. The drug – coated pellets were dried under warm air within the Glatt machine.

Table 2: Formulation of different batches of Rabeprazole sodium core pellets

Ingredients	Formulations (quantities in gms)					
	F1	F2	F3	F4	F5	F6
Rabeprazole sodium	285	285	285	285	285	285
Sodium carbonate	150	225	150	225	0	0
Hydroxy propyl methyl cellulose	80	80	80	80	80	80
Polyplasdone INF 10	225	150	-	-	375	--
Polyplasdone XL 10	---	---	225	150		375
Sugar spheres	660	660	660	660	660	660
Talc	100	100	100	100	100	100

Table 3: composition of Subcoating solution

Material	Quantity (%)
Color coat FC4S	10
Iso Propyl Alcohol	40
Methylene Dichloride	60

Preparation of Coating solution of Color coat FC4S

To prevent interaction between Rabeprazole sodium and Colorcoat EC4S, seal coating of core pellets of Rabeprazole sodium was done by Colorcoat FC4S until weight gain 8-10%. Coating solution was prepared by dissolving Colorcoat FC4S in mixture of Iso Propyl Alcohol (IPA) and Mehtylene Dichloride (MDC) under constant stirring for 15-20 minutes by using propeller stirrer.

Table 4: Composition of enteric coating solution

Material	Quantity (%)
Eudragit L100-55	30
Iso Propyl Alcohol	72.0
Methylene Dichloride	28.0

Preparation of Coating solution of enteric coating solution

Required quantities of solvents were weight in the beaker or other suitable vessel. Propeller stirrer was used for preparation of coating solution. Propeller was kept in the center and as close to the bottom of the vessel as possible, stir the mixture of solvents to form a vortex without entrapment of air in to the liquid. After that required quantity of Eudragit L100-55 (for 30% weight gain) was added in the water and kept continuous stirring for 15-20 minutes.

Coating of core pellets

A protective coating solution was prepared by mixing Opadry clear slowly in the solvent mixture of IPA and MDC (60:40). This coating was then placed into the spray gun of the Glatt machine and sprayed onto the drug – coated pellets while the Glatt machine was set in running condition. After the coating was completed, the protective coating-covered pellets were again dried under warm air within the Glatt machine.

Finally, an enteric coating agent was prepared by mixing Eudragit L100-55 in a mixture of Isopropyl alcohol and Methylen dichloride. This coating agent was placed into the spray gun of the Glatt machine and sprayed onto the protective coating-covered pellets to form the pharmaceutical pellets before final drying of the granules to complete the process of making the enteric coating-covered pellets.

Coating of pellets was done using Glatt fluid bed processor machine. First fixed quantity (1Kg) pellets were put in the product chamber which was readjusted at 50^{o}C temperature for 5 – 10 minutes. Various parameters like spraying rate (8 to 25 gm/min), inlet air temperature (20 to 50^{o}C), atomizing air pressure (1 to 3 bars), % fluidization (10 to 30%) and percent solids content (7%) were adjusted and optimized. After finishing of the coating pellets were dried at 40^{o} C and at 10% fluidization. The coated pellets were removed and evaluated by various parameters.

Evaluation of Parameters

Description: Examine visually and record the observation

Identification: The Retention time of the major peak in the chromatogram of the sample preparation corresponds to that of the standard preparation as obtained in the Assay

Moisture content: Take about 35ml of Methanol in titration flask of Karl Fischer titrator and titrate with Karl Fischer reagent to end point. Grind the pellets to fine powder in a dry mortar, weigh accurately about 0.5mg of the sample, transfer quickly to the titration flask, dissolve by stirring and titrate with Karl Fischer reagent to end point.

Bulk density: Weigh and transfer around 30 g of the sample into a 100 ml measuring cylinder, tap the measuring cylinder 10 to 15 times and record the volume occupied by the sample. Calculate the bulk density by using the formula.

$$\text{Bulk density} = \frac{\text{Weight of the sample (g)}}{\text{Volume occupied by sample (ml)}}$$

Gastric Resistance

Chromatographic conditions

Buffer: Dissolve 2.72 g of Potassium dihydrogen ortho phosphate and 0.525 g of Dipotassium hydrogen ortho phosphate in 1000 ml of water

Mobile phase: Prepare a mixture of Buffer and Acetonitrile in the ratio of 60:40, and adjust pH to 7.4 with Potassium hydroxide solution, filter and degas.

Preparation of 0.1 M NaOH: Dissolve 4 g of NaOH in 1000 ml of water.

Standard Preparation: Weigh about 80.0 mg Rabeprazole sodium working standard in to a 100 ml volumetric flask dissolve and dilute to volume with 0.1 M NaOH and mix. Transfer 2.0 ml of this solution in to a 50 ml volumetric flask and dilute to volume with mobile phase and mix.

Sample Preparation: Weigh and transfer the pellets equivalent to 20 mg of Rabeprazole sodium individually in each of the 6 dissolution jars, containing 900 ml of 0.1 M Hydrochloric acid which has been equilibrated to the temperature of 37±0.5^{0}C. Immediately start the apparatus and run for 2 hours. After 2 hours lift the paddles. Drain the medium completely with out losing any pellet. Carefully transfer the pellets in to a 50 ml volumetric flask individually with the aid of a funnel. Add about 25 ml of 0.1 M Sodium hydroxide and sonicate for 15 minutes and shake for 15 minutes. Dilute to volume with 0.1 M Sodium hydroxide and mix. Centrifuge a portion of the preparation at about 3000 RPM for 15 minutes. Transfer 2.0 ml of the clear supernatant liquid in to a 25 ml volumetric flask and dilute to volume with mobile phase and mix.

Procedure: Separately inject the Standard Preparation and the Sample Preparation into the liquid chromatograph and record the area due to major peaks.

Dissolution in buffer

Dissolution Parameters

Medium : Initially run in 900ml of 0.1 N HCl for 2 hr and pH 8.0 Sodium Phosphate Buffer, 0.5% SLS, 900ml for 30 min

Volume : 1000ml

Apparatus : USP-II (paddle)

Speed : 100 rpm

Temp : 37±0.5^{0}C

Sampling points : 2hr in acid and 10, 20 and 30mins in buffer

Standard Preparation: Weigh accurately 80.0 mg of Rabeprazole Sodium working standard into a 100 ml volumetric flask, dissolve in 10 ml of 0.1 M NaOH and dilute to volume with 0.1M NaOH. Pipette out 2.0 ml above stock solution into a 100 ml of volumetric flask, which contains 20 ml of 0.2 M sodium hydroxide mix immediately, and dilute to 100 ml with dissolution medium.

Sample preparation: Transfer 900 ml of 0.1 N Hcl into each of six dissolution jars the temperature of which has been equilibrated to 37±0.5^{0}C. Transfer the weighed pellets equivalent to 20 mg of Rabeprazole Sodium in to each of six jars. Start the apparatus and run for 2 hrs at 100 rpm. After 2 hrs lift the paddles completely and drain out the acid carefully without loss of pellets. Then add 900 ml of pH 8.0 Phosphate buffer the temperature of which has been equilibrated to 37±0.5^{0}C and run the apparatus. After specified interval withdraw sample about 10 ml from a zone midway between the surface of the medium and top of the rotating blade and not less than 1 cm from the vessel wall and filter through 0.45 micron membrane filter. Immediately transfer 5 ml of filtrate into a 10 ml of volumetric flask already containing 2 ml of 0.2 M sodium hydroxide solution. Mix well immediately and dilute to volume with dissolution media

Procedure: Inject separately Standard and test samples into Liquid chromatograph port and record the areas due to main peaks.

Assay:

Standard Preparation: Weigh accurately about 80.0 mg of Rabeprazole sodium working standard in to a 100 ml volumetric flask. Dissolve and dilute to volume with 0.1 N NaOH and mix. Transfer 2.0 ml of this solution in to a 50 ml volumetric flask and dilute to volume with mobile phase and mix.

Sample Preparation: Grind about 10g of pellets to fine powder in a dry mortar and weigh accurately the quantity of powder equivalent to 20 mg of Rabeprazole sodium in to a 50 ml volumetric flask. Add 25 ml of 0.1N NaOH and dissolve the content by sonicating for 15 min followed by shaking for 10 min, dilute to volume with 0.1N NaOH and mix. Centrifuge a portion of the sample at 3000 RPM for 10 min. Transfer 2 ml of the clear supernatant in to a 25 ml volumetric flask and dilute to volume with mobile phase and mix.

RESULTS AND DISCUSSION

Preformulation studies

From the results of Micromeritic studies of the Rabeprazole sodium it was concluded that Rabeprazole sodium has poor flow property and compressibility property. From the physical observation, no significant Drug-Excipient interaction was notified. So it was concluded that drug and other excipients were compatible with each other.

Table 5: Micromeritic properties of API

Sample	Angle of repose (o)	Bulk density (g/ml)	Tapped density (g/ml)	Compressibility Index (%)	Hausner's ratio
API	34	0.352	0.512	31.25	1.45

Table 6: Drug Excipient compatibility study (Physical observation)

Batch no.	Drug-Excipients combination	D:E Ratio	Initial observation	Final description 1M/ (40^0C / 75%RH 7 days)
1	RS	-	Off White	Off White
2	R S+Mannitol	1:10	White	White
3	RS+ Sodium carbonate	1:10	White	White
4	R S+Titanium dioxide	1:0.25	White	White
5	RS+ Opadry clear	1:1	White	Off white
6	RS+ Talc	1:0.25	Fine white	Fine white
7	R S+ Crospovidone	1:1	White	White
8	R S+Hydroxy Propyl Cellulose	1:1	White	White

Evaluation parameters of the optimized batch of Rabeprazole sodium

From the results of comparative study of dissolution profile of final batch with market preparations. It was concluded that final formulation was shown good similarity with market product.

Accelerated stability study of the optimized batch

From the results of the accelerated stability of the final formulation for 3 months, it was concluded that storage conditions were not found any significant changes in final formulation dissolution profile with market sample.

EVALUATION OF MARKET SAMPLE

ASSAY

The assay of the Market sample was found to be 98.68%.

ACID RESISTANCE

Amount of the drug resisted after 2 hr in acid was 99.75%.

DISSOLUTION

Table 7: Dissolution comparison of F2 sample (capsule) with Market sample in pH 8.0 buffer

S. No.	Time (min)	F2	Market sample
1	10	23.80	20.6
2	20	62.82	58.90
3	30	86.24	84.36

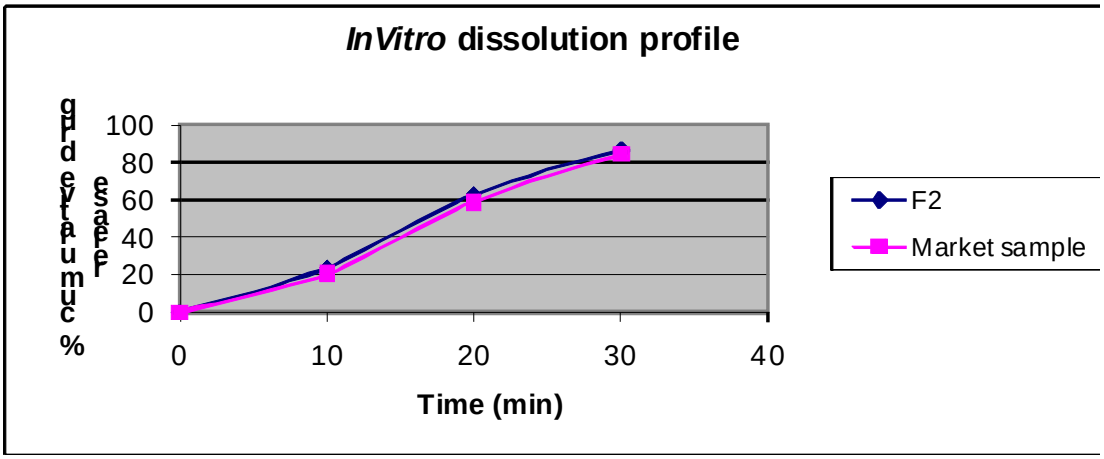


Table 8: Acid resistance test

S. No.	% S.C+ % E.C	Dissolution time(2 hrs)	Remarks
1.	8+22	Fail	Color changed
2.	8+24	Fail	Color changed
3.	8+26	Fail	Color changed
4.	8+28	Pass	Pellets remain same color

DISCUSSION

In coating process the enteric coating was done with the percentage build ups of 22, 24, 26, and 28 with 8% sub coating. Acid resistance test failed up to 26% but at 28% build up acid resistance test passed. But for safer side, we coated up to 30% with 8% sub coating. For optimizing coating process further trails were conducted with increasing sub coat and decreasing enteric coating.

EVALUATION OF RABEPRAZOLE SODIUM COATED PELLETS (CAPSULE)

The following results were compared with Market product.

Table 9: Comparison of Assay, Drug release and Acid resistance of coated Pellets (capsule) with market sample

S. No.	Test %	Market sample	F1	F2	F3	F4
1	**Assay**	11.58	11.64	11.72	11.70	11.72
2	**Drug dissolution**	84.36	76.09	86.24	65.82	69.82
3	**Acid resistance**	98.68	99.08	99.75	93.7	98.2

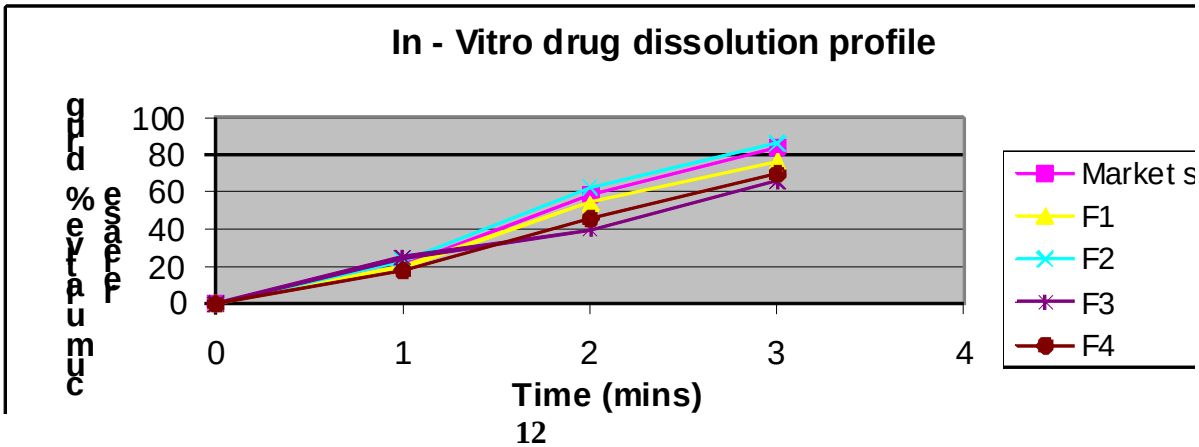
Assay - % labeled amount of Rabeprazole sodium
Dissolution - % labeled amount of Rabeprazole sodium released in Buffer
Acid resistance test - % labeled amount of Rabeprazole sodium retained in acid

Dissolution

Table 10: Comparison of Dissolution profiles of Market sample and coated tablets in p^H8.0 buffer

S. No.	Time (mins)	Market sample	F1	F2	F3	F4
1	10	20.6	20	23.8	25	18
2	20	58.9	54.0	62.82	40.2	45.6
3	30	84.36	76.09	86.24	65.82	69.82

Dissolution profile



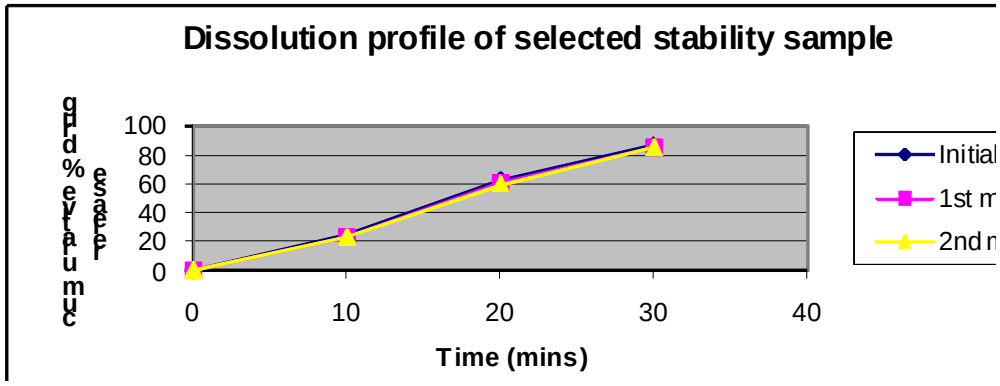
From the above results, we found that F1, F2 , F3 and F4 batches passed in assay and acid resistance tests.
In sub coating process, the pellets were coated to 8% and enteric build up was given upto 30 percentages. Even though acid resistance test passed at 28 % enteric build up for safer side we coated up to 30% of enteric buildup.
Based on results, F2 formulation was found to be satisfactory as it matched with the market sample dissolution profile. So finally F2 was found to be best formula for formulation of Rabeprazole sodium delayed release pellets.

STABILITY DATA OF SELECTED FORMULATION (F2)

Stability studies were conducted at 40ºC / 75% RH for about 3 months in stability chamber (thermo lab). Samples were collected at 1, 2 and 3 months.

Table 11: Stability data

Time	Test (%)	Temperature 40°C / 75% RH
Initial	Assay	11.72
	Acid resistance	99.75
	%DR	86.24
1 month	Assay	11.6
	Acid resistance	99.10
	%DR	85.80
2 months	Assay	11.5
	Acid resistance	98.6
	%DR	85.0



Selected formulation F2 was kept for stability studies and observed that assay, acid resistance and drug release at the end of 1, 2 and 3 months. There was no significant change in i*n-vitro* release profile. It shows that formulation F2 was stable.

SUMMARY AND CONCLUSION

The aim of the present study was to formulate and evaluate delayed release pellets of Rabeprazole sodium by enteric coating. It is an acid labile drug so it is degraded at acidic pH of stomach so an attempt was made to stabilize the drug with super disintegrant with different particle size and alkaline agent Sodium carbonate. Finally enteric coating was given to bypass the stomach. The enteric coating was carried out by using enteric polymer Methacrylic acid copolymer Eudragit L 30D-55. The study includes preformulation of drug and excipients, formulation, evaluation and stability studies of delayed release pellets. The core pellets were prepared using suspension layering technique in fluid bed process. Sub coating was given to core pellets to avoid direct contact of drug with enteric coating materials. Sub coating was given with Opadry clear which contains HPMC, diethyl phthalate which was dispersed in isopropyl alcohol & methylene-di-chloride acting as a solvents system. An average weight build up of 8%w/w was given to core pellets.

Enteric coating was given to sub coated pellets using Eudragit L 30D-55 at an average weight build up of 30% w/w of sub coated tablets and the drug release profile, acid resistance and assay compared with market product (Razo).

13

Stability studies were conducted at 40ºC / 75% RH (accelerated stability testing) for 3 months. Assay, acid resistance, drug release profiles were compared between market sample and selected formulation (F2). Based on the above data it was concluded that drug release from F2 formulation was similar to that of market product.

REFERENCES

1. Thomas N. Tozer and Malcolm Rowland. Introduction to Pharmacokinetics and Pharmacodynamics, 3 rd ed:106.
2. Ijeoma F. Uchegbu and Andreas. G. Schatzlein. Polymers in Drug Delivery: 235.
3. Thomas WYL and Robinson J. The Science and Practice of Pharmacy, 20th ed, Lippinkette, William and Willins: 903-911.
4. Howard C. Ansel, Loyd V. Allen and Nicholas G. Popovich. Ansel's Pharmaceutical Dosage forms and Drug Delivery Systems, 6th ed: 268.
5. Peck GE, Baley GJ, McCurdy VE and Banker G.S. Tablet Formulation Design. In: Schwartz BJ. (ed.) Pharmaceutical Dosage Forms: Tablets. Marcel Decker, New York: 1989. 75-130.
6. Ansel CH and Poppovich NG. (Eds). Pharmaceutical Dosage Forms and Drug Delivery Systems, 6th ed. New Delhi: B.I. Waverly Pvt. Ltd, 1995. 213.
7. Ojantakanen S. Effect of viscosity grade of polymer additive and compression force on release of ibuprofen from hard gelatin capsules. European journal of Pharmaceutical Sciences. 1993;1(2):109-14
8. Folonier N and Doellker E. Biopharmaceutical comparasion of oral multiple unit and single unit sustained release dosage forms. STP Pharma Sciences. 1992;2:141-5.
9. Release Vial-Bernasconi AC, Doelker E and Buri P. Prolonged capsules divided and monolithic forms. STP Pharma Sciences. 1988;4:397-409.
10. Leon Lachman, Herbert A. Lieberman and Joseph L. Kanig. The Theory and Practice of Industrial Pharmacy, 3rded Bombay: Varghese. 331-332, 364-368.
11. Olsen K. Fluid bed equipment. In: Ghebre-Sellassie I. Pharmaceutical Pelletization Technology. New York: Marcel and Dekker. 39-69.