Original Article

FORMULATION AND EVALUATION OF DELAYED RELEASE PELLETS OF RABEPRAZOLE SODIUM

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Abstract
The aim of the present investigation was to prepare delayed release i.e., enteric coated pellets of Rabeprazole sodium by using hydroxypropyl methyl cellulose based sub coating and methacrylic acid copolymer based enteric coating. The different batches of pellets were prepared by drug suspension layering method. Comparative study of dissolution profile of final batch with market preparations was conducted and it was concluded that final batch shown good similarity with market products. The results of the accelerated stability of final formulation for three months revealed that storage conditions were not found any significant changes in final formulation.

Key words: Rabeprazole sodium, Delayed release pellets, Enteric coating.

Introduction

Proton Pump Inhibitors (PPIs) are used in the treatment of acid – related gastro – duodenal disorders by reducing gastric acid secretion[1]. 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. The stability of PPIs in aqueous media is a function of P^H with an increased rate of degradation as the P^H decreases. Degradation of the Rabeprazole leads to a yellow or purple discoloration of the pellets, film layer or dissolution medium. Stability of Rabeprazole sodium also decreases under moisture conditions. 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.

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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 pellets of Rabeprazole sodium by using Methacrylic acid copolymer in Fluid bed processor to prevent degradation in the stomach due to the acidic environment or gastric enzymes and compare with the market sample.

Materials and Methods

Rabeprazole Sodium (I.H.S) was a gift sample from Lee Pharma, Hyderabad, India. Eudragit L30D-55 was a gift sample from Evonik labs, Mumbai, India. Triethyl citrate was gift sample from Signet chemical corporation, Mumbai, India. Opadry clear was gift sample from Colorco, USA. Polyplasdone XL, XL-10 gift sample from ISP, USA. Mannitol (Pearlitol SD200), Sodium Carbonate (I.P), Talc (I.P) and all other chemicals were of analytical grade.

Method

Preformulation studies

Preformulation studies were carried out for appropriate selection of excipients in view of Rabeprazole Sodium modified release pellets.[5,6,7] Micromeritic properties of Rabeprazole Sodium carried

were angle of repose, bulk density and tapped density, Hausner's ratio and drug excipients compatibility study for 4 weeks at accelerated conditions, 40±2°C /75%RH±5% RH.

Formulation development of core pellets of Rabeprazole sodium

The drug suspension was prepared by mixing Rabeprazole sodium, sodium carbonate, crosspovidone and Hydroxypropylmethyl cellulose in purified water. The suspension was then placed into the spray gun system of Glatt fluid bed processor machine and sprayed onto the sugar core pellets while the Glatt machine was set in running condition. This would allow the drug to be evenly coated onto the core pellets to form drug – coated spherical pellets. The drug – coated pellets were dried under warm air within the Glatt machine. The proportion of different batches of Rabeprazole sodium core pellets are given in table 1.

Preparation of Coating solution of Opadry clear

To prevent interaction between Rabeprazole sodium and enteric coating layer, seal coating of Rabeprazole sodium pellets was done by Opadry clear until weight gain 8-10%. Coating solution was prepared by dissolving Opadry clear in mixture of Iso Propyl Alcohol (IPA) and Mehtylene Dichloride (MDC) under constant stirring for 15-20 minutes by using propeller stirrer.

Preparation of Coating solution of enteric coating solution

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 Eudragit L100-55 (for 30% weight gain) was added in the water and kept continuous stirring for 15-20 minutes.

Coating of core pellets

A protective coating solution was prepared by mixing Opadry clear slowly in the solvent mixture of IPA and MDC (60:40). This coating was then placed into the spray gun of the Glatt machine and sprayed onto the drug – coated pellets while the Glatt machine was set in running condition. After the coating was completed, the protective coating-covered pellets were again dried under warm air within the Glatt machine. Finally, an enteric coating was prepared by mixing Eudragit L100-55 in a mixture of Isopropyl alcohol and Methylen dichloride. This coating was placed into the spray gun of the Glatt machine and sprayed onto the protective coating-covered pellets to form the pharmaceutical pellets before final drying of the granules to complete the process of making the enteric coating-covered pellets.

Coating of pellets was done using Glatt fluid bed processor machine. First fixed quantity (1Kg) pellets were put in the product chamber which was pre adjusted at 50°C temperature for 5 – 10 minutes. Various parameters like spray rate (8 to 25 gm/min), inlet air temperature (20 to 50°C), atomizing air pressure (1 to 3 bar), % fludization (10 to 30%) and percent solids content 7% were adjusted and optimized. After finishing of the coating pellets were dried at 40° C and at 10% fluidization. The coated pellets were removed and evaluated by various parameters.

Evaluation parameters

The prepared coated pellets were evaluated and compared with the marketed product.

Physical examination

A Micromeritic property of API is given in table 2. Pellets were examined visually and observation was recorded and given in table 3. The Retention time of the major peak in the chromatogram of the sample preparation corresponds to that of the standard preparation. As obtained in the Assay.

Moisture content

The moisture content in the pellets was determined Karl Fischer titrator

In vitro dissolution studies

Dissolution studies of Rabeprazole sodium enteric coated pellets were performed according to USP XXIII type II apparatus in 0.1N HCl for 2 hrs and in pH 8.0 sodium phosphate buffer 0.5% SLS for 30 min.

Table 1: Formulation of different batches of Rabeprazole sodium core pellets

Ingredients	Formulations (quantities in gms)				
	F1	F2	F3	F4	F5
Rabeprazole sodium	285	285	285	285	285
Sodium carbonate	150	225	150	225	0
Hydroxy propyl methyl cellulose	80	80	80	80	80
Polyplasdone INF 10	225	150	---	---	---
Polyplasdone XL 10	---	---	225	150	375
Sugar spheres	660	660	660	660	660
Talc	100	100	100	100	100

Table 2: Micromeritic properties of API

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

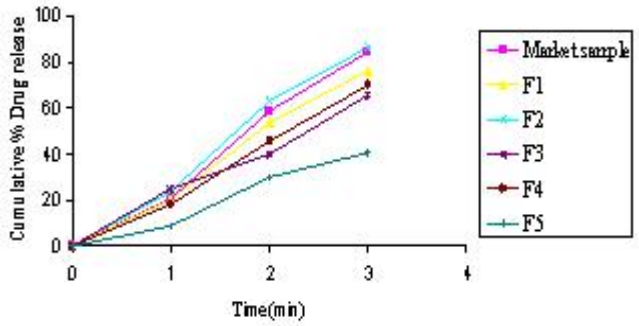
Table 3: Drug excipient compatibility study (Physical observation)

Batch no.	Drug-Excipients combination	D:E Ratio	Initial observation	Final description 1M/ (40OC / 75%RH 7 days)
1	RS	-	Off White	Off White
2	R S + Mannitol	1:10	White	White
3	RS + Sodium carbonate	1:10	White	White
4	RS + Titanium dioxide	1:0.25	White	White
5	RS + Opadry clear	1:1	White	Off white
6	RS + Talc	1:0.25	Fine white	Fine white
7	RS+ Crospovidone	1:1	White	White
8	RS + Hydroxy Propyl Cellulose	1:1	White	White

Table 4: Comparison of Dissolution profiles of Rabeprazole and coated pellets in pH8.0 buffer

S.No	Time (min)	Market sample	F1	F2	F3	F4	F5
1	10	20.6	20	23.8	25	18	9
2	20	58.9	54.0	62.8	40.2	45.6	30.2
3	30	84.36	76.0	86.2	65.8	69.8	40.6

Figure 1:
Dissolution data's of Rabeprazole sodium



The temperature was maintained at 37±0.5°C and the rotation speed was 100 rpm. The samples were withdrawn at 2hrs in acid and 10, 20, 30 min in buffer and analyzed HPLC (SHIMADZU). The in vitro data's are shown in figure 1. The table 4 and figure 2 shows the data's reveals the Comparison of Dissolution profiles of Rabeprazole and coated pellets in pH 8.0 buffer.

Table 5: Stability studies data

Time	Test (%)	Temperature
		40°C / 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 months	Assay	11.5
	Acid resistance	98.6
	%DR	85.0

Figure 2: Dissolution profile of selected stability sample

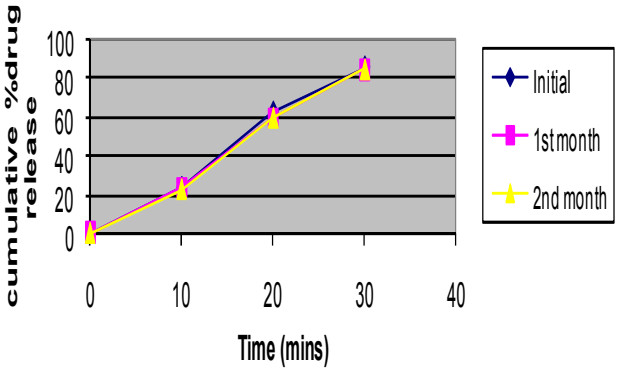


Table 6: Comparison of Assay, Drug release and Acid resistance of coated Pellets (Capsule) with market sample

S.No	Test %	Market sample	F1	F2	F3	F4
1	**Assay**	11.58	11.64	11.72	11.70	11.72
2	**Drug dissolution**	84.36	76.09	86.24	65.82	69.82
3	**Acid resistance**	98.68	99.08	99.75	93.7	98.2

Assay- % labelled amount of Rabeprazole sodium.
Drug Dissolution- % labelled amount of Rabeprazole sodium released in Buffer.
Acid resistance test-% labelled amount of Rabeprazole sodium retained in acid.

Stability Studies

Stability studies were conducted at 40°C / 75% RH for about 3 months in stability chamber (thermo lab)[8]. Samples were collected at 1, 2 and 3 months. The Stability studies data's are given in the table 5.

Results and discussion

Preformulation studies

From the results of Micromeritic studies of the Rabeprazole sodium it was conclude that Rabeprazole sodium has poor flow property and compressibility property. From the physical observation, no significant Drug-Excipient interaction was observed. So it was concluded that drug and other excipients were compatible with each other.

Evaluation parameters of the optimized batch of Rabeprazole sodium

From the results of comparative study of dissolution profile of final batch with market preparations. It was concluded that final formulation was shown good similarity with market product.

Accelerated stability study of the optimized batch

From the results of the accelerated stability of the final formulation for 3 months, it was concluded that storage conditions were not found any significant changes in final formulation dissolution profile with market sample.

Conclusion

In coating process the enteric coating was done with the percentage build ups of 22, 24, 26, and 28 with 8% sub coating. Acid resistance was failed up to 26% but at 28% build up acid resistance was passed. But for safer side, we coated up to 30% with 8% sub coating. For optimizing coating process further trails were conducted with increasing sub coat and decreasing enteric coating. From the above results, we found that F1, F2, F3 and F4 batches were passed in assay and acid resistance tests. Batch F5 is not meeting the specification in terms of dissolution due to the super-disintegrant particle size and lack stabilizing agent (Alkali). Based on results F2 formulation was found to be satisfactory with the market sample dissolution profile. So finally F2 was found to be best formula for formulation of Rabeprazole sodium delayed release pellet.

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