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Influence of plasticizer concentration on physicochemical properties of an antiulcer drug in enteric coated pellets

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ABSTRACT

The present study was designed to investigate the effect of plasticizer i.e., triethyl citrate (TEC) on the *in vitro* drug release kinetics of Rabeprazole sodium from sustained-release pellets. Ammonio-methacrylate copolymer type B (Eudragit RS 100) was used as the release-retarding polymer. The plasticizer was used in different concentrations i.e. 0%, 5%, 10% 15%, and 20% (w/w) of Eudragit 100. Pellets were prepared by powder layering technology and coated with Eudragit RS 100 D using pan coating. Dissolution study was performed by using USP apparatus 2 (paddle type). When dissolution was performed on the pure drug, about 6.28% and 92% drug was dissolved in 2 h in 0.1 N HCl and in 30 min in buffer (pH 7.4), respectively. On comparing all formulations the release of drug in acidic dissolution medium was very negligible except the F1 formulation. It could have resulted due to the non-incorporation of triethyl citrate in Eudragit coating solution. It was observed that in buffer only 62% drug was released after 5 h from enteric coated pellets (F5) containing 20%TEC, thus indicating that Eudragit RS 100 significantly retarded the drug release rate and that drug release was varied according to the amount of plasticizer used. The amount of triethyl citrate in coating formulation significantly affected the drug release profile of the drug.

Key words: Enteric coating, Pellets, Rabeprazole sodium, Eudragit RS 100, Triethyl citrate

INTRODUCTION

Proton pump inhibitors (PPIs) are widely used for the treatment and prophylaxis of (NSAID-associated) duodenal, esophageal reflux disease, and benign gastric ulcers and relief of dyspeptic symptoms. Rabeprazole sodium is the member of a new class of substituted benzimidazoles. Chemically it is a 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl] - methyl] sulfinyl] -1H-benzimidazole sodium. H⁺ /K⁺ Adenosine Tri Phosphate (ATP) is an enzyme present in the secretory surface of the gastric parietal cells which is regarded as the acid (proton) pump within the parietal cell. So, Rabeprazole sodium has been characterized as a gastric proton-pump inhibitor. Rabeprazole sodium blocks the final step of gastric acid secretion in gastric parietal cells.[1,2]

The objective of the present study was thus to design a stable and effective sustained release drug product of Rabeprazole Sodium that utilizes lesser amount of enteric polymer which is well within the gastrointestinal tract limits as well as easily processed and manufactured using lesser amount of polymer and also takes lesser processing time.[5]

MATERIALS AND METHODS**Materials**

Sugar spheres were obtained from Goa Antibiotics & Pharmaceutical Limited. Rabeprazole Sodium was obtained from Metrochem API Private Limited, Hyderabad and Eudragit RS100 was obtained as gift sample from Evonik India Private Limited, Mumbai. All other materials, reagent and chemicals used were of analytical grade.

Experimental Preformulation study

Preformulation studies focus on the physicochemical properties of the drug molecule that could affect its performance and development of stable, safe, effective formulation.

Micromeritic properties of API**1. Angle of repose**

The angle of repose of API powder was determined by the funnel method. The accurately weighed powder blend was taken in the funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation. [7]

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

Where, h and r are the height and radius of the powder cone.

2. Bulk density and tapped density

Both Bulk density (BD) and tapped density (TD) was determined. A quantity of 2 gm of Rabeprazole sodium powder previously shaken to break any agglomerates formed, was introduced in to 10 ml measuring cylinder. After that the initial volume was noted and the cylinder was allowed to fall under its own weight on to a hard surface from the height of 2.5cm. Tapping was continued until no further change in volume was noted. Bulk density and Tapped density were calculated using the following equations. [7]

Bulk density = weight of the powder blend/untapped volume of the packing

Tapped density = weight of the blend/Tapped volume of the packing

3. Compressibility Index

The Compressibility Index of the powder blend was determined by Carr's compressibility index. [7]

$$\text{Carr's Index (\%)} = [(TD-BD) \times 100]/TD$$

4. Hausner's ratio

The Hausner's ratio is a number that is correlated to the flowability of a powder or granular material. The ratio of tapped density to bulk density of the powders is called the Hausner's ratio. It is calculated by the following equation. [7]

$$H = TD / BD$$

Where TD = tapped density, BD = bulk density

5. Drug excipient compatibility study

Drug excipients compatibility studies was carried out by mixing the drug with various excipients in different proportions. Compatibility studies were carried out in glass vials at Accelerated conditions, $40 \pm 20^\circ\text{C}/75\% \text{RH} \pm 5\% \text{RH}$. The studies were conducted for 4 weeks and compared with control at $2 - 8^\circ\text{C}$. Physical observations of the blend were recorded at regular interval of one week [3]

6. Compatibility study by Fourier Transform Infra red Spectroscopy

Fourier –transform infrared (FT-IR) spectra were obtained by powder diffuse reflectance on a FTIR spectrophotometer (Shimadzu, Model 8400S, Japan) in the wave number region of $500-4000 \text{ cm}^{-1}$. The samples were

previously grounded and mixed thoroughly with potassium bromide (KBr), an infrared transparent matrix, at 1:5 ratio respectively. The KBr pellets were prepared by compressing the powder at 5 tons for 5 min in a hydraulic press

Preparation of enteric coated pellets of Rabeprazole Sodium

Rabeprazole sodium pellets were prepared by Powder layering method. At first, the required amount of PEG 4000 was dissolved in isopropyl alcohol to prepare binding solution. Then, the desired size (mesh size 30) of sugar spheres was loaded onto conventional coating pan. The required amount of Rabeprazole sodium powder (20mg) and lactose was sieved through sieve 90 mesh size and mixed properly to prepare the powder blend. The powder blend was loaded manually on sugar spheres with simultaneous spraying of binding solution. After completion of the process, drug-loaded pellets were dried at 60°C for 5 h in hot air oven and then sieved through 20 mesh and 24 mesh, respectively, to get the desired size (20/24).

The coating suspensions were prepared by using Eudragit RS 100, purified talc, and water. Drug-loaded pellets were taken in the coating pan and coating suspension was sprayed. After completion of spraying, the coated pellets were dried at 60°C for 5 h in hot air oven and sieved through 18 and 24 mesh to get the desired size (18/24) of the Rabeprazole Sodium sustained-release pellets. The prepared batch was termed as F1. The same process was followed by adding 5% TEC, 10% TEC, 15% and 20% TEC (w/w of Eudragit RS 100 on a dry basis) and the batches were termed as F2, F3, F4, and F5 respectively. [4, 6, 8, 9, 11]

Dissolution studies

The dissolution of Rabeprazole sodium pellets was studied in accordance with pharmacopoeial method by USP Dissolution apparatus 2 (paddle). The weighed amount of Rabeprazole Sodium pellets (equivalent to 20 mg) was poured in 900 mL of 0.1 N hydrochloric acid medium at 37±0.5°C with a rotation of 100 rpm for 2 hrs. At the end of 2 h, the media was removed and drug content was determined spectrophotometrically. Then, 900 mL of phosphate buffer of pH 7.4 was placed in each vessel and rotated at 100 rpm at 37±0.5°C for 10 hrs. Samples (10 mL) were drawn every 2 h and replaced by fresh medium to maintain the volume constant, and drug content was determined spectrophotometrically at 282 nm. Dissolution study of free Rabeprazole sodium incorporated into capsule shell was also performed simultaneously following the same method. [6, 12, 13, 9]

Stability study

Stability studies were performed as per the ICH guidelines. Selected formulations of Rabeprazole Sodium pellets were sealed in aluminum foil cover and stored at (40 ± 2 °C / 75 ± 5 % R.H) for a period of 3 months. Samples from each formulation which were kept for examination were withdrawn at definite time intervals. The withdrawn samples were evaluated for physical appearance, % cumulative drug release. [3]

RESULTS AND DISCUSSION

The preformulation studies were performed in order to identify the physical and chemical properties of the drug. The results were as shown in table 1 and 2. The results shown in tables 1 and 2 show that Rabeprazole Sodium has poor flow property and compressibility property and there is no significant drug excipient interaction was observed so it shows that drug and all excipients are compatible to each other. The drug excipient compatibility studies were carried out using FTIR and excipients were found to be compatible with Rabeprazole Sodium. (fig 1, 2).

Table No 1: Micromeritic Properties of Rabeprazole Sodium (API)

sample	Angle of repose	Bulk density(g/ml)	Tapped density (g/ml)	Compressibility index (%)	Hausner's ratio
Rabeprazole sodium (API)	33.28	0.379	0.521	32.11	1.42

Pellets were prepared by dry powder layering technique. In drug loading process, PEG 4000 was used as binder to impart mechanical strength to core pellets as well as help in binding of drug to sugar spheres. From the dissolution profiles of all formulations it was observed that formulation F5 had good acid resistance in HCl (pH 1.2) and other formulations did not show this property due to non uniform coating of polymer due to less amount of plasticizer (fig 4). The formulation containing no plasticizer i.e. F1 (Fig.3) showed 18.22% of drug release in acid medium after 2 hrs and 90 % of drug release in phosphate buffer (pH 7.4) after 4 hrs as compared to other formulations which were containing increasing concentrations of the plasticizer. Formulations (F2, F3, F4, and F5) (Fig 3) shows 0.9 %, 0.7%, 0.4%, and 0.2% of drug release in acid medium after 2hrs this indicating good resistance to acidic

environment. Formulation containing no plasticizer (F1) showed more drug release as compared to formulations (F2, F3, F4, F5) in phosphate buffer and it shows that formulation F5 more sustained release profile as compared to other formulations (fig 4).

Table No 2: Drug: excipients compatibility study (physical observation)

BATCH	DRUG : EXCIPIENTS COMBINATION	D:E RATIO	INITIAL OBSERVATION	FINAL RESULT AFTER 4 WEEKS
1	Rabeprazole sodium (RS)		Off white	Off white
2	RS + PEG-4000	1 : 5	White	White
3	RS + Eudragit RS -100	1 : 5	White	White
4	RS + Talc	1 : 5	White	White

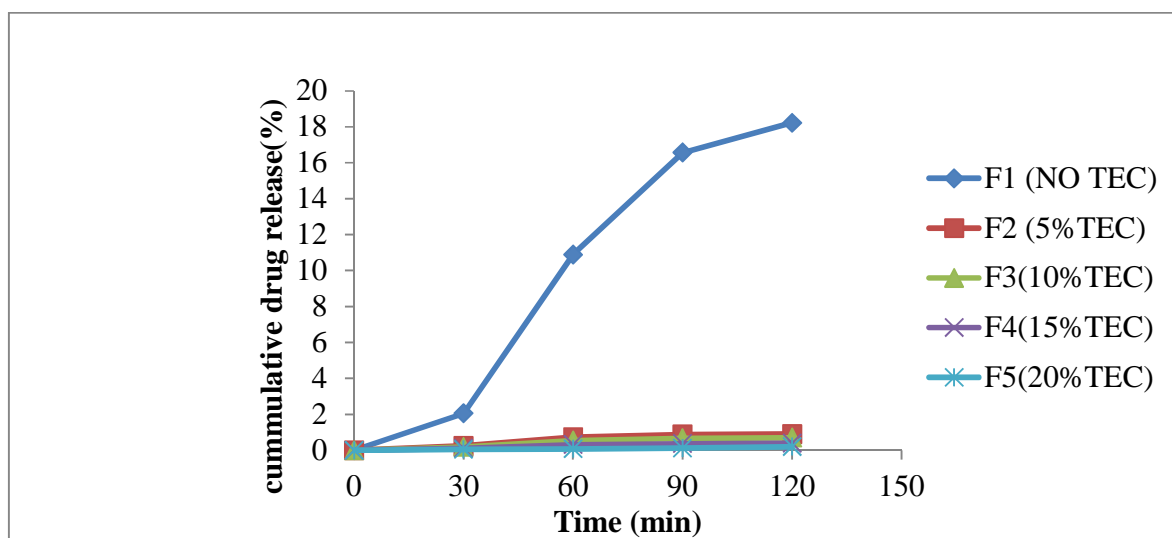


Figure 3: Dissolution profile of pellets in Hydrochloric acid (pH 1.2)

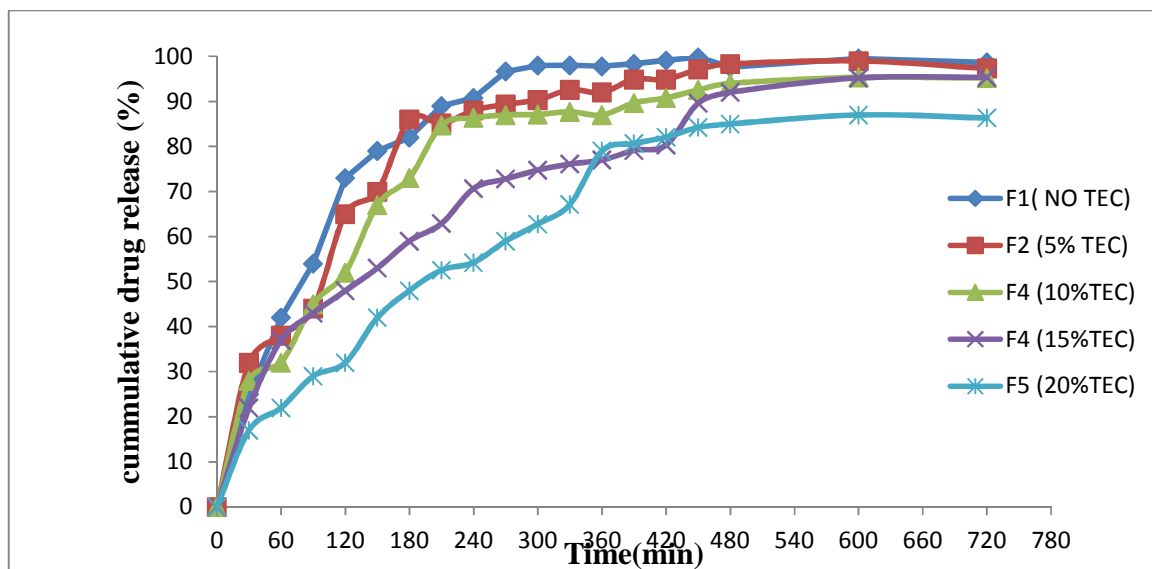


Figure 4: Dissolution Profile of Pellets in Phosphate Buffer (p 7.4)

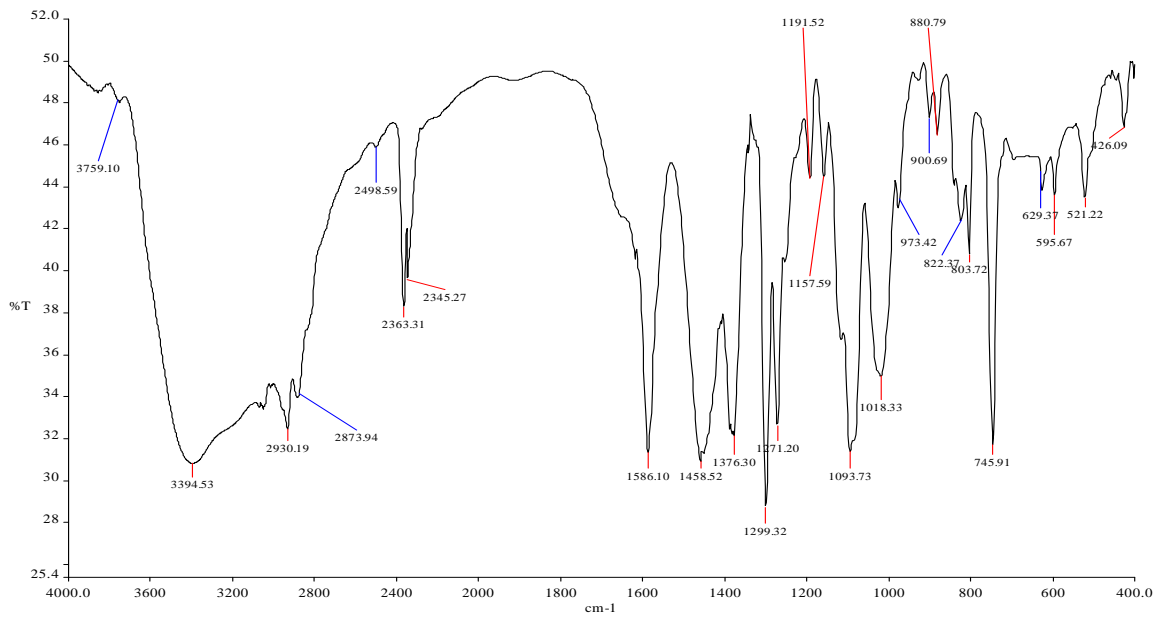


Figure 1: FTIR spectrum of Rabeprazole sodium

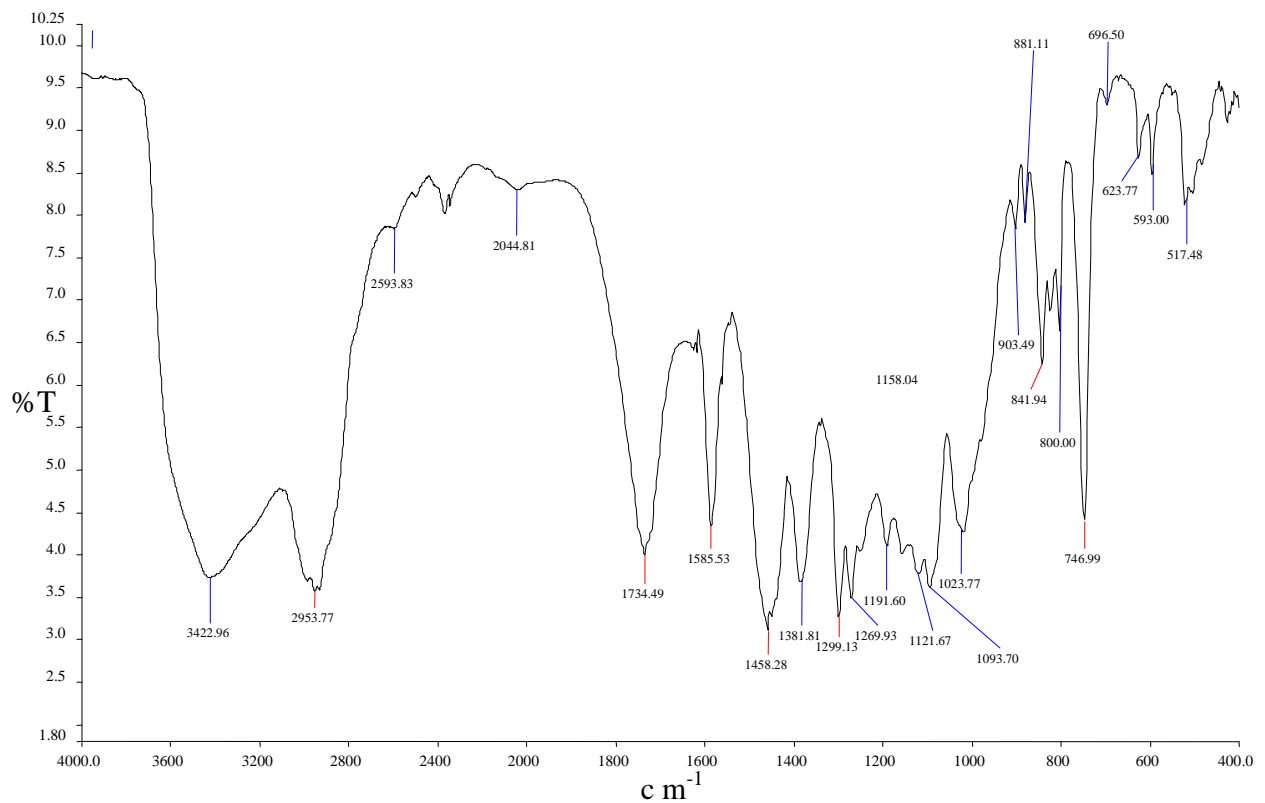


Figure 2: FTIR spectrum of physical mixture of Rabeprazole sodium with Eudragit RS 100

Stability studies

Stability of a drug in a dosage form at different environmental conditions is important as it determines the expiry date of that particular formulation. Changes in the physical appearance, color, odor, taste or texture of the

formulation indicate the drug instability. Among the enteric coated formulations, formulation (F5) was selected for stability studies based on the physicochemical characterization and drug release characteristics.

The stability studies were carried out at 40 ± 2 °C with $75 \pm 5\%$ RH which shown in Table 3. There were no significant changes in the physical appearance and average weight of pellets. It was observed that the initial drug content and the drug contents of the samples analyzed after 1, 2, 3 month of storage were similar. The release profiles also did not show any significant changes indicating thus there were no significant changes in the physical as well as chemical characteristics of the formulation. Hence, it could be concluded from the results that the developed pellets were stable and retain their pharmaceutical properties over a period of 3 months.

Table No 3: Stability study of enteric coated Rabeprazole sodium pellets

Parameters	1 st month	2 nd month	3 rd month
Physical appearance	Off white	Off white	Off white
% cumulative drug release	95.34 ± 0.44	95.28 ± 0.36	95.14 ± 0.03

CONCLUSION

The incorporation of a plasticizer in the system was found to be an important factor, without which a much faster dissolution rate was found. It was revealed that when the percentage of TEC was increased then the drug release rate constant was decreased. A high plasticizer amount (20% w/w, based on the polymer) and thermal treatment were necessary to achieve complete film formation. Higher amount of plasticizer helps in formation of good enteric coated film. The limiting drug release profile was approached after curing the coated pellets at 60°C for 2 h. After curing, Eudragit RS100 coated pellets showed unchanged drug release profiles upon storage. Results obtained from the experiments it can be concluded that Eudragit RS 100 can be used as enteric coated polymer only when it contains appropriate amount of plasticizer. The polymer can protect the drug from the acid environment of stomach and release the drug when it reaches the intestinal pH. From the dissolution studies it was observed that, formulation containing 20% of plasticizer remains intact for 2 hours in acidic medium.

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