International Journal of Pharmacy and Pharmaceutical Sciences
ISSN- 0975-1491 Vol 2, Issue 3, 2010

Research Article

FORMULATION, PROCESS PARAMETERS OPTIMIZATION AND EVALUATION OF DELAYED RELEASE TABLETS OF RABEPRAZOLE SODIUM

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Received: 21 Feb 2010, Revised and Accepted: 20 March 2010

ABSTRACT

The aim of the present investigation was to prepare delayed release i.e., enteric coated tablets of Rabeprazole sodium by using Methacrylic acid copolymer (Colorcoat EC4S) and to optimize coating process parameters which implicate more significant effects on tablet coating process. The different batches of uncoated tablets were prepared by both wet granulation and direct compression method. Batch B_6 of uncoated tablets prepared by direct compression method shown good results of evaluation parameters compared to other batches. Results of the preliminary trials indicated that process parameters individually affected the quality of coated tablets. At this point of time it was seen that spray rate, inlet air temperature and rotating speed of pan had a major effect on tablet coating process, and hence to study the combined effect of this factors on the coating process, 3^3 full factorial design was applied. Comparative study of dissolution profile of final batch with market preparations was conducted and it was concluded that final formulation F shown good similarity with market products. The results of the accelerated stability of final formulation F for 3 months revealed that storage conditions were not found any significant changes in final formulation F. The photoinstability of the rabeprazole sodium showed by the photostabilty studies indicated that special care to avoid exposure of the drug to the light effects must be taken during the manufacture and storage of the pharmaceutical preparations.

Key words: Rabeprazole sodium, Full factorial design, Enteric coating.

INTRODUCTION

Rabeprazole sodium is a substituted benzimidazole. Benzimidazoles are anti-ulcerous compounds known for decreasing gastric acid secretion. These compounds, also known as Proton Pump Inhibitors (PPI) are commonly indicated for the treatment of Gastric ulcer, Peptic ulcer, Duodenal Ulcers, Erosive or Ulcerative GERD (Gastro Esophageal reflux Disease), Symptomatic GERD, Pathological Hypersecretory conditions(Zollinger - Ellison)[1]. Rabeprazole sodium is very soluble in water and in alkaline media. The stability of Rabeprazole sodium is a function of pH; it is rapidly degraded in acid media, and is more stable under alkaline conditions. The degradation is catalyzed by acidic reacting compounds and PPIs are usually stabilized in mixtures with alkaline reacting compounds. Therefore 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 tablets of Rabeprazole sodium by using Methacrylic acid copolymer (Colorcoat EC4S) in side vented perforated coating pan to prevent degradation in the stomach due to the acidic environment or gastric enzymes and to study the factors affecting the film coating of tablets performed in a perforated pan coater. The second aim of present work was optimization of coating process parameters which implicate more significant effects on tablet coating process.

MATERIALS

Rabeprazole Sodium was generous gift sample from Zydus Cadila Ltd. Colorcoat EC4S

Colorcoat FC4S, Mannitol SD-200, Microcrystalline cellulose pH 102, Kollidon CL (Cross povidone), Low substituted HPC were of Corel Pharma Chem., Ahmedabad, India. All other ingredients used were of analytical grade.

EXPERIMENTAL

Preformulation studies[5,6,7]

Preformulation studies were carried out for appropriate selection of excipients in view of Rabeprazole sodium delayed release tablet.

Micromeritic properties of API

1. Angle of repose

The angle of repose of API powder was 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 (BD) was determined. A quantity of 2 gm of API 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 2.5 cm at second intervals. Tapping was continued until no further change in volume was noted. LBD and TDB were calculated using the following equations.

BD= Weight of the powder blend/Untapped Volume of the packing

BD=Weight of the powder 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

The 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 Hasner's ratio. It is calculated by the following equation.

$$H = {}^{\rho}T / {}^{\rho}B$$

Where ${}^{\rho}T$ = tapped density, ${}^{\rho}B$ = bulk density

Drug excipients compatibility study [8,9]

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, 40ºC ± 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. Also DSC studies were carried out to determine the compatibility of excipients with the drug.

Table 1: Compatibility study of Rabeprazole sodium with excipients

Diluents	Drug-Excipients Ratio	40ºC ± 2°C / 75%RH ± 5 % RH
Rabeprazole Sodium	1:1	4 Weeks
Drug +Magnesium oxide	1:5	4 Weeks
Drug + Calcium carbonate	1:4	4 Weeks
Drug + Mannitol	1:2	4 Weeks
Drug + MCC pH 102	1:1	4 Weeks
Drug + Cross povidone	1:0.5	4 Weeks
Drug + Mg-stearate	1:0.25	4 Weeks
Drug + Talc	1:0.25	4 Weeks
Drug + Colorcoat FC4S	1:2	4 Weeks
Drug + All excipients	1:1	4 Weeks

Estimation of Rabeprazole sodium

Two different solution of Rabeprazole sodium were prepared in 0.1 N HCL and 6.8 pH phosphate buffer respectively. The UV spectrums were taken using Shimadzu UV-1700 UV/Vis 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.[10, 11, 12, 13]

Formulation development of core tablet of Rabeprazole sodium [14,15,16]

Rabeprazole sodium tablets were prepared by both wet granulation and direct compression method. Batches B_1 to B_3 were prepared by wet granulation method and Batches B_4 to B_9 were prepared by direct compression method. In both methods all ingredients were passed through 60 mesh sieve.

In wet granulation method, drug and diluents were mixed well and binder part was prepared by mixing Low substituted HPC with Iso Propyl Alcohol and then binded with above mixer.

In Direct compression method, drug and stabilizing agents like Sodium Hydroxide, Calcium carbonate and Magnesium oxide were mixed properly in first part. Other diluents, disintegrant, lubricant and glidant were mixed well in second part. Then first part was added in the second part and mixed well for 15 to 20 minutes. In Direct compression technique, microcrystalline cellulose and Mannitol were used as directly compressible material to improve the flow property of powder blends.

All blends were compressed into tablets using 12 mm diameter punch on Multipunch rotary tablet machine. The prepared tablets were stored in tightly closed glass container and evaluated for various parameters.

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

Ingredients	Wet granulation			Direct compression					
	B_1	B_2	B_3	B_4	B_5	B_6	B_7	B_8	B_9
Rabeprazole Na	20.0	20.0	20.0	20.0	20.0	20.0	20.0	20.0	20.0
Sodium hydroxide	2.0	2.0	2.0	-	-	-	-	-	-
Magnesium oxide	-	30.0	-	60.0	70.0	80.0	-	-	-
Calcium carbonate	-	-	30.0	-	-	-	40.0	50.0	60.0
Mannitol	90.0	60.0	60.0	50.0	60.0	40.0	70.0	80.0	60.0
Mcc PH 102	-	-	-	30.0	10.0	20.0	30.0	10.0	20.0
Low HPC	30.0	30.0	30.0	-	-	-	-	-	-
Isopropyl alcohol	q.s	q.s	q.s	-	-	-	-	-	-
Crosspovidone	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Magnesium stearate	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Talc	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0
Total	153.0	153.0	153.0	171.0	171.0	171.0	171.0	171.0	171.0

Evaluation of powder blend

Powder blend was evaluated for Angle of repose, Bulk density and tapped density, Compressibility Index, Hausner's ratio as described above. Additionally Blend Uniformity was calculated by following procedure:

An accurately weight amount of Rabeprazole sodium powder blend (100 mg) was extracted with 6.8 pH Phosphate buffer and the solution was filter through 0.45µ membrane. The absorbance was measured at 284 nm using a Shimadzu UV-1700 UV/Vis double beam spectrophotometer.

Evaluation of tablets [14,15,16]

1. Appearance

Twenty tablets of each formulation were taken to check any discoloration or degradation of drug in the tablets by visual method. If any discoloration or black spots appears, it shows the degradation or decomposition of the drug in the tablet formulation.

2. Weight variation test

To study weight variation twenty tablets of the formulation were weighed using a Sartorius electronic balance and the test was performed according to the official method.

3. Hardness

The hardness of five tablets was determined using the Dial type hardness tester and the average values were calculated.

4. Thickness and diameter

The Thickness and Diameter of the tables was determined by using vernier calipers. Five tablets were used, and average values were calculated.

5. Friability

The friability of ten tablets was measured by Roche friabilator and average values were calculated.

6. Disintegration time

The disintegration time of the six tablets were measured by using USP Disintegration apparatus at 37.5º C.

7. In vitro dissolution studies

The In Vitro dissolution study of uncoated tablets of Rabeprazole tablets was determined using USP dissolution testing apparatus II (paddle Type). The dissolution test was performed using 900 ml of 6.8 pH Phosphate buffer, at 37 ± 0.5°C and 100 rpm. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus at regular interval for 60 minutes, and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45 µ membrane filter and absorbance of these solutions was measured at 284 nm using a Shimadzu UV-1700 UV/Vis double beam spectrophotometer. Cumulative percentage of drug release was calculated using the equation obtained from a standard curve.

Preparation of coating solution of colorcoat FC4S

To prevent interaction between Rabeprazole sodium and Colorcoat EC4S, seal coating of core tablets of Rabeprazole sodium was done by Colorcoat FC4S until weight gain 3%. Coating solution was prepared by dissolving Colorcoat FC4S in mixture of Iso Propyl Alcohol (IPA) and Methylene Dichloride (MDC) under constant stirring for 15-20 minutes by using propeller stirrer.

Table 3: Composition of Colorcoat FC4S coating solution

Material	Quantity (%)
Colorcoat FC4S	10.0
Iso Propyl Alcohol	40.0
Methylene Dichloride	60.0

Preparation of coating solution of colorcoat EC4S:

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 Colorcoat EC4S (for 8% weight gain) was added in the water and kept continuous stirring for 15-20 minutes.

Table 4: Composition of Colorcoat EC4S coating solution

Material	Quantity (%)
Colorcoat EC4S	10.0
Iso Propyl Alcohol	72.0
Methylene Dichloride	28.0

Coating of tablets

Coating of tablets was done using a side-vented, perforated pan coating apparatus Ganscoater GAC 275 machine. First fixed quantity (1 kg) tablets were put in the pan which was pre adjusted at 50° C temperature for 5-10 minute. Then actual weight of tablet was determined. Then the tube was put in the coating solution. After that the various parameters like spray rate (8 to 25 gm/min), inlet air temperature (20 to 50° C), atomizing air pressure (1 to 3 bar), rotating speed of pan (5 to 20 rpm), and % solid content (8 to 20 %) were adjusted and optimizesd. After finishing of the coating tablets were kept in the pan at 40° C and 2 rpm for curing. Then tablets were removed from the pan and evaluated by various parameters.

Evaluation parameters [17,18]

Coating uniformity (CU)

CU is generally defined as the variation in weight gain of coated tablets within a coating trial. The reported standard deviation (SD) was calculated as

$$\text{Standard deviation (SD)} = \{ \sum [(wt_{ai} - wt_{bi}) - x]^2 / (n-1)\}^{1/2}$$

where wt_{ai} and wt_{bi} are the weights of tablet i after and before coating, respectively, corrected for moisture content by drying to final weight; n is the number of tablets measured; and x is the average weight gain of the n measured tablets from the coating trial. Note that the equation is simply the first standard deviation (SD) of the variation in weight gain within a trial. As SD decreased the coating uniformity increased and as SD increased the coating uniformity decreased.

Coating process efficiency (CPE)

Coating process efficiency (CPE) is a measure of the actual amount of coating applied to the tablets relative to the theoretical quantity of coating applied. It can therefore be another indicator of over wetting or over drying. When over wetting occurs, material can potentially be transferred from the surface of the tablets to the walls of the coating pan, thus reducing CPE. Conversely, when over drying occurs, coating solution can dry prematurely in the air stream and be lost into the exhaust air stream instead of being transferred to the tablets.

Coating process efficiency was determined by the following equation.

$$CPE = (\%wg_a / \%wg_t) \times 100\%$$

Where wgt is the theoretical percent weight gain, which in this experiment was 3% in every coating trial, and wga is the actual percent weight gain, which is computed as

$$\text{Processing } \%\ wg_a = [(wt_a - wt_b)\ wt_b] \times 100\%$$

Where, wt_b and wt_a are the total batch weights before and after coating, respectively.

% LOD

% LOD is the moisture content of the coated tablet expressed as percent weight. The tablets were weighed, dried at 60 °C for 24 h, and then reweighed. All uncoated tablet cores used in this study had an initial moisture content of 3%. %LOD was determined by the following equation.

$$\%\ LOD = [(wtb - wt_a) / wt_b] \times 100\%$$

Where, wt_b and wt_a are the coated tablet weights before and after drying, respectively.

Optimization of various parameters [19]

In film coating of tablets Spray rate (gm/min), Inlet air temperature (°C), Atomizing air pressure (bar), Rotating speed of pan (rpm), and % Solid content were optimized.

Optimization of spray rate [20,21]

Coating was performed at different spray rate of 8, 12, 16, 20, 25 gm/minute at constant atomizing air pressure (1.5 bar), inlet air temperature (30° C), rotating speed of pan (10 rpm), and % solid content (12%) and the spray rate was optimized for coating uniformity, coating process efficiency and % LOD.

Optimization of inlet air temperature[22,23,24]

Coating was performed at different inlet air temperature 20, 30, 40 and 50° C at constant spray rate of (12 gm/min), atomizing air pressure (1.5 bar), rotating speed of pan (10 rpm), % solid content (12%) and the inlet air temperature was optimized for coating uniformity, coating process efficiency, surface roughness and % LOD. where spray rate previously optimized was used.

Optimization of atomizing air pressure[25,26,27]

Coating was performed at different atomizing air pressure 1, 1.5, 2, 2.5, 3 bar at constant spray rate of (12 gm/min), inlet air temperature (40°C), rotating speed of pan (10 rpm), % solid content (12%) and the atomizing air pressure was optimized for coating uniformity, coating process efficiency, surface roughness and % LOD where spray rate of and inlet air temperature previously optimized were used.

Optimization of rotating speed of pan[28,29]

Coating was performed at different rotating speed of pan 5, 10, 15 and 20 rpm at constant spray rate of (12 gm/min), atomizing air pressure (2 bar), inlet air temperature (40° C), % solid content (12 %) and the rotating speed of pan was optimized for coating uniformity, coating process efficiency, surface roughness and % LOD. where spray rate, inlet air temperature of and atomizing air pressure previously optimized were used.

Optimization of % solid content [29]

Coating was performed at different % solid content of 8, 10, 12, 16, 20 % at constant spray rate of (12 gm/min), atomizing air pressure (2 bar), inlet air temperature (40°C), and rotating speed of pan (15 rpm) and the % solid content was optimized for coating uniformity, coating process efficiency surface roughness and % LOD where spray rate, atomizing air pressure, inlet air temperature of and rotating speed of pan of previously optimized were used.

Three level full factorial design[30, 31]

A 3^3 full factorial design was employed to study combine effect of independent variables spray rate (X_1), inlet air temperature (X_2) and rotating speed of pan (X_3) on dependent variables coating uniformity, coating process efficiency, and %LOD on the basis of the preliminary trials.

Variables level	Low (-1)	Medium (0)	High (+1)
Spray rate (gm/min)X_1	8	12	16
Temperature(°C) X_2	35	40	45
Pan speed (rpm) X_3	12	16	20

Evaluation parameters of enteric coated tablets

1. Weight variation test

To study weight variation twenty tablets of the formulation were weighed using a Sartorius electronic balance and the test was performed according to the official method.

2. Dimensional changes

Dimensional changes were included both diameter and thickness changes of coated tablets. Both diameter and thickness changes were measured by vernier calipers.

3. % Loss on drying

Weighed glass stoppered bottle was dried for 30 minutes at 60°C in vacuum. 1 gm of the finely powdered tablets was placed in the bottles. By gentle, sidewise shaking, the sample was distributed evenly. The loaded bottle was placed in the oven, removes the stopper and leaved it also in the oven. The sample was dried at 60°C in vacuum for 3 hours. Upon opening the oven, the bottle was close promptly and allowed it to come room temperature in a desiccator before weighing. It was calculated by following formula:

% LOD = (Loss in weight of the sample/Weight of sample) * 100

4. % Weight gain

% Weight gain defined by difference between weight of tablets after coating (Wt_a) and weight of tablets before coating(Wt_b)divided by weight of tablets before coating. It was calculated by following equation.

$$\%\text{Weight gain} = (Wt_a - Wt_b)/ Wt_b * 100$$

5. Hardness

The hardness of five tablets was determined using the Dial type hardness tester and the average values were calculated.

6. Friability

The friability of ten tablets was measured by Roche friabilator and average values were calculated.

7. Uniformity of content

The enteric coated tablets of Rabeprazole sodium were tested for their drug content. Ten tablets were finely powdered; quantities of the powder equivalent to 20 mg of Rabeprazole sodium were accurately weighed and transferred to a 100 ml of volumetric flask. The flask was filled with phosphate buffer pH 6.8 and mixed thoroughly. Volume was made up to mark with phosphate buffer pH 6.8 and filtered. The absorbance of the resulting solution was measured at the 284nm using a UV/Vis double beam spectrophotometer. The linearity equation obtained from calibration curve as described previously was use for estimation of Rabeprazole sodium in the tablets formulations.

8. Disintegration Time

Disintegration testing of coated dosage forms was carried out in the six tablet basket rack USP disintegration apparatus. One tablet was introduced into each tube of the basket rack assembly of the disintegration apparatus without disc. The assembly was positioned in the beaker containing 0.1N HCL (pH 1.2) maintained at 37°C ± 2°C and operated the apparatus for 2 hours. After 2 hours 0.1N HCL was replaced with phosphate buffer 6.8 pH. A disc was added to each tube and operated for further 60 minutes. The disintegration time of each tablet was recorded.

9. In-vitro drug release studies

Drug release studies were carried out using a USP type II dissolution test apparatus at 100 rpm for 2 hr in 0.1 N HCl (900 ml) maintained at 37°C ± 0.5°C. 10 ml of sample was taken and sample was analyzed using UV spectrophotometer at 260 nm. Then the dissolution medium was replaced with pH 6.8 phosphate buffer (900 ml) and tested for drug release for 1 hr at same temperature and same rotation speed. After 10, 20, 30, 45 and 60 minutes, 10 ml of the samples were taken out and 10 ml Volume of fresh phosphate buffer pH 6.8 was added to kept volume of dissolution medium constant and sample was analyzed using UV spectrophotometer at 284 nm.

Comparison of dissolution profiles with marketed products

The similarity factor (f_2) given by SUPAC guidelines for modified release dosage form was used as a basis to compare dissolution profile. The dissolution profiles are

considered to be similar when f_2 is between 50 and 100. A value of 100% for the similarity factor suggests that the test and reference profiles are identical. This similarity factor was calculated by following formula,

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

Where, n is the number of dissolution time and R_t and T_t are the reference and test dissolution values at time t.

Accelerated Stability study of the optimized batch F [32]

In order to determine the change in evaluation parameters and in-vitro release profile on storage, stability study of optimized batch F was carried out at accelerated storage condition at temperature 40 ± 2^0 C and 75% ± 5% RH in a humidity chamber for 3 month. Sample were withdrawn after one-week interval and evaluated for change in in-vitro drug release pattern, physical appearance thickness, hardness and disintegration time. The similarity factor (f_2) was applied to study the effect of storage on formulation.

Photostability study of core and coated tablets of Rabeprazole sodium [33, 34, 35]

According to ICH, the intrinsic photostability characteristics of new drug substances and products should be evaluated to demonstrate that light exposure does not result in unacceptable changes.[22] Core and coated tablets were put onto a glass petridish and introduced into a light cabinet of UV chamber. Protected samples of core and coated tablets i.e., wrapped in aluminium foil were used as dark controls to compare test samples.[23, 24] Test samples and controls were analyzed by UV/Vis spectrophotometer at 284 nm in phosphate buffer pH 6.8 after 1 month.

RESULTS AND DISCUSSION

Preformulation studies

From the Results of Micromeritic studies of the API, it was concluded that Rabeprazole sodium has poor flow property and compressibility property. So, to improve the flow and compressibility property, it was beneficial to use the directly compressible grade components in the formulation of tablet.

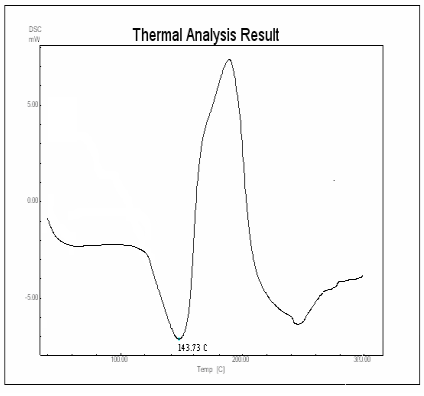
From the DSC Study and physical observation, no significant Drug-Excipient interaction was observed. So, from DSC study, it was concluded that drug and other excipients were compatible which each other.

Table 5: Micromeritic properties of API

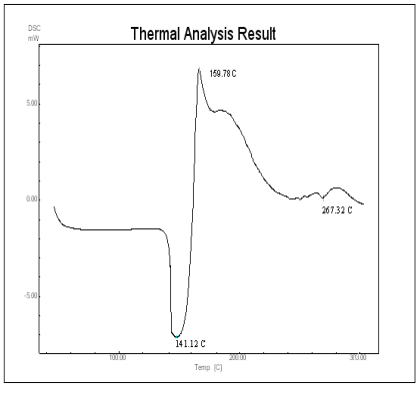
Sample	Angle of repose (^{0})	Bulk density (g/ml)	Tapped density (g/ml)	Compressibility Index (%)	Hausner's ratio
API	34	0.352	0.512	31.25	1.45

Table 6: Drug excipients Compatibility Study

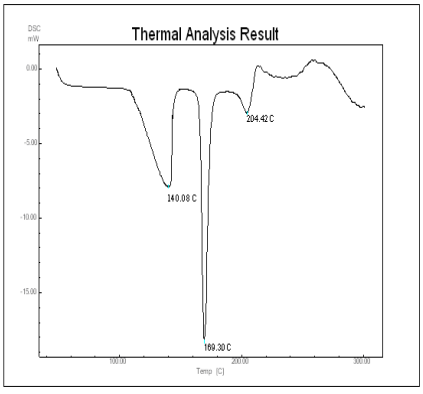
Materials	Initial Observation	Drug: excp. ratio	Duration in weeks				
			0	I	II	III	IV
Rabeprazole Sodium	A Yellowish white powder	1:1	Complies	Complies	Complies	Complies	Complies
Dug + $Caco_3$	A Yellowish white powder	1:4	Complies	Complies	Complies	Complies	Complies
Drug +Magnesium oxide	A Yellowish white powder	1:5	Complies	Complies	Complies	Complies	Complies
Drug + Mannitol	A Yellowish white powder	1:2	Complies	Complies	Complies	Complies	Complies
Drug + MCC pH 102	A Yellowish white powder	1:1	Complies	Complies	Complies	Complies	Complies
Drug + Cross povidone	A Yellowish white powder	1:0.5	Complies	Complies	Complies	Complies	Complies
Drug + Mg-stearate	A Yellowish white powder	1:0.25	Complies	Complies	Complies	Complies	Complies
Drug + Talc	A Yellowish white powder	1:0.25	Complies	Complies	Complies	Complies	Complies
Drug + Colorcoat FC4S	A Yellowish white powder	1:2	Complies	Complies	Complies	Complies	Complies
Drug + All excipients	A Yellowish white powder	1:1	Complies	Complies	Complies	Complies	Complies



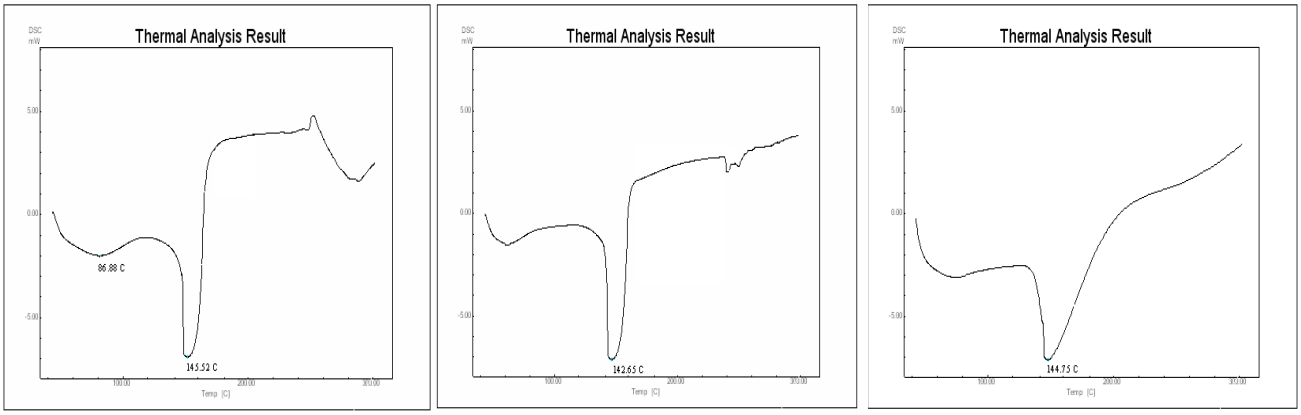
Drug



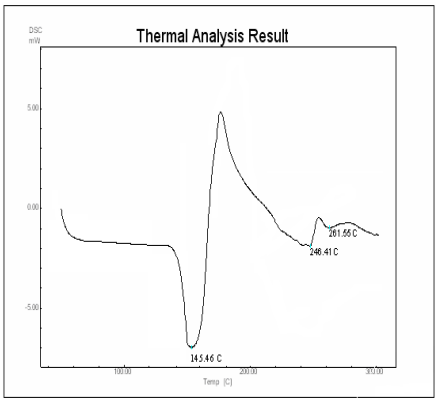
Drug + MCC



Drug + Mannitol



Drug + Crosspovidone **Drug + Mgo** **Drug + $CaCo_3$**



Drug + Colorcoat FC4S

Fig 1: DSC spectra of drug alone and in combination of various excipients.

Evaluation of powder blend and tablets

The uncoated tablets prepared by direct compression method did not show any black spots just like formulations prepared by wet granulation method. So, it was concluded that direct compression method was better than wet granulation for the formulation of uncoated tablets of Rabeprazole sodium.

From the micromeritic studies of powder blends of different batches prepared by direct compression, it was concluded that powder blends of B4 to B6 batches had good flow properties as compare to B7 to B9 batches. Batch B6 was shown better flowability as compare to all other batches.

From the results of friability, it was concluded that calcium carbonate containing batches had more friability than batches containing magnesium oxide. B6 batch was shown good disintegration time and drug release as compare to other batches. Finally, Batch B6 was selected for further study.

Table 7: Micromeritic properties of powder blends of different batches

Powder blend	Angle of repose (^{0})	Bulk density (g/ml)	Tapped density (g/ml)	Carr's Index (%)	Hausner's ratio	Drug content (%)
B_4	20	0.438	0.520	15.0	1.18	99.14
B_5	23	0.432	0.519	16.0	1.20	98.89
B_6	21	0.421	0.504	16.5	1.19	99.85
B_7	28	0.391	0.514	23.0	1.31	97.52
B_8	27	0.386	0.526	26.0	1.36	98.63
B_9	30	0.396	0.538	27.0	1.35	98.84

Table 8: Evaluation parameters of Uncoated Tablet of Rabeprazole sodium

Parameters	Batches								
	B_1	B_2	B_3	B_4	B_5	B_6	B_7	B_8	B_9
Appearance	Black spots	Black spots	Black spots	-	-	-	-	-	-
Weight variation	153±2.54	153±.69	153±1.83	171±1.68	171±2.41	171±1.75	171±2.64	171±2.55	171±1.86
Diameter (mm)	8.04	8.04	8.04	8.04	8.04	8.04	8.04	8.04	8.04
Thickness (mm)	2.75	2.76	2.75	2.93	2.93	2.94	2.97	2.96	2.98
Hardness	6.0	6.5	5.5	6.5	5.5	6.5	6.0	5.5	5.0
Friability (%)	0.59	0.43	0.68	0.35	0.62	0.52	0.64	0.72	0.81
Disintegration time (min.)	5.56	6.40	5.35	6.45	5.10	4.50	6.35	5.20	4.58

Table 9: Cumulative Percentage Release of Core tablets of Rabeprazole sodium

Time (min)	Cumulative Percentage Release of different Batches								
	B_1	B_2	B_3	B_4	B_5	B_6	B_7	B_8	B_9
0	0	0	0	0	0	0	0	0	0
10	8.23	12.44	15.78	14.08	15.59	16.33	14.23	17.52	16.25
20	19.65	26.39	27.01	29.85	32.70	28.95	22.56	29.64	28.39
30	42.38	57.21	53.48	61.22	59.03	62.31	53.14	60.24	62.04
45	63.54	74.32	69.50	85.46	88.12	90.40	83.76	89.76	91.23
60	82.69	86.55	88.07	97.56	98.75	99.89	98.20	99.37	98.79

Table 10: Optimization of spray rate

Batch	Spray rate (gm/min)	Standard deviation (mg)	Coating process efficiency (%)	%LOD	Problem during coating
RS-EC-01	8	3.41	70.58	2.05	Rough Surface
RS-EC-02	12	3.25	87.16	2.37	-
RS-EC-03	16	3.37	82.36	3.12	-
RS-EC-04	20	3.52	76.88	4.65	Rough Surface
RS-EC-05	25	3.64	68.91	5.22	Sticking and Picking

Optimization of inlet air temperature

At higher inlet air temperature tablets surface became rougher because of the drying of coating solution and at lower temperature sticking was observed. At 40 °C good coating efficiency as well as smooth surface was observed. Hence, it was concluded that 40 °C inlet air temperature was optimum and would be kept constant in optimization of other parameters.

Optimization of atomizing air pressure

At higher atomizing air pressure small droplets were formed and at lower pressure big droplets were formed which affect the coated tablets. Smaller droplets were dried fast and so coating efficiency of process decreased. Maximum coating efficiency was observed at 2 bar pressure. Hence, it was concluded that 2 bar atomizing air pressure was optimum and would be kept constant in optimization of other parameters.

Optimization of rotating speed of pan

At higher Rotating speed of pan was mainly affect the coating uniformity of tablets. Higher rotating speed of the pan improves the mixing of the tablets and distribution of the coating solution onto the tablet bed. At 15 rpm pan speed, coating process efficiency was found to be more than other rotating speed of pan. Thus, it was concluded that 15 rpm pan speed is optimum and was utilized in further studies.

Optimization of % solid content

Higher % solid content affects the quality of coated tablets; at higher % solid content surface of tablet became rougher. At 10% solid content coating process efficiency was higher than others. Thus, it could be concluded that 10 % solid content would be added in formulation trials in further studies.

Three level full factorial design

Coating uniformity

The equation for coating uniformity was as below:

Coating uniformity = $2.198 + 0.033X_1 + 0.096X_2 - 0.830X_3 - 0.01X_1X_2 + 0.009X_2X_3 + 0.007X_1X_3 + 0.007X_1X_2X_3 + 0.133X^2_1 - 0.007X^2_2 + 0.263X^2_3$

The oating uniformity for coated tablets varied from 1.54 to 3.45 and showed good correlation coefficient (0.9928). Results of the regression analysis indicated that the effect of X3 (Rotating speed of pan) was more significant than X1 (Spray rate) and X2 (inlet air temperature) because p value for pan speed was found to be < 0.05. Response surface plot shows that rotating speed of pan had a negative effect on standard deviation (i.e., as Rotating speed of pan increased, the standard deviation decreased) and as standard deviation decreases coating uniformity increases.

Table 11: Optimization of inlet air temperature

Batch	Inlet air temperature (°C)	Standard deviation (mg)	Coating process efficiency (%)	%LOD	Problem during coating
RS-EC-01	20	3.25	79.36	4.66	Sticking and Picking
RS-EC-02	30	2.65	86.17	3.05	-
RS-EC-03	40	2.25	91.26	2.64	-
RS-EC-04	50	3.32	72.92	1.22	Choking of Nozzle

Table 12: Optimization of atomizing air pressure

Batch	Atomizing air pressure (bar)	Standard deviation (mg)	Coating process efficiency (%)	%LOD	Problem during coating
RS-EC-01	1.0	3.52	69.19	4.42	Sticking and Picking
RS-EC-02	1.5	3.36	83.73	3.89	-
RS-EC-03	2.0	3.18	89.56	2.61	-
RS-EC-04	2.5	3.25	63.33	1.57	-
RS-EC-05	3.0	3.64	56.29	1.24	Excess dust Formation

Table 13: Optimization of Rotating speed of pan

Batch	Rotating speed of pan (rpm)	Standard deviation (mg)	Coating process efficiency (%)	%LOD	Problem during coating
RS-EC-01	5	3.95	76.51	2.08	-
RS-EC-02	10	3.16	87.68	2.56	-
RS-EC-03	15	2.71	90.05	2.81	-
RS-EC-04	20	3.87	79.85	3.83	sticking

Table 14: Optimization of % solid content

Batch	% Solid content (%)	Standard deviation (mg)	Coating process efficiency (%)	%LOD	Problem during coating
RS-EC-01	8	2.72	79.12	2.10	-
RS-EC-02	10	2.81	89.24	2.25	-
RS-EC-03	12	2.90	87.28	2.75	-
RS-EC-04	16	3.15	72.68	3.31	-
RS-EC-05	20	3.60	64.90	3.52	Rough surface

Table 15: 3^3 full factorial design layout.

Batch No.	Variable level in coded form			Standard deviation (mg)	Coating process efficiency (%)	%LOD
	X_1	X_2	X_3			
1	-1	-1	-1	3.31	93.71	1.46
2	-1	-1	0	2.23	94.52	1.62
3	-1	-1	1	1.62	93.92	1.71
4	-1	0	-1	3.41	89.13	1.32
5	-1	0	0	2.30	87.33	1.48
6	-1	0	1	1.72	86.41	1.63
7	-1	1	-1	3.45	76.95	1.20
8	-1	1	0	2.43	78.82	1.34
9	-1	1	1	1.75	79.90	1.43
10	0	-1	-1	3.20	94.47	1.89
11	0	-1	0	1.89	96.31	1.94
12	0	-1	1	1.54	93.59	2.25
13	0	0	-1	3.32	90.23	1.83
14	0	0	0	2.13	90.88	1.87
15	0	0	1	1.69	91.14	2.09
16	0	1	-1	3.40	83.36	1.79
17	0	1	0	2.34	84.69	1.82
18	0	1	1	1.81	83.51	2.01
19	1	-1	-1	3.40	89.35	3.85
20	1	-1	0	2.31	88.62	4.10
21	1	-1	1	1.73	87.91	4.37
22	1	0	-1	3.45	91.23	2.5
23	1	0	0	2.40	90.35	2.89
24	1	0	1	1.75	89.22	3.04
25	1	1	-1	3.45	92.60	2.10
26	1	1	0	2.51	93.13	2.45
27	1	1	1	1.83	93.89	2.60

Coating process efficiency

The equation for coating process efficiency was as below:

Coating process efficiency = $90.58 + 1.978X_1 - 3.641X_2 - 0.085X_3 + 5.018X_1X_2 + 0.541X_2X_3 - 0.216X_1X_3 - 0.001X_1X_2X_3 - 1.076X^2_1 - 0.699X^2_2 - 0.487X^2_3$

The Coating process efficiency for coated tablets varied from 76.95 to 96.31 and showed good correlation coefficient (0.9292). Results of the regression analysis indicated that the effect of X1 (spray rate) and X2 (Inlet air temperature) were more significant than X3 (Pan speed) on coating process efficiency because p values of spray rate and inlet air temperature were found to be < 0.05. Response surface plot shows that Inlet air temperature had a negative effect on Coating process efficiency. This could be due to at high temperature solvent evaporation is very fast and particles are dried before reaching to the tablets.

% LOD:

The equation for %LOD was as below:

% LOD = $1.844 + 0.817X_1 - 0.358X_2 + 0.177X_3 - 0.362X_1X_2 - 0.015X_2X_3 + 0.064X_1X_3 + 0.001X_1X_2X_3 + 0.339X^2_1 + 0.146X^2_2 + 0.002X^2_3$

The %LOD for coated tablets varied from 1.20 to 4.37 and showed good correlation coefficient (0.9443). Results of the regression analysis indicated that X1 (Spray rate), X2 (Inlet air temperature) and X3 (Rotating speed of pan) were more significantly affect on % LOD because p values of all were found to be less than 0.05. Response surface plot shows that Inlet air temperature had a negative effect on Coating process efficiency (i.e., as Inlet air temperature increased, the %LOD decreased). And it also shows that as spray rate and pan speed increases, the % LOD increases. For the optimization of coating process parameters, minimum standard

deviation, maximum coating process efficiency, minimum % LOD was required.

Batch no.11 (spray rate of coating solution 12 gm/min, inlet air temperature 35°C and rotating speed of pan 16 rpm) showed the maximum coating process efficiency (96.31%), optimum standard deviation(1.89) and % LOD (1.94). Therefore, batch 11 may be considered as a promising batch for optimum coating of Rabeprazole sodium tablets in Ganscoater GAC 275 coating machine.

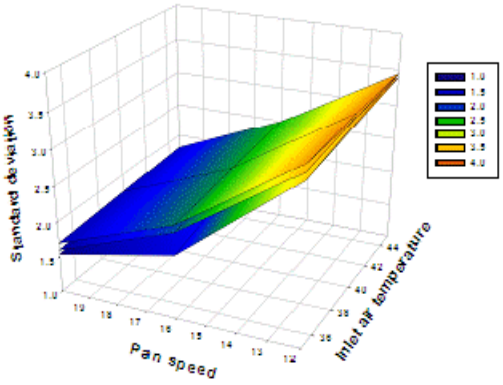


Fig : 2 matrix plots of pan speed and inlet temperature vs. coating uniformity

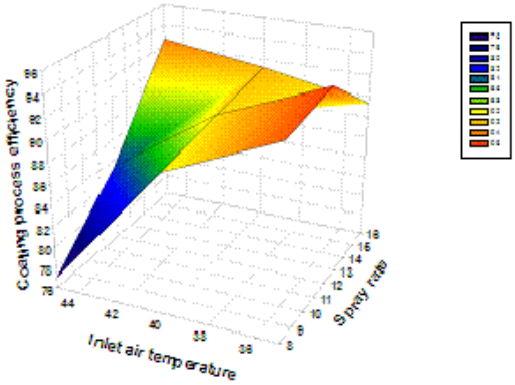


Fig 3: Response surface plot for the effects of spray rate and inlet air temperature on coating process efficiency

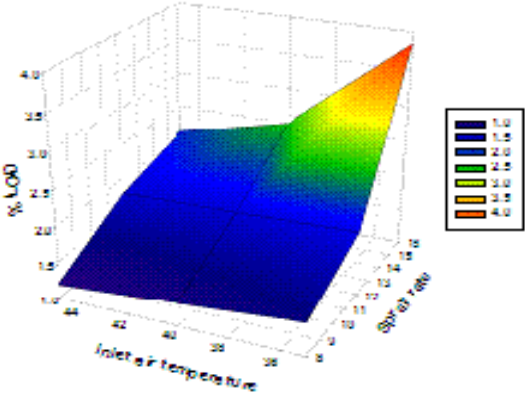


Fig. 4: Response surface plot for the effects of pan speed and inlet air temperature on % LOD

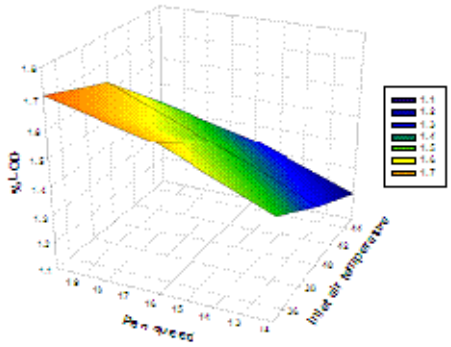


Fig. 5: Response surface plot for the effects of spray rate and inlet air temperature on % LOD

Selection of best batch

Evaluation parameters of the optimized batch F of Rabeprazole Na

From the results of comparative study of dissolution profile of final batch with market preparations, it was concluded that final formulation F was shown good similarity (i.e., more than 50) with market products.

Accelerated stability study of the optimized batch F:

From the results of the accelerated stability of final formulation F for 3 months, it was concluded that storage conditions were not found any significant changes in final formulation F. From the results of similarity factor (f2) applied in accelerated stability study, it was concluded that final formulation F after 3 months was shown good similarity (i.e., more than 50) with initial formulation.

Table 16: Evaluation parameters of the optimized batch F of Rabeprazole Na

Evaluation parameters	Batch F
Weight variation (mg)	190.0 ± 1.20
Diameter (mm)	8.25
Thickness (mm)	2.86
% LOD	1.12 ± 0.4
Hardness (kg/cm²)	6.5
Friability (%)	0.34
Content uniformity (%)	99.54
Disintegration time (min.)	In 0.1N HCL: Intact tablets In phosphate buffer pH 6.8: 8.5 min.

Table17: Comparison of dissolution profiles of optimized batch F with market preparations

Time (min)	Cumulative percentage release (%)		
	Batch F	Marketed product 1	Marketed product 2
0	0.00	0.00	0.00
10	15.73	15.04	16.56
20	29.05	27.66	30.24
30	58.96	61.35	56.45
45	89.38	87.89	86.65
60	99.67	98.64	99.32
Similarity factor (f_2)	**-**	**88.43**	**85.90**

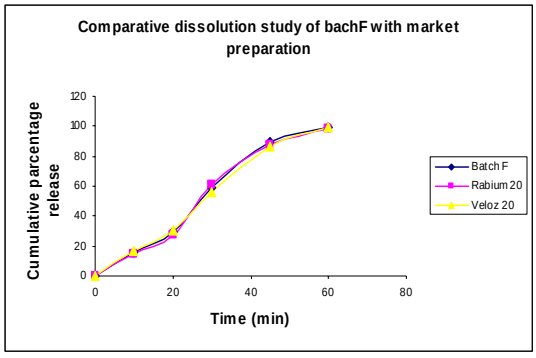


Fig. 6: Comparative dissolution study of optimized batch F with market preparation.

Table 17: Accelerated stability study of optimized batch F

Parameters		Storage condition: 40 ± 2° C/ 75 ± 5% RH			
		Initial	1 Month	2 Month	3 Month
Weight variation (mg)		190.0 ± 1.20	190.0 ± 1.05	190.0 ± 1.25	190.0 ± 1.40
Diameter (mm)		8.25	8.25	8.26	8.26
Thickness (mm)		2.86	2.85	2.86	2.87
% LOD		1.12 ± 0.4	1.24 ± 0.6	1.22 ± 0.5	1.31 ± 0.43
Hardness (kg/cm^2)		6.5	6.5	6.5	6.5
Friability (%)		0.34	0.38	0.41	0.35
Content uniformity (%)		99.54	99.63	99.87	99.21
Disintegration time (min) (In Phosphate buffer pH 6.8)		8.5	8.3	9.0	8.55
In vitro dissolution study	**Time (min)**	**Cumulative percentage release (%)**			
	0	0.00	0.00	0.00	0.00
	10	15.73	15.23	16.05	14.59
	20	29.05	27.38	30.51	27.12
	30	58.96	57.01	56.39	56.10
	45	89.38	87.35	88.64	88.47
	60	99.67	99.51	99.21	99.34
	Similarity factor (f_2)	-	88.70	89.63	86.85

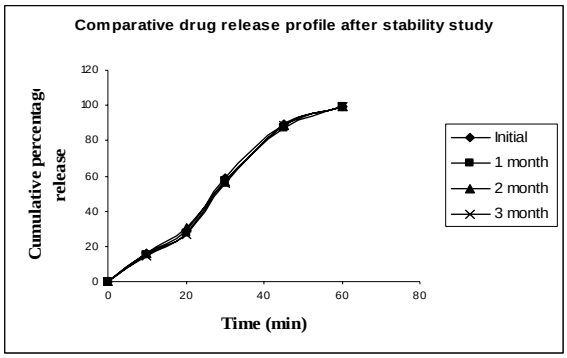


Fig. 7: Comparative drug release profile after stability study

Photostability study of core and coated tablets of RABEPRAZOLE Na

Table 17 shows the results of cumulative percentage release of test sample of core tablets (S1) and its control (C1), test sample of coated tablets (S2) and its control (C2) after 1 month photostability study. Result of test sample of core tablets (S1) shows the almost 80% of rabeprazole sodium was degraded under UV light after 1 month. Whereas, dark control of core tablets did not show any significant change in drug release profile. The amounts of Rabeprazole degraded were less for coated tablets (S2).

From the results of photostability study it was concluded that enteric coating prevents the degradation of rabeprazole sodium. The photoinstability of the rabeprazole sodium showed by the present studies indicates that special care to avoid exposure of the drug to the light effects must be taken during the manufacture and storage of the pharmaceutical preparations.

Table 17: Cumulative percentage release of test samples and controls of core and coated tablets of rabeprazole after photostability study

Time (min)	Cumulative percentage release (%)			
	S_1	C_1	S_2	C_2
0	0	0	0	0
10	5.71	16.33	15.32	15.73
20	10.26	28.95	28.45	29.05
30	17.84	62.31	56.98	58.96
45	20.53	90.40	89.03	89.38
60	21.01	99.89	99.52	99.67

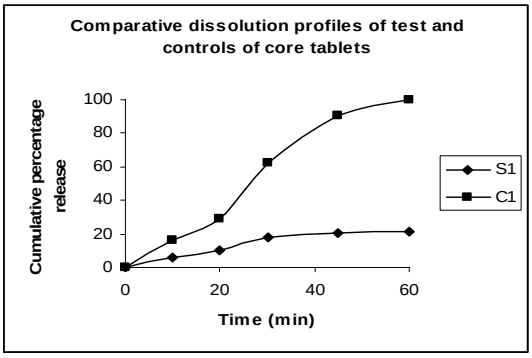


Fig. 8: Comparative dissolution profiles of test and controls of core tablets after photostability study

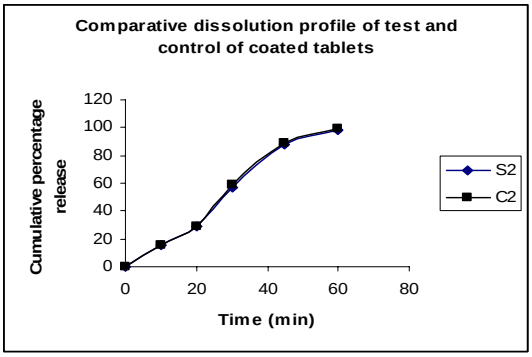


Fig. 9: Comparative dissolution profiles of test and controls of coated tablets after photostability study

CONCLUSION

Attempts were made in the present investigation to prepare a stable composition of delayed release tablets of Rabeprazole sodium. These results clearly reflect that the prepared formulation offers effective resistance in acidic environment and starts its release in the alkaline environment of small intestine. Thus, Colorcoat EC4S can be successfully employed to retard the release pattern of rabeprazole sodium thereby enhancing the therapeutic efficacy. The final formulation also shows good comparative dissolution profile with marketed preparation.

ACKNOWLEDGEMENT

Authors are sincerely thankful to Corel Pharma Chem, Ahmedabad for providing instrument facility to conduct this project.

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