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Formulation, characterization and evaluation of sustained release tablet of rabeprazole sodium

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ABSTRACT

The main aim of the work is to develop a stable, pharmaceutical equivalent and robust, sustained release tablets of Rabeprazole sodium. This is a proton pump inhibitor which is used in the treatment of Gastric and duodenal ulcer. To achieve this goal, various prototype trials were taken and evaluated with respect to the various quality parameters such as bulk density, sieve analysis, drug uniformity, and dissolution. Rabeprazole sodium is highly acid labile and presents many formulation challenges and to protect it from acidic environment of the stomach an enteric coated tablet formulation is tried in the present study. Rabeprazole sodium sustained release tablets (20mg) were developed by changes of Copovidone, Crospovidone HPMC K 15 M, Magnesium oxide, Methylparaben and Mannitol SD 200 of all the trials. From the dissolution the formulation F-VII shows highest percentage of drug release. The F-VII was found to respectively formulation compared to innovator product. Hence these two products were considered similar and comparable. The tablets were prepared by direct compression method. F-VII was found to be best formulation compared to other formulations and that profile matching the innovator product. Further optimized formulation was coated with varying the compositions of seal coating and enteric coating.

Keywords: Rabeprazole sodium, Crospovidone, direct compression method

INTRODUCTION

Oral route is the most acceptable route of drug administration among all routes that have been explored for the systemic delivery of drug via various pharmaceutical products of different dosage form. Solid medicaments may be administered orally as powders, pills, cachets, capsules or tablets. These dosage forms contain a quantity of drug which is given as a single unit and they are known collectively as solid unit dosage forms, even in the case of sustained action preparations which, technically, contain the equivalent of several normal doses of drug[1]. Tablets and capsules, on the other hand, currently account for well over two third of the total number and cost of medicines produced all over the world[2].

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Tablets are solid dosage forms usually obtained by single or multiple compressions of powders or granules. In certain cases tablets may be obtained by moulding or extrusion techniques. They are uncoated or coated. Tablets are normally right circular solid cylinders, the end surfaces of which are flat or convex and the edges of which may be beveled. They may have lines or break-marks (scoring), symbols or other markings. Tablets containing active ingredients having a narrow therapeutic window should generally not be presented with break-marks for subdivision. Non-functional break-marks should be avoided. Tablets contain one or more active ingredients[3].

A sustained-release dosage form is designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. These systems try to mimic zero-order release by providing drug in a slow first-order fashion. The most commonly used pharmaceutical sustained release solid dosage forms today include tablets, capsules, granules, pellets[3].

Rabeprazole sodium is an antiulcer drug in the class of proton pump inhibitors. It is a prodrug - in the acid environment of the parietal cells it turns0 into active sulphenamide form. Rabeprazole inhibits the H+, K+ATPase of the coating gastric cells and dose dependent oppresses basal and stimulated gastric acid secretion. Rabeprazole Sodium prevents the production of acid in the stomach. It reduces symptoms and prevents injury to the esophagus or stomach in patients with gastroesophageal reflux disease (GERD) or ulcers. Rabeprazole is also useful in conditions that produce too much stomach acid such as Zollinger-Ellison syndrome[4,5,6].

MATERIALS & METHODS

Rabeprazole Sodium was obtained as a gift sample from Safe Formulations, Gollapadu, Guntur. Crospovidone was procured from Atulya Chemicals, Mumbai. Methacrylic Acid procured from Shree Mahalaxmi Chemicals, Mumbai. Sodium Carbonate Anhydrous was procured from Elim Chemicals, Hyderbad.

Preformulaion Study of Rabeprazole Sodium:[7,8]

Preformulation studies are designed to determine the compatibility of initial excipients with the active substance for a biopharmaceutical, physicochemical and analytical investigation in support of promising experimental formulations. Successful formulations take into account a drug's interactions with the physicochemical properties of other ingredients [and their interactions with each other] to produce a safe, stable, beneficial and marketed product. The basic purpose of the preformulation activity are to provide a rational basis for the formulation approaches, to maximize the chances of success in formulating an acceptable product and to ultimately provide a basis for optimizing drug product quality and performance.

Description: It is the initial evaluation during preformulation studies which assess the colour and taste of the substance. This was only a descriptive test.

Solubility: Aqueous solubility is an important physicochemical property of drug substance, which determines its systemic absorption and in turns its therapeutic efficacy.

Table 1: Solubility Specifications

Descriptive terms	Approximate volume of solvent in milliliters per gram of solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Partially insoluble	More than 10,000

Drug Excipient Compatibility Study

Compatibility was performed by preparing compatibility blends at different ratio of different excipients with API, based on the tentative average weight. The blends were stored at accelerated condition of 40°C ± 2°C/ 75% ± 5% RH for 30 days. The samples were compared with initial samples data after the 2nd and 4th week of the study.

Table 2: Drug excipients compatibility study

S. No.	Composition	Ratio (Drug : Excipient)
1	Rabeprazole sodium	-
2	Rabeprazole sodium + Mannitol anhydrous	1:1
3	Rabeprazole sodium + Copovidone	1:1
4	Rabeprazole sodium + Crospovidone	1:1
5	Rabeprazole sodium + Methylparaben	1:1
6	Rabeprazole sodium + Magnesium stearate	1:1
7	Rabeprazole sodium + Magnesium oxide	1:1
8	Rabeprazole sodium + Instacoat moist shield white	1:1

FTIR

Infra red spectra matching approach was used for the detection of any possible chemical reaction between the drug and the excipients. A physical mixture (1:1) of drug and excipients was prepared and mixed with suitable quantity of potassium bromide. About 100 mg of this mixture was compressed to form a transparent pellet using a hydraulic press at 10 tones pressure. It was scanned from 4000 to 150 cm-1 in a shimadzu FTIR spectrophotometer. The IR spectrum of the physical mixture was compared with those of pure drug and excipients and matching was done to detect any appearance or disappearance of peaks.

Formulation of Rabeprazole Sodium Uncoated Tablets[9,10]

Sustained release tablets of Rabeprazole sodium (20 mg) were prepared through direct compression method as per the composition shown in Table 3. The formulation codes, F-I to FVII, were prepared by direct compression method. Various steps (sieving, dry mixing, lubrication and compression) involved in the tablet production by direct compression method were mentioned below.

Table 3: Composition of Rabeprazole Sodium Sustained Release Tablets

Ingredients	Quantity per tablet (mg)						
	F-I	F-II	F-III	F-IV	F-V	F-VI	F-VII
Rabeprazole sodium	20	20	20	20	20	20	20
Mannitol anhydrous	173	169	165	161	161	161	161
Copovidone	-	4.00	4.00	4.00	4.00	4.00	4.00
Crospovidone	-	-	4.00	8.00	8.00	8.00	8.00
Magnesium oxide	4.00	4.00	4.00	4.00	4.00	4.00	4.00
Methylparaben	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Magnesium stearate	2.00	2.00	2.00	2.00	2.00	2.00	2.00
Avg. wt. of the un coated tablets	**200**	**200**	**200**	**200**	**200**	**200**	**200**
Seal Coating							
Instacoat moist shield white	-	-	-	3.80	3.80	3.80	3.80
Isopropyl alcohol	-	-	-	25.00	25.00	25.00	25.00
Methylene dichloride	-	-	-	50.00	50.00	50.00	50.00
Lake iron oxide red	-	-	-	0.20	0.20	0.20	0.20
Enteric coating							
Protectab Enteric M1	-	-	-	4.80	9.80	14.80	19.80
Isopropyl alcohol	-	-	-	25.50	51.00	76.50	102.00
Methylene dichloride	-	-	-	25.50	51.00	76.50	102.00

Lake iron oxide red	-	-	-	0.20	0.20	0.20	0.20
Polish coating							
Insta coat glow	-	-	-	1.00	1.00	1.00	1.00
Isopropyl alcohol	-	-	-	3.50	3.50	3.50	3.50
Avg. Wt. of Enteric Coated Tablets				**210.00**	**215.00**	**220.00**	**225.00**

Evaluation of Precompression Parameters[11,12,13]

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

$$\mathbf{Tan\ \theta = h/r}$$

Where, h = Height of the powder cone,
R = Radius of the powder cone.

Table 4: Flow properties

Flow property	Angle of repose	Compressibility index (%)	Hausner's ratio
Excellent	25-30	<10	1.00 – 1.11
Good	31-35	11 – 15	1.12 – 1.18
Fair	36-40	16 – 20	1.19 – 1.25
Passable	41-45	21 – 25	1.26 – 1.34
Poor	46-55	26 – 31	1.35 – 1.45
Very poor	56-65	32 – 37	1.46 – 1.59
Very very poor	>66	>38	>1.60

Bulk density and Tapped density**:** Both Bulk density (BD) and tapped density (TD) 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[2]**.** Tapping was continued until no further change in volume was noted. LBD and TDB were calculated using the following equations.

Compressibility 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[3]**.**

$$\textbf{Compressibility index (\%)} = [\boldsymbol{TD - BD}\ /] \times \mathbf{100}$$

BD= Weight of the powder blend/Untapped Volume of the packing
TD= Weight of the powder blend/Tapped Volume of the packing.

Hausner's ratio**:** The Hausner's ratio is a number that is correlated to the flowability of a powder or granular material. Hausner's ratio was calculated from the bulk and tapped density using the following formula**.**

$$\textbf{Hausner's ratio} = \boldsymbol{Tappeddensity}\ /\ \boldsymbol{Bulkdensity}$$

Evaluation of Post Compression Parameters[14,15,16]

Hardness: Tablet requires a certain amount of mechanical strength to withstand the shock of handling in its manufacture, packaging, shipping and dispensing. The crushing strength that just causes the tablet to break is recorded by means of Monsanto hardness tester.

Thickness: Thickness should be controlled within 5% or less of an established standard value. Excessive variation in tablet thickness can result in problems with packaging as well as consumer acceptance.

Friability: Friability is the measure of a tablet's ability to withstand both shock and abrasion without crumbling during the handling of manufacturing, packing, shipping and consumer use. The weight of 10 tablets was noted and placed them in Roche type friabilator.

Disintegration test:The disintegration test was carried out according to IP procedure on six tablets using disintegration test apparatus with discs in 0.1N HCL (pH 1.2) maintained at 37°C ± 2°C for 2 hours.

In vitro **Drug Release Studies:** Drug release studies were carried out using a USP type II paddle dissolution test apparatus at 50 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 284 nm. After 10, 20, 30 and 45 minutes, 10 ml of the samples were

taken out and 10 ml Volume of fresh phosphate buffer pH 7.4 was added to kept volume of dissolution medium constant and sample was analyzed using UV spectrophotometer 284 nm.

Stability Studies: Stability studies was carried out at 25°C/60% RH and 40°C/75% RH for optimized formulation (F-VII) for 12 weeks.

RESULTS & DISCUSSION

Preformulation Studies

The colour, odour, nature and taste of the API were evaluated. It was found to be as per the monograph.

Solubility: The results revealed that the drug was soluble in water, methanol and ethanol.

Table 5: Description of Rabeprazole Sodium

Tests	Results
Colour	White
Odour	Unpleasant
Nature	Crystalline
Taste	Bitter

Drug - Excipient Compatibility Study: From the drug excipients compatibility study, it was observed that there was no change between drug and excipients.

Table 6: Drug Excipients Compatibility Study

S. No.	Composition	Description		
		Initial Period	2nd Week	4th Week
1	Rabeprazole sodium	white to off white powder	NCC	NCC
2	Rabeprazole sodium + Mannitol anhydrous	white to off white powder	NCC	NCC
3	Rabeprazole sodium + Copovidone	white to off white powder	NCC	NCC
4	Rabeprazole sodium + Crospovidone	white to off white powder	NCC	NCC
5	Rabeprazole sodium + Light magnesium oxide	white to off white powder	NCC	NCC
6	Rabeprazole sodium + Methylparaben	white to off white powder	NCC	NCC
7	Rabeprazole sodium + Magnesium stearate	white to off white powder	NCC	NCC
8	Rabeprazole sodium + Instacoat moist shield white	white to off white powder	NCC	NCC

NCC – No Characteristic change

Compatibility Studies by FTIR: In FTIR spectra the peaks of Fig 1 & Fig 2 physical mixture were compared with the Pharmacopoeia reference spectra. Same peaks were observed, indicates no possible molecular interaction between the drug and the Excipients.

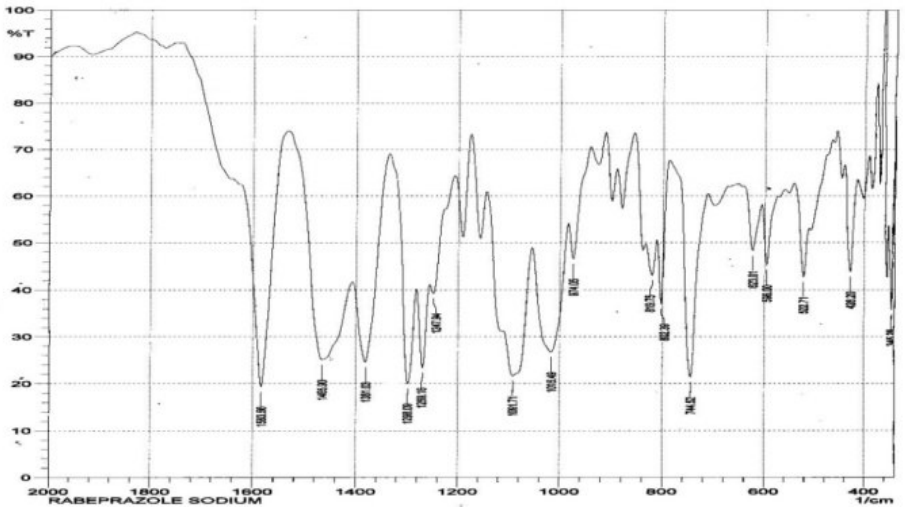

Figure 1: FTIR Spectra of Rabeprazole Sodium

Table 7: FTIR Spectral Data of Rabeprazole Sodium

S. No	Wave Number (cm-1)	Functional Group
1	1085	N-H Bending of Primary Amines
2	1296	N-O Symmetric stretching of Nitro compounds
3	1461	C-N Stretching
4	1585	C-C Stretching of Benzene

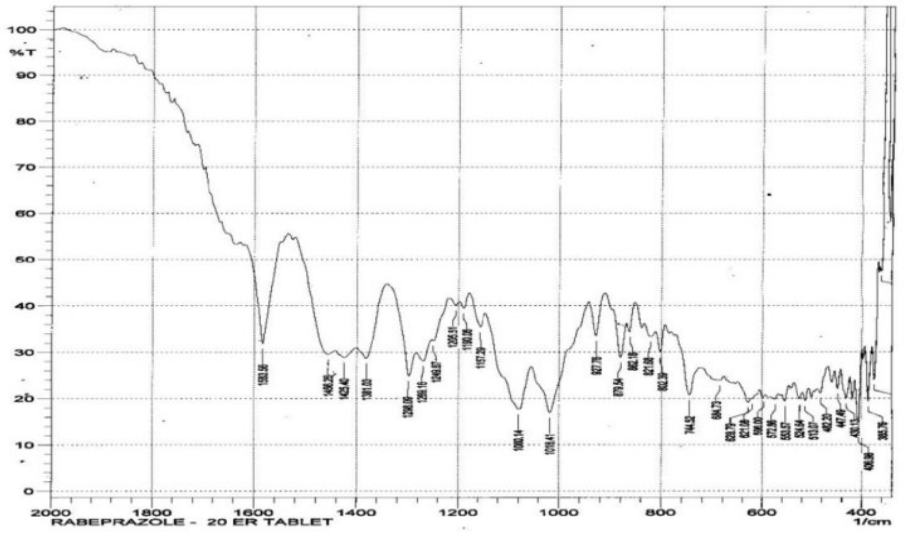

Figure 2: FTIR Spectra of Rabeprazole Sodium Enteric Coated Tablets

Table 8: FTIR Spectral Data of Rabeprazole Sodium Enteric Coated Tablets

S. No	Wave Number (cm-1)	Functional Group
1	1085	N-H Bending of Primary Amines
2	1296	N-O Symmetric stretching of Nitro compounds
3	1461	C-N Stretching
4	1585	C-C Stretching of Benzene

Evaluation of Precompression Parameters

The angle of repose was found to be in the range of 24.3 ± 0.2 to 29.8 ± 0.3 for all formulations. If the angle of repose was within 30◦, it shows excellent flow properties.

The result proved that all the formulations showed excellent flow properties. The bulk density of all formulations was measured by using bulk density apparatus. The bulk density was in the range 0.31 ± 0.1 to 0.32 ± 0.2 g/cm3.

The tapped density of all formulations was measured by using tapped density apparatus. The tapped density was found in the range of 0.36 ± 0.1 to 0.37 ± 0.3 g/cm3**.**

The compressibility index was in the range of 15.1 ± 0.6 to 16.5 ± 0.2 %. It proved that the flow behaviours and compressibility of the granules are good. The hausner's ratio lies in the range of 1.15 ± 0.2 to 1.19 ± 0.3. Hence the flow properties of all formulations were good.

Table 9: Precompression Parameters of Rabeprazole Sodium Powder

Formulation Code	Angle of Repose (θ)	Bulk Density (g/ml)	Tapped Density (g/ml)C	Compressibility index (%)	Hausner's ratio
F-I	27.6 ± 0.3	0.31 ± 0.1	0.37 ± 0.3	16.0 ± 0.1	1.19 ± 0.3
F-II	29.8 ± 0.3	0.31 ± 0.3	0.37 ± 0.1	15.8 ± 0.3	1.19 ± 0.2
F-III	24.3 ± 0.2	0.31 ± 0.1	0.37 ± 0.1	15.1 ± 0.6	1.19 ± 0.2
F-IV	29.2 ± 0.1	0.31 ± 0.2	0.36 ± 0.1	16.5 ± 0.2	1.16 ± 0.1
F-V	27.5 ± 0.4	0.32 ± 0.2	0.37 ± 0.2	15.5 ± 0.7	1.15 ± 0.2
F-VI	26.4 ± 0.3	0.32 ± 0.1	0.37 ± 0.1	15.3 ± 0.5	1.15 ± 0.3
F-VII	25.2 ± 0.2	0.31 ± 0.4	0.36 ± 0.2	15.85 ± 0.3	1.16 ± 0.2

Mean ± SD; n=3.

Evaluation of Post Compression Parameters

General Appearance: The tablets are round in shape and red in colour. All the tablets showed elegance in appearance.

Thickness: Thickness of the tablets was found to be in the range of 3.29 ± 0.030 mm to 3.43 ± 0.020 mm.

Hardness: The hardness of all the formulations was found to be in the range of 7.00 ± 0.27 to 7.60 ± 0.49 kg/cm2.

Weight variation test: The results showed that weight variation was ranging from 200 ± 1.39 to 205 ± 0.19mg

Friability test: The maximum and minimum friability values among 7 formulations were found to be in the range of 0.01 ± 0.002 to 0.46 ± 0.003% respectively.

Drug content: The assay of Rabeprazole sodium sustained release tablets were found in the range between 98.65±3.05 and 102.63±2.51.

Table 10: Evaluation of Rabeprazole sodium Uncoated Tablets

Formulation Code	Avg.Thickness (mm)	Hardness (kg /cm2)	Weight Variation (%)	Friability (%)	Drug Content (%)
F-I	3.33 ± 0.042	7.50 ± 0.32	202 ± 1.42	0.01 ± 0.002	100.50 ± 1.30
F-II	3.31 ± 0.014	7.20 ± 0.29	200 ± 1.39	0.06 ± 0.001	99.32 ± 2.69
F-III	3.29 ± 0.030	7.00 ± 0.27	201 ± 2.78	0.28 ± 0.001	98.65 ± 3.05
F-IV	3.37 ± 0.022	7.60 ± 0.49	205 ± 0.19	0.46 ± 0.003	101.96 ± 1.78
F-V	3.43 ± 0.020	7.10 ± 0.24	200 ± 3.10	0.32 ± 0.005	100.72 ± 1.39
F-VI	3.32 ± 0.054	7.50 ± 0.21	202 ± 1.90	0.20 ± 0.002	99.21 ± 2.87
F-VII	3.41 ± 0.020	7.50 ± 0.22	201 ± 2.30	0.15 ± 0.004	102.63 ± 2.51

Mean ± SD; n=3.

Evaluation of Coated Tablets

In F-IV to F-VI formulations, the disintegration time in acid medium was found to be 35, 75 and 103 minutes. It was not within the limit. The disintegration time for F-VII formulation in acid medium was found to be within the limit. When compared with marketed sample, it showed better disintegration time.

Table 11: Evaluation of Rabeprazole sodium Sustained Release Tablets

Formulation Code	Thickness (mm)	Weight Variation (%)	Disintegration test		Drug Content (%)
			Acid medium (mins)	Buffer medium Mins / sec	
F-IV	3.52 ± 0.032	211.05 ± 0.19	35	-	101.98 ± 1.78
F-V	3.56 ± 0.071	214.20 ± 3.10	75	-	100.75 ± 1.39
F-VI	3.63± 0.046	221.36 ± 1.90	103	-	99.80 ± 2.87
F-VII	3.69 ± 0.026	225.45 ± 2.30	120	10.50''	102.60 ± 2.51
Marketed sample	2.90 ± 0.055	210.63 ± 2.50	120	15.20''	99.10 ± 1.65

Mean ± SD; n=3.

***In Vitro* Drug Release Studies**

The results revealed that the drug released from marketed product was fairly matching with the drug release from Rabeprazole sodium sustained release tablet formulation F-VII. Based on this, F-VII was selected as best formulation other than F-IV,F-V,F-VI and subjected for stability studies**.**

Table 12: In vitro Drug Release of Rabeprazole sodium Sustained Release Tablets

Dissolution media	Sampling time	% Drug release				
		F-IV	F-V	F-VI	F-VII	Marketed sample
(0.1 N HCl)	2 hrs	2.51 ± 0.67	2.25 ± 0.12	1.5 ± 0.12	1.6 ± 0.50	1.7 ± 0.58
(6.8pH Phosphate buffer)	5 mins	4.75 ± 0.38	2.52 ± 0.43	6.4 ± 0.67	7.34 ± 0.33	7.10 ± 0.12
	10 mins	7.6 ± 0.12	5.16 ± 0.43	14.19 ± 0.14	19.77 ± 0.67	18.25 ± 0.24
	15 mins	28.36 ± 0.14	29.43 ± 0.21	30.26 ± 0.22	40.37 ± 0.58	39.45 ± 0.36
	20 mins	32.48 ± 0.67	34.27 ± 0.58	52.29 ± 0.12	75.28 ± 0.38	73.32 ± 0.14
	30 mins	40.19 ± 0.58	46.15 ± 0.43	72.36 ± 0.12	87.19 ± 0.22	85.56 ± 0.43
	45 mins	44.72 ± 0.12	59.54 ± 0.4	86.15 ± 0.36	99.67 ± 0.18	98.68 ± 0.21

Mean ± SD; n=3.

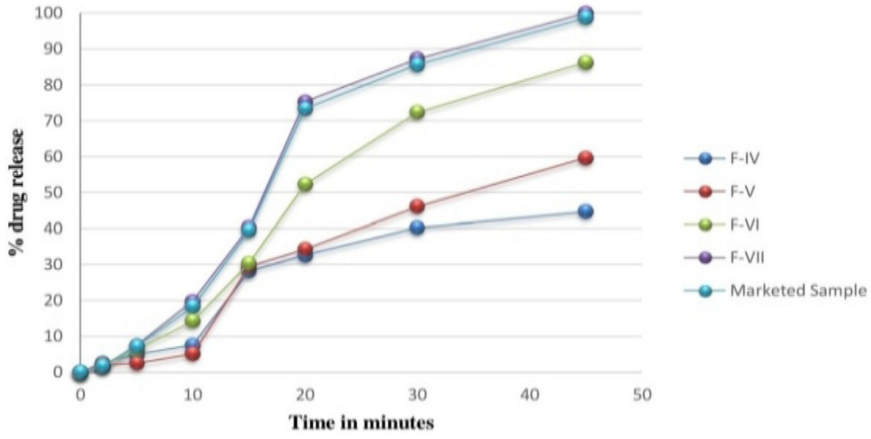

Figure 3: Dissolution Profile Study of Rabeprazole sodium Sustained Release Tablets.

Stability Studies

F-VII formulation was kept for stability studies. No physical changes were observed at end of 1st, 2nd and 3rd month. But average weight gradually increased every month, this may be due to increase in moisture content. Assay data showed no significance variation during stability studies.

Table 13: Stability studies for F-VII Rabeprazole sodium Sustained Release Tablets

Parameters	40□C ± 2□C/ 75% RH ± 5%RH			
	Initial Period	1st Month	2nd Month	3rd Month
Description	Round shaped red colour	Round shaped red colour	Round shaped red colour	Round shaped red colour
Average weight (mg)	225.57 ± 2.30	226.52 ± 2.13	227.15 ± 1.98	227.86 ± 1.84
Hardness (kg/cm2)	7.45 ± 0.22	7.48 ± 0.23	7.45 ± 0.20	7.43 ± 0.41
Thickness (mm)	3.76 ± 0.02	3.71 ± 0.02	3.68 ± 0.22	3.68 ± 0.08
Disintegration time (mins)	129.50''	130.34''	132.25''	133.14''
Assay (%)	102.63 ± 2.51	101.98 ± 2.14	101.56 ± 2.04	101.13 ± 1.34

Mean ± SD; n=3.

F-VII was kept for stability studies. The in vitro dissolution profile was remained without any significant changes at the end of 1st, 2nd and 3rd months. Hence it was concluded that the formulated Rabeprazole sodium sustained release tablets were stable.

Table 14: Stability study dissolution data for F-VII formulation

Dissolution media	Sampling time	Storage condition 40□C ± 2□C / 75% RH ± 5% RH			
		Initial Period	1st Month	2nd Month	3rd Month
Simulated gastric fluid (0.1 N HCl)	2 hrs	1.6 ± 0.63	1.6 ± 0.73	1.7 ± 0.56	1.7 ± 0.87
Simulated intestinal fluid (6.8pH Phosphate buffer)	5 mins	7.28 ± 0.33	7.30 ± 0.17	7.36 ± 0.41	7.39 ± 0.28
	10 mins	19.63 ± 0.67	18.72 ± 0.51	19.76 ± 0.28	19.82 ± 0.46
	15 mins	40.52 ± 0.58	40.42 ± 0.44	41.28 ± 0.29	41.45 ± 0.34
	20 mins	75.12 ± 0.38	74.56 ± 0.24	75.32 ± 0.49	74.89 ± 0.35
	30 mins	87.19 ± 0.22	87.35 ± 0.24	88.12 ± 0.31	88.36 ± 0.21
	45 mins	99.92 ± 0.12	99.99 ± 0.14	98.96 ± 0.22	98.92 ± 0.34

CONCLUSIONS

Formulation and evaluation of sustained release tablets of Rabeprazole sodium for the effective treatment of duodenal ulcer was successfully carried out. The preformulation studies, formulation of Rabeprazole sodium sustained release tablets, selection of the best formulation based on disintegration time and in vitro studies for sustained release tablets and stability studies were performed. The final product was correlated with the marketed product. From all the above observations it was concluded that the F-VII formulation was better one compared to the other formulations. Thus the study concluded that sustained release tablets of Rabeprazole sodium prepared by direct compression method. The tablets were coated with Protectab Enteric M1 as a polymer for the effective therapy for duodenal ulcer.

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