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Formulation and Evaluation of Rabeprazole Sodium Delayed Release Tablets

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ABSTRACT

Rabeprazole sodium is a proton pump inhibitor used to treat peptic ulcer, duodenal ulcer, gastro oesophageal reflux disease by inhibiting the enzyme H+ /K+ATPase, the acidic pump. It is also used to treat Zollinger-Ellison syndrome, erosive esophagitis. This study is aimed to develop pharmaceutically equivalent and stable enteric-coated tablets of Rabeprazole sodium comparable to innovator product. The present work aims to avoid degradation of drug in acidic environment of stomach. Ten Formulations of Rabeprazole core tablets were developed using mannitol as diluents, magnesium stearate and talc as lubricant and glidant, Ethyl cellulose as seal coating, Eudragit L-30, Plasacrylic HTP, Instacoat EN HPMC Pthalate as enteric coated. Among the ten uncoated tablet batches F9 obtained good drug release profile compared to innovator. So a batch F9 was selected for further steps of formulation i.e., sub coating and enteric coating. After enteric coated batches F9 was evaluated for acid resistance test and *in-vitro* dissolution test compared with innovator found to be suitable for Rabeprazole sodium delayed release tablet. The stability studies were conducted at 40^{o}C/75% RH for 3 months.

Keywords: Rabeprazole sodium, gastro oesophageal reflux, Enteric coated tablets, Dissolution, stability

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INTRODUCTION

Gastro esophageal reflux disease (GERD) is a common chronic, relapsing condition caused by the combination of excess reflux of gastric juice and impaired clearance of this refluxate from the esophagus. It is one of the most prevalent gastrointestinal disorders affecting all age groups and carries a risk of significant morbidity and possible mortality from resultant complications thus affecting the quality of life of the patient. [1,2]

GERD is commonly due to transient or permanent changes in the barrier between the esophagus and the stomach, which can be due to incompetence of the lower esophageal sphincter (LES), transient LES relaxation, impaired expulsion of gastric refluxate from the esophagus, or association with a hiatal hernia. Reflux of gastric contents can cause esophageal mucosal abnormalities, such as ulcers and peptic strictures, as well as reflux-induced asthma and acid laryngitis. Left untreated esophageal adenocarcinoma can develop in approximately 0.2 - 2.0% of patients with Barrett's esophagus, a complication of GERD.[3-4]

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. [5]

Rabeprazole sodium drug is a sodium salt of 2-((4-(3-methoxypropoxy)-3-methylpyridin-2-yl) methylsulfinyl)-1H-benzo[d]imidazole belongs to a class of proton pump inhibitors (PPIs). It suppress gastric acid secretion by specifically inhibiting the H+/K+- ATPase enzyme system at the secretory surface of the gastric parietal cell [6]. The aim of proposed work was to formulate and characterize enteric coated tablets Rabeprazole sodium for delayed release of drug in stomach for treatment of gastric and duodenal ulcers.

MATERIALS AND METHOD

Materials:

Rabeprazole sodium (Madras Pharma india), Mannitol (Roquette, France), Eudragit L-30, Plasacrylic HTP, Instacoat EN HPMC Pthalate, Low substituted Hydroxy propyl cellulose (L-HPC, Shinetu Chemicals, Japan), Ethyl cellulose (Colorcon Asiapvtltd.,India). All other reagents were of analytical grade.

Methods:

Preparation of core Rabeprazole sodium tablets:[7,8]

The initial trials were taken with dry mixing and direct compression method than follow wet granulation technique because a good distribution and uniform content of low-dosage drugs was possible in wet granulation process. A lab scale trial batch was taken with the following composition, manufacturing procedure and studied for tablet physical and dissolution parameters. The details are given below.

Table 1- Prototype formulation of Rabeprazole sodium

Batch NO **Ingredients**	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
Intra granular part:										
Rabeprazole Sodium	21.07	21.07	21.07	21.07	21.07	21.07	21.07	21.07	21.07	21.07
Mannitol(Pearlitol DC 400)	30.00	-	-	-	-	-	-	-	-	-
Mannitol Powder	-	30.00	30.00	71.68	36.00	36.00	36.00	36.00	36.00	36.00
Light magnesium oxide DC	74.93	-	-	-	-	-	-	-	-	-
Light magnesium oxide	-	71.68	71.68	30.00	65.68	65.18	66.93	68.93	68.93	68.93
Low Substituted Hydroxy Propyl Cellulose LH 11	17.00	17.00	17.00	-	-	-	-	-	-	-
Low Substituted Hydroxy Propyl Cellulose LH 21	-	-	-	17.00	17.00	17.00	5.00	5.00	5.00	5.00
Binder part:										
Hypromellose 6cps	-	1.50	1.50	1.50	1.50	2.00	2.00	2.00	2.00	2.00
Dichloromethane	-	-	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Iso propyl Alcohol	-	-	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Extra granular part:										
Low Substituted Hydroxy Propyl Cellulose LH 21	-	-	-	-	-	-	10.00	10.00	10.00	10.00
Magnesium stearate	2.00	3.75	3.75	3.75	3.75	3.75	2.00	2.00	2.00	2.00
Tablet Wight (Core)	**145.0**	**145.0**	**145.0**	**145.0**	**145.0**	**145.0**	**145.0**	**145.0**	**145.00**	**145.00**
SEAL COATING										
Ethyl cellulose	-	-	1.0	1.0	1.0	1.0	2.0	2.0	4.25	4.25
Light magnesium oxide	-	-	1.0	1.0	1.0	1.0	2.0	2.0	0.75	0.75
Iso propyl alcohol	-	-	Q.S	-	-	-	-	-	q.s	q.s
Hydroxy propyl methyl cellulose(Pharmacoat 606)	-	-	Q.S	-	-	-	-	-	-	-
ENTERIC COATING:										
Acryl EZE Yellow (93O92157)	-	15.00	13.00	-	-	-	-	-	-	-
Eudragit L-30 D 55	-	-	-	10.26	10.26	10.26	10.26	-	-	-
Plasacrylic HTP	-	-	-	2.74	2.74	2.74	2.74	-	-	-
	-	-	-	-	-	-	-	11.00	10.00	10.00
Purified Water	-		Q.S	91.00	91.00	91.00	91.00	-	-	-
Isopropyl Alcohol	-	-	-	-	-	-	-	73.15	66.50	66.50
Dichloromethane	-	-	-	-	-	-	-	135.85	123.50	123.50
Total weight of tablet(Enteric coated)	**-**	**160.0**	**160.0**	**160.0**	**160.0**	**160.0**	**160.0**	**160.0**	**160.0**	**160.0**

Manufacturing Procedure of Final Batch No F9 & F10

1. Dispensing

All the ingredients were dispensed accurately by using digital balance (Swiss India)

2. Geometrical Mixing and Sifting

Rabeprazole Sodium was mixed with equal amount of light magnesium oxide & co-sifted through #30 sieves The above blend was co-sifted with equal amount of light magnesium oxide in geometrical progression through # 30. Sift remaining amount of light magnesium oxide, mannitol, low substituted hydroxypropyl cellulose LH 21 through #30 sieves by using vibrosifter (Elicon Pharma).

3. Dry Mixing

The above sifted blends of step **(i)** were loaded into the rapid mixer granulator (Elicon Pharma) and mixed for 10 minutes at Impeller slow speed (50 RPM) and Chopper off.

4. Binder Preparation & Granulation:

HPMC 6cps was slowly added in isopropyl alcohol and dichloromethane under stirring for 30min and poured it into the dry mix blend of step **(ii)** for granulation as mentioned below with intermittent racking.

Table 2: Granulation Process

Granulation steps	Time	Impeller Speed	Chopper Speed
Binder addition	2 min	Slow (50 rpm)	Off
Kneading	1 min	Fast (100 rpm)	Off
Kneading	1 min	Fast (100 rpm)	Fast (2000 rpm)

After granulation if granules not formed than further added additional solvent was added.

Drying

Granules were dried in a Retsch drier (Retsch) till the LOD reaches 2.0 - 4.0% Checked at 105°C for 5 minutes in Moisture analyzer (Mettler Toledo).

Sifting

The resulting granules were passed through #24 sieves.

Blending/Mixing:

The above granules were mixed with previously sifted extra granular Low substituted hydroxypropylcellulose 21 (#40 sieve) in a octagonal blender (Gansons Ltd.) for 15 min.

Lubrication

Pre-sifted Magnesium Stearate (#60 sieve) was added to the blend of step (VI) and mixed in octagonal blender (Gansons Ltd.) for 5 min.

Compression

The lubricated blend was compressed in rotary compression machine (Acura) with 7.0 mm round, biconcave punches (Parle Elizabeth).

Coating

Seal coating:

Light magnesium oxide was slowly added in iso propyl alcohol with continuous stirring then after few minutes ethyl cellulose was added in it then stir it continuously for 45 min. Then passed the coating solution through muslin cloth. Solid content of seal coating dispersion kept 10% w/w. Seal coating was done in auto coater (Solace).

Enteric coating:

Instacoat EN HPMCP yellow was slowly added in isopropyl alcohol & stirring the solution for 10 min then dichloromethane was slowly added in it and stir the solution for 45 min. Solid content of enteric coating dispersion was kept 5% w/w. Enteric coating was done in auto coater (Solace).

Coating parameters:

Table 3: Coating parameters

Parameters	Seal coating	Enteric coating
Pan Size (inches)	12	12
Solid content (%)	10	5
Inlet temperature (°C)	45°C±5°C	45°C±5°C
Outlet temperature (°C)	35°C±5°C	35°C±5°C
Pan speed (RPM)	12	12
Peristaltic pump speed (RPM)	12	10
Inlet blower	60%	60%
Outlet blower	80%	80%
Atomizing air pressure	1kg/cm^2	1kg/cm^2

Preformulation studies: [9-11]

Pre-formulation investigations are designed to identify those physiochemical properties and excipient that may influence the formulation design, method of manufacture, and pharmacokinetic-biopharmaceutical properties of the resulting product.

Bulk Density:

Bulk density is determined by constant mass method by using graduated cylinder. It is an apparent density. It is the ratio of mass of an untapped powder sample to its volume, including the contribution of the inter particulate void volume. It is expressed in a gm/ml.

$$\textbf{Bulk density } (\rho_B) = M/V_O$$

Where, M = mass of the blend (weight taken in gm)

V_o= untapped volume (volume in ml)

Tapped Density:

Tapped density is the ratio of total mass of the powder to the tapped volume of the powder. When quantity of drug was taken into a graduated cylinder. Volume occupied by the drug was noted down. Then the cylinder was subjected to 500, 750, and 1250 taps in tap density apparatus.

$$\textbf{Tapped Density } (\rho_T) = M/V_T$$

Where,

M = Mass of the powder (weight taken in gm)

V_T = Tapped volume (volume in ml)

Carr's Index (Compressibility):

The compressibility index are measures of the property of powder to be compressed. It is an indirect parameter to assume flow property of powder. Compressibility index is determined by measuring the initial volume (V_O) and final volume (V_F) after complete tapping of powder sample in a measuring cylinder.

$$\text{Carr's Index} = [(V_O - V_f)/ V_O] \times 100$$

Where, V_o= Initial volume (volume in ml)

V_F= Final volume (volume in ml)

Hausner ratio:

It is indirect index to predict of powder flow. I is calculated by using this formula.

$$\text{Hausner ratio} = V_O/ V_f$$

Where, V_o= Initial volume (volume in ml)

V_F= Final volume (volume in ml)

Angle of Repose:

The angle of repose is used to characterize the flow properties of solids. Angle of repose is a characteristic related to inter particulate friction or resistance to movement between particles. This is the maximum angle possible between surface of pile of powder or granules and the horizontal plane.

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

$$\theta = \tan^{-1} (h/r)$$

Where θ = angle of repose

h = height

r = radius.

Drug excipient compatibility study:

The compatibility of drug and formulation component is important prerequisite before formulation. It is therefore necessary to confirm that the drug does not react with the polymers and excipients under experimental conditions and affect the shelf life of product or any other unwanted effects on the formulation.

According to the functional category these excipients were mixed in different ratios with API (Table 4). The mixture in quadruplet was sealed in ambered colored vial and was exposed for 1 month at 40°C±2°C/75%±5% RH and 25°C±2°C/60%±5%RH. API (rabeprazole sodium) or excipients alone was also stored in similar condition as control sample. Observations for physical appearance were made after 4 weeks. The samples were also checked for related substances.

Table 4: Composition for Drug Excipients Compatibility Studies

S.No.	Composition	Ratio
1	API (Rabeprazole sodium)	1:1
2	API+ Mannitol	1:1
3	API+ LHPC	1:1
4	API+ Light magnesium oxide	1:1
5	API+ Hypromellose	1:1
6	API+ Magnesium Stearate	1:1
7	API+ Ethyl cellulose	1:1
8	API+ Opadry acryl Eze	1:1
9	API+ HPMC Pthalate	1:1
10	API: Mannitol: LHPC: Light magnesium oxide: Hypromellose: Magnesium Stearate : Ethyl cellulose : Opadry acryl Eze: HPMC Pthalate:	1:1
11	All excipients without API	NA

Evaluation of developed tablets:

Size, shape, thickness and diameter

The size and shape of the tablet can be dimensionally described, monitored and controlled. Tablet thickness is counting by using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Ten tablets were taken, and their thickness was recorded using Vernier calipers (Precise).

Uniformity of weight

Weight of the tablets determined individually and collectively on a digital weighing balance, (Swiss India). The average weight of one tablet was determined from the collective weight.

Individual weights of 20 tablets were taken and the average weight was calculated by using the following formula.

$$\text{Weight Variation: } \frac{\text{(Target weight of tablet – Average weight)}}{\text{Target weight of tablet}} \text{ X 100}$$

Tablet hardness

Hardness of tablet is defined as force required breaking a table across the diameter. The hardness of tablet indicates the strength of the tablet. Hardness of the tablet of each formulation was determined using the conventional hardness tester (Monsanto Hardness tester, Pfizer hardness tester, etc.). The pressure required to break the tablets is measured as a function of hardness (kg/ cm^2). Hardness of rabeprazole sodium tablet was recorded by using strong cob (Electro lab).

Friability

Friability of the tablet was determined using Roche friabilator. Friability is to measure the extent of tablet breakage during physical stress conditions like Packing, transportation, etc. Friability limit is less than 1%. Friability of rabeprazole sodium tablet was recorded by using Roche friabilator (Electro lab).

$$\text{\% Friability} = \frac{\text{(Initial weight – Final weight)}}{\text{Initial weight}} \text{ X 100}$$

Disintegration time

The test was carried out by selecting 6 tablets was measured using the disintegration test apparatus. The average time required for disintegration was calculated and compared with standards. Temperature required for disintegration test is 37°C±2°C.

Dissolution studies of drug product and RLD[12]

Dissolution (*In-Vitro* release)

The preferred apparatus for a tablet dosage form was paddle type (USP-II). The known quantity of 0.01N HCl & 8.0 pH tris buffer was taken as a dissolution media. The volume of dissolution media was kept 1000 mL. The dissolution was performed at 37^0C±0.5°C at 100 rpm. Absorbance of sample was taken by UV spectrophotometer at 280 nm.

Accelerated Stability Study:[13]

The ICH guidelines have established that long term stability testing should be done at 25^0C/60% RH; stress testing should be done at 40^0C/75% RH for 3 months. If significant change occurs at these stress condition, then the formulation should be tested at an intermediate condition i.e. 30^0c/65% RH. For stability charging used stability chamber (Thermo)

RESULTS AND DISCUSSION

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-05)

Table 05: Micromeritic properties of API

S. No.	Characteristics	Observations
1.	Description	Off white to pale yellow colored amorphous powder
2.	Tapped density	0.714 gm/mL
3	Bulk density	0.400 gm/mL
4.	Carr's index	44.00 %
5.	Hausner ratio	1.786 %
6.	Angle of repose	44.628
7.	Solubility	Soluble in methanol and in water

Table 06: Drug Excipients Compatibility Study (Physical Observation)

Batch no.	Initial	Conditions and Observation 25ºC/60%RH (4 Weeks)	40ºC/75%RH (4 Weeks)
1.	Rabeprazole	No color change	No color change
2.	Rabeprazole : Mannitol	No color change	No color change
3.	Rabeprazole : LHPC	No color change	No color change
4.	Rabeprazole : Light magnesium oxide	No color change	No color change
5.	Rabeprazole : Hypromellose	No color change	No color change
6.	Rabeprazole:Magnesium stearate	No color change	No color change
7.	Rabeprazole : Ethyl cellulose	No color change	No color change
8.	Rabeprazole : Acryl EZE	No color change	No color change
9.	Rabeprazole : HPMC Pthalate	No color change	No color change
10.	Rabeprazole: Mannitol: Light magnesium oxide : LHPC :Hypermellose : Magnesium Stearate : Ethyl cellulose: Acryl Eze: HPMC Pthalate	No color change	No color change
11.	Mannitol: Light magnesium oxide: LHPC : Hypermellose : Magnesium Stearate : Ethyl cellulose: Acryl Eze: HPMC Pthalate	No color change	No color change

Table 07: Lubricated blend flow property

Batch no.	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Hausner's ratio	Angle of repose	Inference
F1	0.489±0.005	0.715±0.007	31.608±0.438	1.462±0.010	47.74±0.618	Poor flow
F2	0.555±0.005	0.720±0.008	22.917±1.229	1.297±0.021	42.31±0.015	Passable
F3	0.512±0.004	0.680±0.005	24.705±1.147	1.328±0.020	41.25±0.030	Passable flow
F4	0.494±0.002	0.648±0.002	23.76±0.471	1.312±0.008	41.20±0.020	Passable flow
F5	0.486±0.001	0.637±0.001	23.70±0.037	1.31±0.005	41.52±0.035	Passable flow
F6	0.588±0.005	0.769±0.010	23.529±0.435	1.308±0.008	42.66±0.263	Passable flow

F7	0.577±0.009	0.768±0.004	24.870±1.246	1.331±0.023	42.32±1.627	Passable flow
F8	0.489±0.010	0.651±0.006	24.885±1.358	1.331±0.025	42.54±1.213	Passable
F9	0.525±0.005	0.660±0.005	20.455±1.076	1.257±0.017	39.10±0.251	Fair
F10	0.534±0.003	0.669±0.005	20.179±0.124	1.253±0.002	38.91±0.692	Fair

Table 08: Parameters of enteric coated tablet: (In process tablet parameters)

Batch No.	Description	Weight (mg)	Thickness (mm)	Disintegration time	
				In 0.1N HCl for 2 Hrs	In pH 6.8 Buffer
F1	Weight variation observed due to poor powder flow property so compression was not done				
F2	Yellow coloured, round, biconvex tablet	161.2±5.977	4.22±0.077	Fail	ND
F3	Yellow coloured, round, biconvex tablet	164.6±2.836	4.29±0.034	Pass	17 min 20 sec to 18 min 18 sec
F4	White coloured, round, biconvex tablet	163.1±4.12	3.91±0.134	Pass	8 min 10 sec to 11 min 32 sec
F5	White coloured, round, biconvex tablet	162.1±1.663	4.18±0.052	Pass	7 min 30 sec to 8 min 42 sec
F6	White coloured, round, biconvex tablet	160.4±2.118	4.37±0.051	Pass	8 min 22 sec to 10 min 38 sec
F7	White coloured, round, biconvex tablet	163.6±3.717	4.20±0.385	Pass	8 min 20 to 14 min 40 sec
F8	Yellow coloured, round, biconvex tablet	160.2±3.259	4.09±0.034	Pass	4 min 20 sec to 6 min 50 sec
F9	Yellow coloured, round, biconvex tablet	159.1±2.233	4.00±0.056	Pass	3 min 50 sec- 5 min 20 sec
F10	Yellow coloured, round, biconvex tablet	159.1±0.994	4.08±0.080	Pass	4 min 10sec – 6 min 50 sec

Table 09: Drug content (Assay) of Trial Batches

Acceptance Limit		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Assay	95.0% to 105.0%	ND	ND	99.1	100.3	98.7	101.5	99.3	98.9	100.6	99.2

***In-Vitro* Dissolution Profile between RLD and Trail Batches with F2:**

Table 9a: Dissolution of trial batches in 0.1N HCl

	% Release in 0.1N HCl, 700ML											
Time Point	**Acceptance Limit %**	**RLD (Pariet®20)**	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
2 Hrs	NMT 10%	1.2	Not Done	Not Done	15	1.5	2.0	1.8	1.1	0.8	0.6	0.8

F1: Not done due to physical parameters were not satisfactory

F2: Not done due to tablet became black during seal coating and also failed in DT

Table 9b: Dissolution of trial batches in Tris buffer (pH 8.0)

	% Release in OGD media (pH 8.0 Tris Buffer)										
Time Point	**RLD (Pariet®20)**	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
0	**0**	Not	Not	Not	**0**	**0**	**0**	**0**	**0**	**0**	**0**
5	0.70	done	done	done	92	94	0	6	0	0.9	2
10	50.00				97	99	80	63	38	54	57
15	98.90				96	99	92	87	89	92	89
20	99.20				94	98	93	90	93	96	97
30	96.60				89	95	91	90	90	97	98
45	93.90				88	91	87	87	87	89	92
60	88.70				85	87	84	84	81	87	86
F2					**20.4**	**20.0**	**45.1**	**52.7**	**55.1**	**68.5**	**65.2**

F1: Dissolution was not done due to physical parameters were not satisfactory

F2: Dissolution was not done due to tablet became black during seal coating and also failed in DT at 0.1N HCl media.

F3: Dissolution in pH 8.0 Tris buffer was not done due to tablets failed in 0.1N HCl media during dissolution results was already showed in table no:

Dissolution graph of RLD Pariet 20mg with final formulation F9 and its reproducible batch F9:

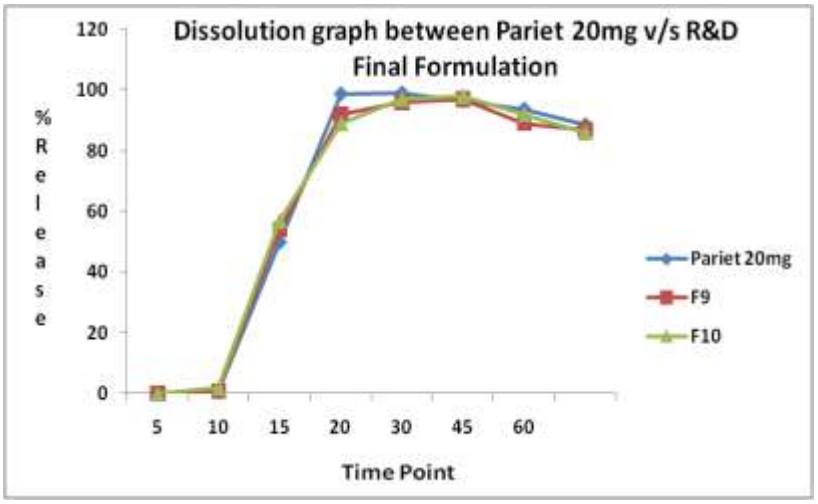

Figure 1: Dissolution between Pariet 20mg v/s Final Formulation F9 and F10

Stability Data of Selected Formulation:

Stability studies were conducted at 40ºC66 / 75% RH for about 3 months in stability chamber (thermo lab). Samples were collected at 1,2 and 3 months.

Table 10: Stability data

Time	Test (%)	Temperature 40ºC / 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 month	Assay	11.5
	Acid resistance	98.6
	% DR	85.0
3 month	Assay	11.5
	Acid resistance	97.9
	% DR	84.2

SUMMARY AND CONCLUSION

Attempt was made to prepare a delayed release formulation of rabeprazole as enteric coated tablets. The core tablet consists of rabeprazole sodium (21.07mg), mannitol (36mg) , light magnesium oxide (68.93), L-Hydroxypropylcellulose(15mg), Hypromellose (2mg) and magnesium stearate (2mg).The core tablets were given a sub coating with ethyl cellulose and magnesium oxide (2.75%w/w).An enteric coating was then given with HPMC phthalate (7.38%w/w). The release profile of enteric coated formulation (F9) was comparable to that obtained with innovator product i.e. Pariet20mg. These results clearly reflect that the prepared formulation offers effective resistance to acidic environment and starts drug release at the elevated pH of intestine. The developed delayed release tablet formulation was quite stable with regard to drug content and dissolution in the accelerated stability testing condition for 3 months.

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