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Formulation and evaluation of rabeprazole sodium delayed release tablets

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ABSTRACT

The main purpose of this work is to develop delayed release stable tablet formulation of Rabeprozole sodium by direct compression and wet granulation method and enteric coating of tablets. All enteric coated tablets are delayed release tablets but all delayed release tablets are not enteric coated tablets. The present work aims to avoid degradation of drug in acidic environment of stomach. Preformulation studies like angle of repose, bulk density, tapped density, Carr's index, hausner's ratios, and drug/excipient compatibility study were conducted, five batches for direct compression and one batch for wet granulation were formulated and evaluated for hardness, friability, weight variation, drug content, disintegration and in-vitro dissolution. Among the six uncoated tablet batches F_5 and F_6 obtained good drug release profile compared to innovator. So batches F_5 and F_6 were selected for further steps of formulation i.e., sub coating and enteric coating. After enteric coated batches F_5 & F_6 were evaluated for acid resistance test and in-vitro dissolution test compared with innovator (ACIPHEX) found to be suitable for Rabeprazole sodium delayed release tablet. In case of stability studies, were conducted at 40^{o}C/75% RH for 3 months. Impurities of these two batches F_5 & F_6, among these f_6 has shown increased amount of impurities than F_5. Based on the above data f_5 (Direct compression) batch was considered to be best formulation.

Key words: delayed release tablet, direct compression method, enteric coating tablet, wet granulation, Rabeprazole sodium.

INTRODUCTION

Rabeprazole sodium drug is a sodium salt of 2-((4-(3-methoxypropoxy)-3-methylpyridin-2-yl) methylsulfinyl)-1*H*-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 [1]. Enteric coated tablets are solid unit dosage forms meant for oral administration and are designed to bypass the stomach [2] and release the

drug in small intestine. Rabeprazole sodium delayed release tablet are prepared by direct compression and wet granulation method and coated using polymers like OPadryOY-C-7240 clear and Instacoat EN-HPMCP yellow to delay the release. Rabeprazole used to treat duodenal and gastric ulcers and it is also used for the treatment of gastric oesophageal reflux disease [3]. Its half life is around 1-2 hrs. For once in day administration. The delayed release tablet is intended to release the drug after some delay or after tablet pass GI Tract. All enteric coated tablets are delayed release tablet but all delayed release tablet are not enteric coated tablets.

Delayed release dosage form is best formulations which are used for drugs that are destroyed in 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 & enteric coating layer [4] .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 METHODS

Rabeprazole sodium was obtained as gift sample from Hetro drugs. Crospovidone, silicondioxide, magnesium stearate, Mannitol, L-HPCLHII, Instacoat (EN-HPMCP) A34G00031, Opadry OY-C-7240 Clear were obtained as gift sample from apex pharmaceutical, Chennai.

Preparation of core Rabeprazole sodium tablets:

Direct compression method [5,6,7]

The enteric coating tablet was prepared by direct compression method. The weighed quantity of Rabeprazole sodium, mannitol, granular magnesium oxide and L-HPC LHII were sieved through 40 # size. The above shifted materials were lubricated with crospovidone, syloid and magnesium stearate for 5min octagonal blender. These blended materials were ready for compression. The different formulas were given in (Table 1).

Table 1: Formula for preparation of core tablets by direct compression method

S. No	INGREDIENTS	Various Formulation Trials (mg/tab)				
		F1	F2	F3	F4	F5
1.	Rabeprazole sodium	20	20	20	20	20
2.	Mannitol	83.5	68.5	68.0	47.5	37.0
3.	Granular magnesium oxide	20	20	20	20	20
4.	L-HPCLHII	10	10	10	10	10
5.	Crospovidone	15	30	30	30	30
6.	Silicon dioxide(syloid Z44EP)	_	_	0.5	1.0	1.5
7.	Magnesium stearate	1.5	1.5	1.5	1.5	1.5
Total weight of the core tablet(mg)		150	150	150	150	150

Wet granulation Method:

All the ingredients including drugs and other excipients are mixed using cad mach miller except lubricant, then blender solution is added and passed through suitable sieve and granules are allowed to dry. Then lubricant is added to the dried granules and as sifted then compressed into a tablet using rotary punching machine (12 stations). The formula was given in (Table no: 2)

Table 2: Formula for preparation of core tablets by wet granulation method

S.NO	INGREDIENTS	Trial Batch F (mg/tab)
1.	Rabeprazole sodium	20
2.	Mannitol	37
3.	Granular magnesium oxide	50
4.	L-HPCLHII	10
5.	Crospovidone	30
6.	Silicon dioxide (syloid Z44EP)	1.5
7.	Magnesium stearate	1.5
Total weight of the core tablet(mg)		150

From the above formulas F_5 for direct compression and F_6 for wet granulation batches have been selected for sub coating and enteric coating process due to its specification.

Procedure for preparation of sub coating of the core tablets:

Sub coating of the compressed tablets is achieved by standard coating pan technique. Coating solutions of opadryOY-C-7240 prepared separately with plasticizers in 5 % concentrations respectively. Thus solutions are applied over tablets using spray gun at appropriate pressure. The coated tablets are dried at 35-40^{o}c for 10min .1%, 2%, 3%, and 4% of sub coating percentage has been given to the core tablet.

Procedure for preparation of enteric coating of the sub coated tablets:

The sub coated tablets are loaded into containing bed is warmed till the temperature reaches to 38^0 C - 40^{0}C. Then spray gun is switched on to spray the enteric coating dispersion using INSTACOAT EN-HPMCP Yellow in more than 12% of enteric coating percentage has been given to the sub coated tablets. The formula given in (Table no.3)

Table 3: Different combinations of sub coating & enteric coating percentages

Trial batches	Sub coating (%) + Enteric coating (%)
F_5A	1+22
F_5B	2+20
F_5C	3+18
F_5D	4+16
F_6A	2+12

Preformulation studies [8, 9, 10]

Angle of Repose

Angle of repose is the maximum angle that can be obtained between the free standing surfaces of the powder heap and the horizontal plane. It is a characteristic related to the interparticulate friction or resistance to movement between particles. The method used to find the angle of repose is to pour the powder in the form of a conical heap on a flat surface and measure the inclined angled with the horizontal pile.

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

Where h = height of the heap

r = radius of the heap

Bulk density
Bulk density is given by the mass "m" of the powder occupying a known volume "v" according to the relationship

$$Pb = (m/v)\ g/cc$$

It depends on particle size, shape, tendency of particle to adhere.

Tapped density
Weighed powder sample was transferred to a graduated cylinder and was placed on tapped density apparatus, was operated for a fixed number of taps (100). It is ratio of weight of sample to tapped volume.

$$Tapped\ density = \frac{\text{mass}}{\text{Tapped volume}}$$

Carr's index
Based on the apparent bulk density and the tapped density, the percentage compressibility of the bulk drug was determined by using the following formula.

$$\%\ Compressibility = \frac{\text{tapped desity} - \text{bulkdensity}}{\text{tapped density}} * 100$$

Hausner's ratio
The ratio of tapped density to bulk density of the powder is called the hausner ratio.

Drug/Excipient compatibility study
The objective of drug/excipient compatibility considerations and practical studies is to delineate, as quick as possible, real and possible interactions between potential formulation excipients and the active pharmaceutical excipient .Homogeneous mixtures of drug and excipients were prepared and filled in glass vials and self-seal LDPE (Low density Poly Ethylene) bags. The glass vials were maintained at 60± 2^0 C for 2 weeks. Those packed LDPE bags were maintained at 40±2^0 C/75± 5% RH for 1 month. Controlled conditions (2-8^0 C) maintained for comparison purpose.

Evaluation of core tablets:
Hardness test [11]
Pfizer hardness tester was used for the determination of hardness of the tablets.

Thickness and diameter:
Thickness and diameter of the tablet were recorded during the process of compression using vernier calipers.

Friability:
10 tablets were accurately weighed and placed in the friabilator (VEEGO-tablet friabilator) and operated for 100 revolutions. The tablet were dedusted and reweighed. The tablets that loose less than 1% weight were considered to compliant.

Weight variation:
10 tablets were selected randomly from the 10% and weighed individually to check for weight variation.

Disintegration test [12]
Tablets were taken and introduced one tablet in each tube of disintegration apparatus and placed in 1 liter beaker and the time of disintegration was recorded. The study was done at room temperature.

Dissolution studies [13]
The *in-vitro* dissolution study was carried out in the USP dissolution (Electro lab) paddle type. 900ml of the dissolution medium was taken and the temperature was maintained at 37±0.5^{o}c. The speed of paddle was set at 100rpm. Sampling was done at regular intervals. For each sample 10ml of the dissolution medium was withdrawn and same amount was replaced. The sample was filtered and diluted with dissolution medium and then analyzed in UV-spectrophotometer. The absorbance was measured at 352 nm and % drug release was calculated.

In-vitro drug release for enteric coated tablets
Drug release studies were carried out using a USP type II dissolution test apparatus at 100rpm for 2hr in 0.1N HCL (900ml) maintained at 37±0.5^{o}c. 10ml of sample was taken and sample was analyzed using UV-spectrophotometer at 260nm. Then the dissolution medium was replaced with 0.6M tris buffer, pH 8.0 (900ml) and tested for drug release for 1 hr at same temperature and rotation speed. After 10, 20, 30, and 45mts, 10ml of the samples were taken out and 10ml volume of fresh tris buffer pH 8.0 was added to kept volume of dissolution medium constant and sample was analyzed using UV spectrophotometer at 284nm.

Accelerated stability studies of the optimized batch [14]
In order to determine the change in evaluation parameters and in-vitro release profile on storage, stability study of optimized batch F_5 D and F_6 A was carried out at accelerated storage condition at temperature 40^{o} C/75%RH in a humidity chamber for 3 months. Sample were withdrawn after one week interval and evaluated for change in in-vitro drug release pattern, impurities.

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 tablets (Table no.4).Flow properties of powder, resistance to particle to particle movement can be judged by using angle of repose. This measurement gives qualitative and quantitative assessment of internal cohesive and frictional force under low level of externals. Load as might be applied in mixing and tablet compression. Values for angle of repose were found in the range of 26.1 - 44.9. The hausner's ratio of 0.45 – 0.64. The Carr's index ration was in the range of 7.46 - 25.0 & the tapped density ratio was in the range of 0.60 – 0.67. The prepared blends F_3, F_4, F_5 &F_6 showed good flow properties and since no interaction has occurred between the drug and all other excipients, the selected excipients were found to be compatible with drug (Table no.5)

Table 4: Micromeritic properties of API

S. No	Characteristics	Results
1	Description	Off-white to pale yellow colored amorphous powder
2	Bulk density	0.53gm/ml
3	Tapped density	0.69gm/ml
4	Carr's index	32.1%
5	Hausner's ratio	4.17
6	Angle of repose	36

Table 5: Drug/ exicipients Compatibility study

S. No	Composition Details	D:E ratio	Observation at various storage conditions and durations						
				40/75% RH		60± 2^0 C		2-8^0 C	
			Initial	2W	4W	1W	2W	2W	3W
1	Rabeprazole Sodium (D)		Off White	NC	NC	NC	NC	NC	NC
2	D + Mannitol	1:10	Off White	NC	NC	NC	NC	NC	NC
3	D + MgO	1:10	Off White	NC	NC	NC	NC	NC	NC
4	D + L-HPC LH11	1:1	Off White	NC	NC	NC	NC	NC	NC
5	D + Crospovidone	1:1	Off White	NC	NC	NC	NC	NC	NC
6	D + Syloid 244FP	1:0.25	Off White	NC	NC	NC	NC	NC	NC
7	D + Mg.Stearate	1:0.25	Off White	NC	NC	NC	NC	NC	NC
8	D + Opadry OY-C-7240	1:1	Off White	NC	NC	NC	NC	NC	NC
9	D + Instacoat EN-HPMCP A34G00031 Yellow	1:1	Yellow	NC	NC	NC	NC	NC	NC

Table 6: Physical parameters of Rabeprazole sodium uncoated tablets

Trial batch	Average wt(mg)	Thickness (m)	Hardness (kp)	Friability	Disintegration Time (min)
F1	151.2	4.0 - 4.1	6 – 8	0.75	12 – 13
F2	149.5	4.0 - 4.1	6 – 8	0.70	8 – 9
F3	150.6	4.0 - 4.1	6 – 8	0.64	6 – 7
F4	151.4	3.8 - 3.9	5 – 7	0.63	4 – 5
F5	150.0	3.5- 3.6	5 – 7	0.69	2 – 3
F6	150.2	3.5 - 3.6	9 – 11	0.56	5 – 6

Evaluation of core tablets:

The core tablet was evaluated for its thickness, friability, hardness, weight variation, and disintegration time. From the result it was found to be formulation F_1, F_2, F_3, F_4 were failed to comply with specification. Formulation F_5 (direct compression) and F_6 (Wet Granulation) batch shown that all parameters complies with the limit. The result shown in (Table no. 6)

By comparing the dissolution profile of all the individual and final batch core tablets with the innovator, the trial batch F_5 (direct compression method) and trial batch F_6 (wet granulation) has been found to show good drug releases (Table no.7) (fig.1)

Table 7: Dissolution test of core tablets

Time interval	Innovator (AcipHex)	Trial batch formulations					
		F1	F2	F3	F4	F5	F6
10	88	91	88	95	90	89	90
20	92	97	93	99	96	93	97
30	96	95	95	97	94	97	99
45	93	90	95	91	90	91	91

Fig 1: Dissolution profile for core tablet

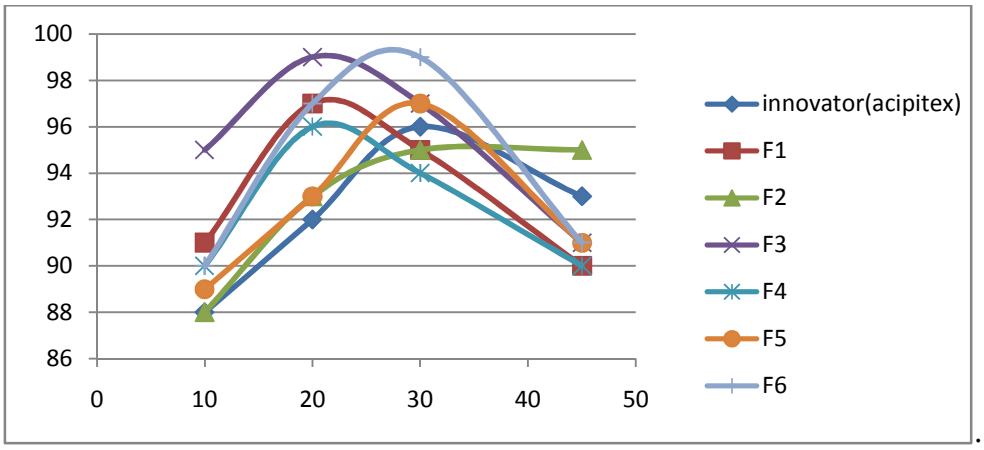


Table 8: Acid resistance Test for 2 hours

S. No	Trial Batches	% S,C+ %E.C	Result	Remarks
1	F_5A	1+8	Failed	Tablet Opened
2	F_5B	2+8	Failed	Tablet opened
3	F_5C	2+10	Failed	Tablet opened
4	F_5D	2+12	Passed	Tablet remained intact
5	F_6A	4+16	Passed	Tablet remained intact

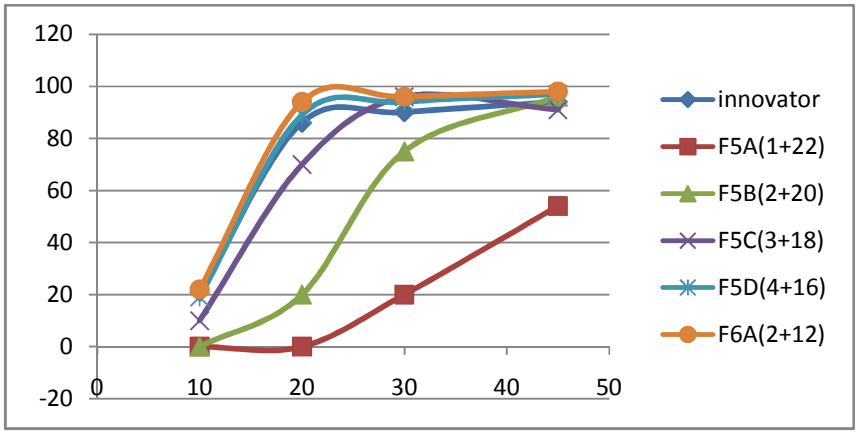
Evaluation of enteric coated tablets:

Normally 2% is the minimum percentage for the sub coating and 12% is the minimum percentage for enteric coating that has to be applied to get a delayed release. In the evaluation of enteric coated tablets it was found that F_5A, F_5B, F_5C batches are failed because of low acid resistance in 0.1N Hcl, but batches F_5D (2%SC – 12% EC) and F_6A (4% SC – 16% EC) was found to have good acid resistance in 0.1N Hcl (Table No 8). *In-vitro* drug release for enteric coating tablets of selected batches F_5A, F_5B, F_5C, F_5D (Direct Compression) and F_6A (Wet Granulation) enteric coated tablets with that of the innovator (AcipHex).The dissolution profile of the trial batch F_5D (direct compression method) and F_6A (wet granulation method) have been found to show drug releases of 96% &97 %(Table No 9) (Fig No:2).

Table 9: Dissolution test for Enteric coated tablets

Time interval	Innovator (AcipHex)	F5A 1+22	F5B 2+20	F5C 3+18	F5D 4+16	F6A 2+12
10	21	0	0	10	19	22
20	86	0	20	70	89	94
30	90	20	75	96	94	96
45	94	54	96	91	97	98

Fig 2: Dissolution profile for Enteric Coating Tablet

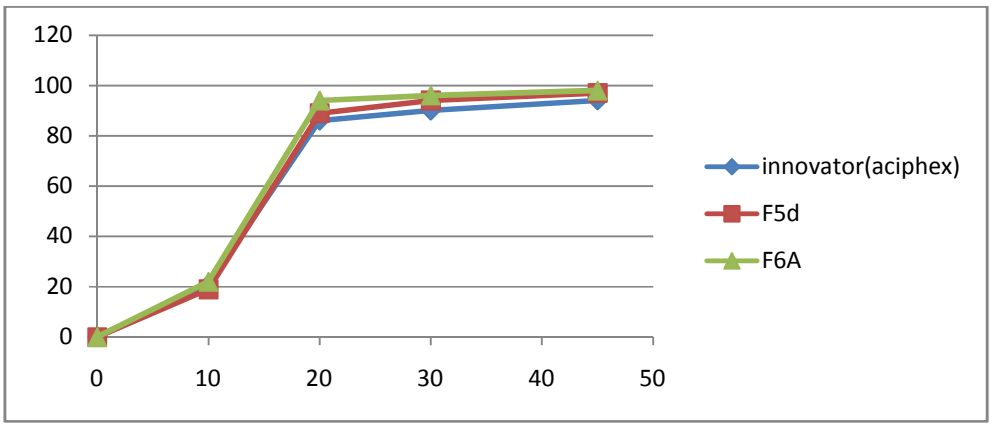


After dissolution profiles of enteric coated tablets, the best formulation of trial batches such as F_5 D and F_6A compared with innovator in pH 8.0 buffer along with standard deviations were calculated(Table No.10)(Fig 3). So F_5 D and F_6A were considered to be carried out stability studies.

Table 10: Dissolution profiles of best formulation with innovator along with standard deviation in pH 8.0 tris buffer

Time intervals	AcipHex DR%± SD	F_5D DR%± SD	F_6 A DR%± SD
10	21±0.56	19±0.96	22±1.5
20	86±0.95	89±1.25	94±0.6
30	90±0.70	94±0.75	96±0.7
45	94±1.0	97±0.45	98±1.0

Fig. 3: Dissolution profiles of best formulation with innovator along with standard deviation in pH 8.0 tris buffer



Finally Rabeprazole sodium DR tablets batch F_5D &F_6A kept for its stability at different storage condition at 40^o C/75%RH for 3 months of stability studies, a very minute difference have been found between those values. For F_6A batch has shown increased amount of impurities than F_5D batch indicating a stability problem in F_6A batch (Table No 11). Based on the above stability

data F_5D batch prepared by direct compression method has been selected as the optimized formulation (Table No 12)

Table 11: Stability test data of F_5D & F_6A Batches

Test	F_5D Direct compression				F_6D Wet granulation			
	Initial	1m	2m	3m	Initial	1m	2m	3m
Acid resistance (%)	100.9	100.1	99.9	99.2	100.6	100.0	99.7	98.9
Impurities (%)	0.562	0.634	0.656	0.745	0.596	0.692	0.796	1.06
% Cumulative drug release	100	99.8	99.0	98.5	99	98.6	98.0	97.2

Table 12: Formula for preparation of Enteric coated tablets by Direct compression method

S.NO	INGREDIENTS	Trial Batch F (mg/tab)
1.	Rabeprazole sodium	20
2.	Mannitol	37
3.	Granular magnesium oxide	50
4.	L-HPCLHII	10
5.	Crospovidone	30
6.	Silicon dioxide (syloid Z44EP)	1.5
7.	Magnesium stearate	1.5
Total weight of the core tablet(mg)		150
8	Sub Coating (Opadry OY-C-7240 Clear)	4%
9	Enteric Coating(Instacoat EN-HPMCP) A34G00031 Yellow	16%
Final weight of the tablet		170mg

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, Instacoat EN-HPMCP A34G00031 Yellow 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.

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