DESIGN, DEVELOPMENT AND CHARACTERIZATION OF STABLE RABEPRAZOLE SODIUM DELAYED RELEASE TABLETS

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Abstract

Rabeprazole sodium is one of the most effective proton pump inhibitor, belongs to the group of benzimidazole, used against peptic ulcer disease to suppress excess acid secretion in the stomach. Benzimidazoles are antiulcerous compounds known for decreasing gastric acid secretion. Thesecompounds, also known as Proto n Pump Inhibitors (PPIs) are commonly indicated for the treatment ofGERD (Gastro Esophageal refl ux Disease), Pathological Hypersecretory conditions (Zollinger - Ellison). It is a challenging drug due to its sensitivity to excipients or environmental variables such as light, high temperatures, acidic or basic conditions, humidity, and oxidative environment. Due to its acid-labile nature, the medication is designed as an enteric-coated dose form, like most other PPIs. The purpose of this study was to investigate the formulation development, stability and enteric performance of Rabeprazole sodium (Na) tablets coated with a hypromellose phthalate based enteric coating system. Acid labile PPI may further decompose if it is coated with enteric coating acidic substance. This restriction was overcame by coating the core of the device, which contained acid labile PPI and alkalizers, with a water-insoluble polymer and a non-hygroscopic alkalizer (stabiliser), followed by an enteric coating was done on seal coated tablet, with a polymer to prevent its exposure to acidic environment of GIT and facilitate absorption through intestinal fluid. Rabeprazole sodium delayed release tablets were prepared by wet granulation method. All the Excipients are tested for compatibility with drug, which revealed that there was no physical and chemical interaction occurred. Different formulations of Rabeprazole core tablets were developed using pearlitol as diluent and L-HPC as disintegrant in different proportions. A further optimised formulation was coated utilising different subcoating and enteric coating compositions employing enteric yellow and opadry white. Compatibility studies were performed for drug, physical mixture tablet which shows no interaction. From the dissolution the formulation 91% shows highest percentage of drug release. The optimized formulation was packed in Alu-Alu blister and charged for stability study at 40°C/75%RH. Over a period of six months, it was noted that the formulation was stable with contaminants under control.

Keywords: Rabeprazole, PPI, GERD, Delayed release, Enteric coating.

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1. Introduction

The final stage of stomach acid secretion is carried out by the H+ -ATPase and K+ -ATPase, which are permanently blocked by proton pump inhibitors (PPIs). PPIs achieve this by passing through the parietal basement membrane and accumulating in the secretory canaliculus, where they become activated when the gastric acid pH is <4. They are then converted to the sulfenamide form and covalently bind the cysteine group in the proton pump, thereby irreversibly inhibiting acid secretion [1,2]. PPIs are benzimidazole derivatives, of which rabeprazole, omeprazole, and esomeprazole are the most frequently prescribed [3,4]. Amongst all Proton-Pump Inhibitors (PPIs), Rabeprazole is the most potent acid secretion inhibitor during first day of dosing (5). Rabeprazole is chemically 2-[[4-(3-methoxypropoxy)-3-methylpyridine-2-yl] methyl sulfinyl]-1H-benzimidazole(6) , mainly used for treatment of acidity by decreasing acid secretion through inhibiting especially H + /K+ /ATPase enzymatic system present on the secretary surface of gastric parietal cells (7,8) .Clinically, rabeprazole sodium is administered as delayed-release enteric coated tablets for the treatment of gastroesophageal reflux disease, duodenal ulcers and pathological hypersecretory conditions, including Zollinger-Ellison syndrome (9)as well as a high eradication rate of the microorganism Helicobacter pylori when associated with antimicrobial therapy.[10]The stability of rabeprazole sodium is function of pH; it is rapidly degraded in acid media, and is more stable under alkaline condition. (11) At acidic or neutral pH, rabeprazole is converted non-enzymatically primarily to thioetherrabeprazole, resulting in the discoloration of drugs in solution as well as in solid-state. Due to the pH sensitivity of drug in solution and solid-state, the selection of optimal pharmaceutical excipients with different functional groups is crucial to maximize drug stability in the development of a stable dosage form of rabeprazole. (12-15)Therefore exposure of Rabeprazole sodium to the acidic content of the stomach would lead to significant degradation of the drug and hence, reduced bioavailability. (16)

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. S uch preparations contain an alkaline core material comprising the active substance, a separating laye r and enteric coating layer.[17-19] Delayed drug release is commonly achieved by the application of an enteric coating on dosage forms such as tablets, capsules and multiparticulates. The main function of an enteric coating is to confer protection. It might be needed to avoid gastric mucosa irritation when exposed to certain drugs, such as non-steroidal, anti-inflammatory drugs (NSAIDs), or to avoid the degradation of acid-sensitive actives, such as enzymes, peptides or proton pump inhibitors (PPIs) in gastric juice. Protection can be easily provided with the application of polymeric coatings, which build films that are insoluble at acidic pH values. For more than 60 years EUDRAGIT® L 30 D-55, a fully synthetic (meth)acrylic copolymer that is soluble above pH 5.5, has been a widely used coating to confer gastric resistance.[20] The enteric coating of the tablets utilizes the pH differences of gastric pH 1-3 and intestinal pH 6- 8.[21]

The aim and objectives of the present study is to develop a pharmaceutically stable and robust 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.

2. Materials and methods

Rabeprazole sodium (Nifty Labs Pvt. Ltd., Hyderabad), Mannitol (DFE Pharma), Light magnesium oxide (Sudeep Pharma), Low substituted Hydroxy propyl cellulose (Ashland), Hydroxy propyl cellulose (Ashland), Ethyl cellulose (Colorcon Asia pvt ltd., India), Hypromellose phthalate (Shin Etsu chemical co. Ltd.), Isopropyl alcohol (Finar Chemical Pvt. Ltd., Gujarat), Methylene dichloride (Finar Chemical Pvt. Ltd., Gujarat),Ethanol (Finar Chemical Pvt. Ltd., Gujarat) and Magnesium stearate (Valtris). All other reagents were of analytical grade and they were used as received from manufacturer or supplier.

Experimental

2.1 Preformulation studies

The goal of pre-formulation research is to compile a database of knowledge about the drug material that will serve as a set of guidelines for carrying out comprehensive formulation design. Pre-formulation investigations are intended to recognize the physicochemical characteristics of drug components and excipients that may affect the formulation design, manufacturing process, and biopharmaceutical properties of the finished product. [22,23, 24]

2.2 Drug- excipients compatibility study

Sample No.	Sample details	Drug + Excipient ratio
1.	API	NA
2.	API + Mannitol	1:1
3.	API + light magnesium oxide	1:1
4.	API + low substituted hydroxy propyl cellulose	1:1
5.	API + Hydroxypropylcellulose	1:1
6.	API + Magnesium stearate	1:0.5
7.	API + Ethyl cellulose	1:0.25
8.	API + Hypromellose phthalate	1:1
9.	API + Talc	1:0.25
10.	API + Titanium oxide	1:0.25
11.	API + Ferric oxide yellow	1:.25

Table 1: Drug-Compatibility Study

2.3 Formulation batches

Different formulation batches were formulated containing Rabeprazole as the active ingredient along with other suitable ingredients as tabulated below in table 1.

PRELIMINARY TRIAL FORMULATION

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12* (RB)	F13* (RB)
Intragranular ingredients													
Rabeprazole sodium	20	20	20	20	20	20	20	20	20	20	20	20	20
Mannitol	40	39	37.5	37	36.5	36	36	36	36	36	36	36	36
Light magnesium oxide	67	67	67	67	67	67	67	67	67	67	67	67	67
L-HPC	3	3	3	3.5	4	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5
Binder ingredients													
HPC	4.5	5.5	7	7	7	7	7	7	7	7	7	7	7
Ethanol	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.
Extragranular ingredients													
L-HPC	3	3	3	3	3	3	3	3	3	3	3	3	3
Magnesium stearate	2.50	2.50	2.50	2.50	2.50	2.50	2.50	2.50	2.50	2.50	2.50	2.50	2.50
Total weight	**140**	**140**	**140**	**140**	**140**	**140**	**140**	**140**	**140**	**140**	**140**	**140**	**140**
Seal coating													
Ethyl cellulose	NA	NA	NA	NA	NA	NA	1	1.25	1.17	1.17	1.17	1.17	1.17
Light magnesium oxide							2.33	2.33	2.33	2.33	2.33	2.33	2.33
Ethanol							Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.
Total weight							**147**	**145.6**	**144.2**	**144.2**	**144.2**	**144.2**	**144.2**
Enteric coating													
Hypromellose phthalate	NA	NA	NA	NA	NA	NA	NA	NA	19.18	19.18	19.18	19.18	19.18
Myvacet									1.91	2.30	2.18	2.18	2.18
Talc									1.15	1.15	1.15	1.15	1.15
Carnauba wax									0.03	0.03	0.03	0.03	0.03
Titanium oxide									2.56	2.56	2.56	2.56	2.56
Ferric oxide yellow									0.77	0.77	0.77	0.77	0.77
IPA									Q.S.	Q.S.	Q.S.	Q.S.	Q.S.
MDC									Q.S.	Q.S.	Q.S.	Q.S.	Q.S.
Total weight									**158.62**	**161.50**	**164.38**	**164.38**	**164.38**

Table 2: Preliminary trial formulation

2.5 Preparation of granulation (F1- F6)

In **step 1**, The intragranular materials are Rabeprazole Sodium and light magnesium oxide co- sifted through sieve # 40 and mixed in the dry state in RMG (Rapid mixer granulator) for 5mins at slow speed of impeller. Co- sift Mannitol and L-HPC through sieve # 40 and loaded these materials along with the above materials in same granulator then mixed it for 10mins at slow speed of impeller. In **step 2**, weighed Hydroxypropyl cellulose was completely dissolved in absolute alcohol with continuous stirring. This binding solution was slowly added to pre-mixed intra-granular material in RMG mentioned above and mixed at 75 RPM of Impeller speed for 5 minutes. Then prepared wet mass was dried in Fluidized Bed Dryer (FBD-Retsch® TG-200) at inlet temperature of 50ºC-60ºC and outlet temperature of 40ºC-45ºC for approximately 50 minutes, until LOD not more than 2.0% w/w at 105ºC for 4 minutes was achieved. Dried granules were sifted through multi-mill (Cadmill®, Cadmach Machinery Co. Ltd.) equipped with 1.5-5.0 mm screen at 500-600 RPM and collected in polyethylene lined drum.

The dried milled granules were transferred to double cone blender and extra-granular material were added to it and mixed for 10 minutes in same blender.

In **Step 3**, The prelubricated blend was ready for lubrication. For lubrication magnesium stearate was added in double cone blender and mixed at 10 RPM for 5 minutes. Sampling was done to check the uniformity of the blend. The final blend was compressed into core tablet using round shaped plain standard concave die-punches set of 9/32" dimension in rotary tablet press (RIMEK®, India).

2.6 Procedure for preparation of sub-coating of the core tablets

Rabeprazole sodium is acid labile, and seal coating serves as a separating layer to stop interactions with acidic enteric coating materials. Materials for seal coatings were distributed as mentioned in Table 2 and dissolved in pure alcohol. This was agitated for 45 minutes until a homogenous suspension was achieved, which was then filtered through a 60# screen. In accordance with predetermined guidelines, seal coating of core tablets was carried out in a 24" auto coater (Ganson Auto Coater® GAC-275, India), as mentioned in Table 4.[25,26]

2.7 Procedure for preparation of enteric coating of the sub-coated tablets

The temperature of the confining bed at which the subcoated tablets are loaded must be between 38 and 40 degrees Celsius. The enteric coating dispersion utilising HPMC-P is then sprayed over the subcoated tablets in an amount greater than 8%, according to the enteric coating percentage supplied.[25,26] Due to Rabeprazole's instability at stomach pH, enteric coating was applied to the tablet's seal coating to prevent Rabeprazole from being released into acidic medium. For enteric coating, accurately weighed Hypromellose Phthalate and myvacet as mentioned in Table 2 was slowly added into Methylene dichloride (MDC) and mixed for 30 minutes. Then dissolved talc, titanium oxide, ferric oxide yellow color in IPA (Isopropyl alcohol)and mixed for 15 min Seal coated tablets were preheated in coating pan for 10 minutes at 40ºC - 45ºC. The tablets were coated in 24" auto coater (Ganson Auto Coater® GAC-275, India) to achieve 14% weight gain. After enteric coating (up to 14% weight gain), average weight gain and average thickness was checked for 20 tablets. Enteric coated tablets were dried to achieve constant weight gain.[24,25,26]

2.8 Evaluation of lubricated blend of formulation

2.8.1 Pre compression studies

Pre compression parameters such as angle of repose, bulk and tapped densities, compressibility index, and Hausner ratio was done according to the procedure stated for characterization of Rabeprazole delayed release tablets.[27,28]

2.8.2 Post compression studies

The tablet compacts were tested for Description, Thickness, Hardness, Friability, Weight variation, Uniformity of drug content, In-vitro drug release of enteric coated tablets, Accelerated Stability Studies.[29,30]

2.9 Stability Studies

Final optimized formulation was packed in Alu-Alu blister (cold formed foil: made up of 25 micron OPA Film /Adhesive/45 micron Aluminium foil/ Adhesive/60 micron PVC film) and charged for accelerated stability study for 6 months at 40°±2°C and 75%±5% RH 15 in stability chamber (Thermolab ®, India).The robustness of the well-designed Rabeprazole sodium delayed release tablet was performed in accordance with the ICH guidelines.[30]

3. Results and Discussions

Present study was done on enteric coating tablets with different formulation F1 to F9. Rabeprazole sodium were prepared by wet granulation method using different concentration of, mannitol, L-HPC, HPC, magnesium stearate, ethyl cellulose and hypromellose phthalate were used as enteric coating polymer, which prevent drug degradation from gastric pH and release in intestinal pH.

3.1 Preformulation studies

- **Description**

S.No.	Tests	Results
1.	Colour	White or slightly yellowish- white
2.	Odor	Odorless
3.	Taste	Tasteless
4.	Nature	Crystalline

Table 3 : Physicochemical parameter of Rabeprazole sodium

- **Related substance**

Impurities	Specification
Impurity A	NMT 0.15%
Unspecified impurities	NMT 0.10%
Total impurities	NMT 0.5%

3.2 Drug- excipient compatibility study

S.No.	Composition	Observation at various storage conditions and durations		
		Initial	40ºC/75% RH	
			2W	4W
1.	API	Off- white	NC	NC
2.	API + Mannitol	Off- white	NC	NC
3.	API + light magnesium oxide	Off- white	NC	NC
4.	API + low substituted hydroxy propyl cellulose	Off- white	NC	NC
5.	API + Hydroxy propyl cellulose	Off- white	NC	NC
6.	API + Magnesium stearate	Off- white	NC	NC
7.	API + Ethyl cellulose	Off- white	NC	NC
8.	API + HPMC 5 cps	Off- white	NC	NC
9.	API + Triethyl citrate	Off- white	NC	NC
10.	API + Hypromellose phthalate	Off- white	NC	NC
11.	API + Eudragit	Off- white	NC	NC
12.	API + Talc	Off- white	NC	NC
13.	API + Titanium oxide	Off- white	NC	NC
14.	API + Diacetylated monoglycerides	Off- white	NC	NC
15.	API + Ferric oxide yellow	Off- white	NC	NC
17.	API + Crospovidone	Off- white	NC	NC
18.	API + Sodium hydroxide	Off- white	NC	NC

*NC = No change **Table no. 4:** Drug- excipient compatibility study

3.3 Pre-compression studies

Formulation	Blend Property					
	B.D. (g/ml)	T.D. (g/ml)	C.I. (%)	H.R.	Angle of repose	Property
F1	0.73	0.65	26.12	1.35	42	Poor
F2	0.712	0.869	18.15	1.19	35	Fair
F3	0.458	0.715	19.22	1.25	33	Fair
F4	0.503	0.601	24.30	1.28	38	Passable
F5	0.540	0.686	22.56	1.32	40	Passable
F6	0.564	0.654	23.22	1.34	36	Passable
F7	0.324	0.372	12.23	1.16	25	Good
F8	0.358	0.385	14.55	1.12	27	Good
F9	0.315	0.390	15.31	1.18	30	Good
F10	0.322	0.410	12.45	1.12	26	Good
F11	0.325	0.386	14.21	1.16	26	Good
F12	0.310	0.342	11.33	1.14	28	Good
F13	0.324	0.356	11.67	1.12	27	Good

Table 5: Flow properties of different formulations

3.4 Post Compression studies

Batch no.	Thickness (mm)	Friability (%)	Hardness (N)	Disintegration (min)	Weight Variation
F1	3.2±0.2	Pass	44-52	18-20	138-140
F2	3.2±0.2	Pass	43-50	16-18	136-142
F3	3.2±0.2	Pass	46-53	15-16	139-143
F4	3.2±0.2	Pass	40-50	12-16	138-142
F5	3.2±0.2	Pass	42-50	13-15	138-141
F6	3.2±0.2	Pass	47-52	12-15	139-142

Table 6: Physical evaluation of core tablet

Batch no.	Weight (mg)	Thickness(mm)	Disintegration Time (min)
F7	146 ±2	3.25±0.2	14-15
F8	145.6 ±2	3.25±0.2	13-15
F9	144.2 ± 2	3.25±0.2	12-14

Table 7: Physical evaluation of Seal coated tablets

Batch no.	Weight (mg)	Thickness (mm)	Disintegration time	
			0.1N HCL (2 hrs)	pH 6.8 phosphate buffer (45min)
F10	**158.62**	3.40±2	Fail	ND
F11	161	3.40±2	Pass	20-30
F12	164.38	3.40±2	Pass	28-32
F13	164.38	3.40±2	Pass	30-35

Table 8: Physical evaluation after enteric coating

3.5 In-Vitro Dissolution:

Media	Buffer pH 6.8		Buffer pH 7.4	
Batch no. / Time (min)	Test (F11)	Reference (Pariet)	Test (F11)	Reference (Pariet)
0	0	0	0	0
10	67.7	62.1	80.1	78.2
15	43.3	42.7	71.5	68.0
20	31.5	31	60.5	58.4
25	20.0	21.7	51.1	50.3
30	13.6	15.3	45.9	45.0

Table 9: In-Vitro Dissolution of Core tablets

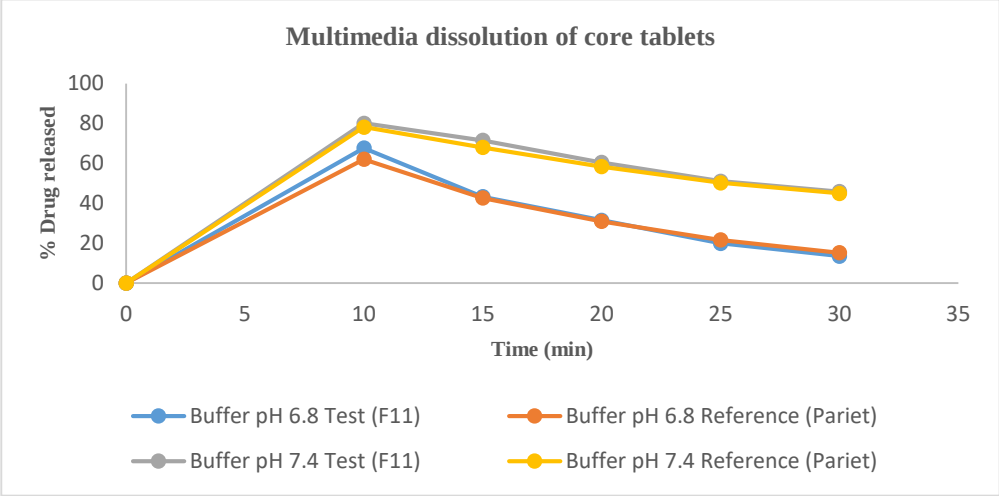

Fig 2: Comparision of In- vitro drug release profile of core tablet of optimized formulations (F11) and reference drug.

Media	Buffer pH 6.8		Buffer pH 7.4	
Batch no. / Time (min)	Test (F11)	Reference (Pariet)	Test (F11)	Reference (Pariet)
0	0	0	0	0
10	60.3	52.6	80.5	79.4
15	38.1	33.9	68.9	68.5
20	11.7	12.1	43.1	43.6
25	3.5	4.2	27.5	28.4

Table 10: In-Vitro Dissolution of Seal Coated tablets

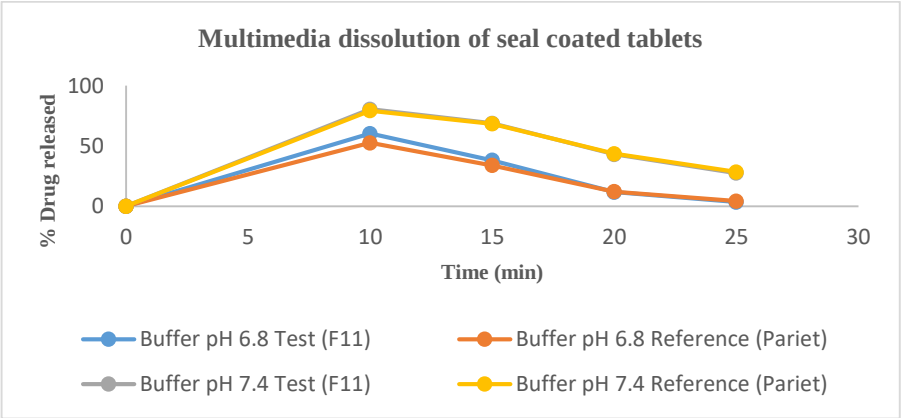

Fig 3: Comparision of In- vitro drug release profile of seal coated tablet of optimized formulations (F11) and reference drug.

Media	0.1 N HCL followed by pH 6.8 buffer		0.1 N HCL followed by pH 7.4 buffer	
Batch no.	Test (F11)	Reference (Pariet)	Test (F11)	Reference (Pariet)
Time (min)				
0	0	0	0	0
130	10.9	6.4	12.1	6.7
135	34.3	27.7	28.5	21.9
150	46.2	38.8	57.1	53.8
165	65.8	72.5	68.5	67.8
180	85.2	89.4	88.5	90.2

Table no. 17: In-Vitro Dissolution of Enteric Coated tablets

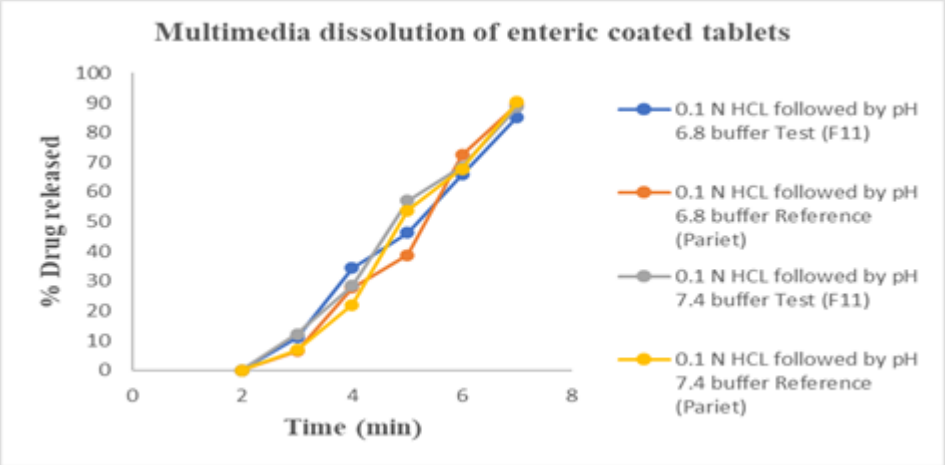

Fig 4: Comparision of In- vitro drug release profile of enteric coated tablet of optimized formulations (F11) and reference drug.

Conclusion

The main challenge in the formulation of Rabeprazole tablets was the degradation of Rabeprazole upon exposure to acidic environment which results into high impurity level. Thus, to prevent exposure of Rabeprazole in gastric acidic environment enteric coating was done and to prevent interaction between Rabeprazole and acidic enteric coating material, seal coating was done over the core tablet.This research is oriented to design delayed- release dosage form of Rabeprazole sodium as this API available in market with higher impurity limit (NMT 1%) noted as per ICH Q3B guideline. Now, we are using API which is under pharmacopoeial grade according to Ph. Eur.(CEP)i.e., an API's Certificate of Suitability and the impurity limit can be controlled as compared to previous impurity limit of market available API. As finished product impurity specification required as per ICH guideline. Hence we are developing stable and robust product with respect to impurity profile. Among all 11 formulations, formulation F11 passed in all IPQC parameters and it showed similar disintegration and dissolution profile as shown by Pariet®. Formulation F11 did not release Rabeprazole in gastric acidic pH and released 91% of Rabeprazole in 45 minutes at intestinal alkaline pH. Stability study is carried out for 3 months at 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. In order to build the formulation and conduct further research necessary for a successful product launch, the identified formula must be used.

List of abbreviations

PPIs- Proton pump inhibitors

NSAIDs- Non-steroidal,anti-inflammatory drugs.

L-HPC- Low substituted hydroxypropylcellulose

HPC- Hydroxy propyl cellulose

API- Active pharmaceutical ingredient

IPA- Isopropyl alcohol

MDC- Methylene dichloride

RB - Reproducible batch

NA- Not applicable

QS- Quantity sufficient

RMG - Rapid mixer granulator

FBD- Fluidized Bed Dryer

GERD- Gastrooesophageal reflux disease

NC- No change

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