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Design and Development of Modified Release Multiple Unit Pellets of Rabeprazole Sodium

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ABSTRACT: The aim of the present study was to design and develop delayed release (Enteric coated) and controlled release Multiple Unit Pellets of Rabeprazole sodium by Extrusion and Spheronization technique using Hydroxy propyl methyl cellulose (HPMC), and Ethyl cellulose as controlled released polymers. Rabeprazole is one of the most useful proton pump inhibitors to treat peptic ulcer, gastro esophageal reflux (GERD) and Zolinger Ellison syndrome. The multiple unit pellets (MUPS) has become most successful dosage form for modified drug release. The MUPS were prepared by Extrusion and Spheronization a promising pelletization technique. The dissolution study of the optimized batch shows satisfied controlled release behavior .Accelerated stability testing of the optimized batch found no significant change *in in-vitro* release profile.

KEY WORDS: Rabeprazole sodium, Controlled release, Modified Release, Extrusion and Spheronization, Multiple Unit pellets (MUPS).

I. INTRODUCTION

Peptic Ulcer disease (PUD) refers to painful sores (or) ulcers in the lining of the stomach (or) duodenum. Every year peptic ulcer disease affects millions of people around the world. Proton pump inhibitors (PPIs) are one of the most commonly prescribed medications in acid peptic disease. PPIs include Omeprazole, Lansoprazole, Rabeprazole, Pantoprazole and Esomeprazole have superior gastric acid suppression than histamine H_2 receptor Blockers. PPIs have few side effects and considered safe for long term treatment.

Rabeprazole sodium belongs to a class of anti secretary compounds. (Substituted benzimidazole proton pump inhibitors) that don't exhibit histamine H_2 receptor antagonist properties, but suppress gastric parietal cell. It blocks the final step of gastric acid secretion[5]. The antisecretory begins within one hour after oral administration. It has a short pharmacokinetic half life of 1-2 hours[1]. It is official in Indian pharmacopoeia. The Rabeprazole have the molecular formula of $C_{18}H_{20}N_3NaO_3S$ and the molecular weight is 381.43 and the oral bioavailability is about 52%. To increase the oral bioavailability of it was made to formulate controlled release multiple unit pellets which enclosed in a enteric coated capsule.

II .MATERIALS AND METHODS

MATERIALS

Rabeprazole sodium was received as a gift sample from Zydus Cadila and Hydroxyl propyl methyl cellulose (HPMC) and Ethyl cellulose from Triveni chemicals and all other chemicals were of analytical grade.

METHODS

A. Identification of Pure Drug

Rabeprazole Sodium pure drug was identified by FT-IR and compared with the reference spectrum of drug.

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B .Calibration Curve

Calibration curve was performed with 0.1N HCl and Phosphate buffer pH 6.8 .The absorbance of the solution were measured spectrophotometrically at 260nm and 283nm respectively.

C .Drug-Excipients Compatibility Studies

The compatibility studies between Rabeprazole and polymers were carried out by Fourier Transform infrared spectroscopy (FT-IR). FTIR spectra were obtained sample about 5mg was mixed thoroughly with 100 mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12 psi for 3 minutes. The resultant disc was mounted in holder in IR spectrophotometer and the IR spectrum was recorded from 4000 cm -1 to 625cm-1 in a scan time of 12 minutes. The resultant spectrum was compared for any spectral changes.

PREFORMULATION STUDIES

D .Angle of Repose [1,2,3]

Angle of repose is used to determine the flow properties of powders (or) pellets. The accurately weighed powders/ pellets were poured through a funnel to form a cone. Stop pouring the material when the pile reached a predetermine height. The inverse tangent of the ratio is the angle of repose. The angle of repose was calculated using the formula.

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

'h' and 'r' are height and radius of the powder cone.

E.Bulk Density[2]

The bulk density of a material is the ratio of the mass to the volume (including inter particulate void volume) of an untapped powder sample. The bulk density is obtained by adding a known mass of powder to a granted cylinder. The bulk density is calculated as mass/ volume

F Tapped Density[3]

The tapped density is obtained by mechanically tapping a graduated cylinder containing the sample until little further volume change was obtained. The tapped density was obtained by mechanically tapping a graduated cylinder containing the sample until little further volume change was observed. The tapped density was calculated as

Tapped density = weight of granules/tapped volume of granules

G. Hausner's Ratio [1,2,3]

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 powder is called Hausner's ratio. A Hausner's ratio is greater than 1.25 is considered to be an introduction of poor flowability

H. Carr's Compressibility Index[2,3]

The Carr's index is an indication of the compressibility of a powder. A Carr index greater than 25 is considered to be an indicator of poor flowability and below 15 is good flowability.

$$\text{Carr's index} = (V_B - V_T/V_B) \times 100$$

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Table No: 1 Pre formulation specifications of optimized formulation

Sl. No	Characteristics	Results
1	Angle of Repose(°)	29.6±0.4
2	Bulk density(g/ml)	0.43±0.2
3	Tapped density(g/ml)	037±0.3
4	Compressibility index	16.1±0.5
5	Hausner's ratio	1.17±0.8

Formulation Of Rabeprazole Multiple Unit Pellets

Extrusion and Spheronization process:

- Extrusion and Spheronization is one of the potential technique and also as a future method of choice for the preparation of MUPs control release dosage form.
- The method has ability to incorporate higher level of active components without producing excessive large particles.
- The multi steps involved in the process were mixing, wet granulation, extrusion, spheronization drying and screening.

Fig: 1 FT-IR Spectra of Rabeprazole sodium

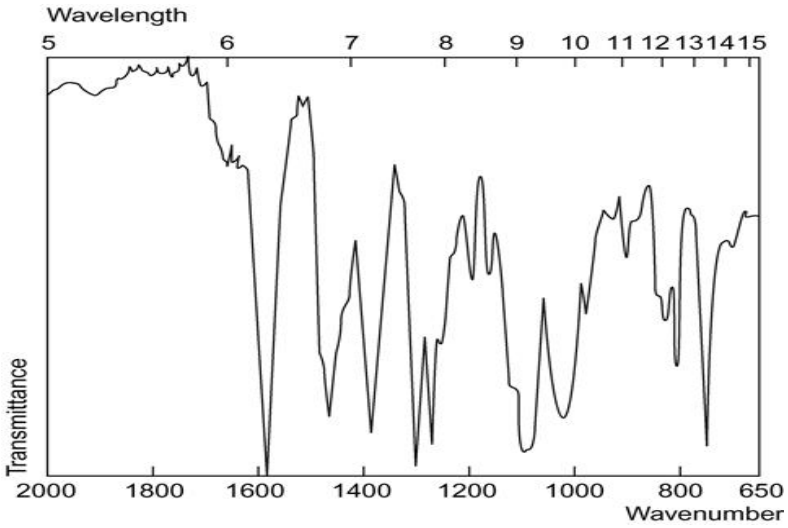

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Fig 2 Extruder Fig 3 Spheronizer Fig 4 Pellets

FORMULATION DEVELOPMENT

Required quantity of Rabeprazole sodium, controlled release polymers Hydroxy propyl methyl cellulose, Ethyl cellulose, diluents lactose, spheronization enhancer Microcrystalline cellulose, binders polyvinyl pyrrolidine were mixed and prepared a wet mass, in which the powder mixer was converted into a plastic mass that was easily extruded is called extrusion. The extruded strands were transferred into a spheronizer, where they were broken into short spherical rods and rounding the particles into spheres. Different ratios of controlled release polymers were examined. Out of all formulations the HPMC and drug (1:1 ratio) shows good micromeritics properties.

EVALUATION OF PELLETS [4,5]

A.Estimation of Rabeprazole sodium

Drug content was estimated by HPLC, Phosphate buffer PH 6.8. acetonitrile was used as mobile phase in the ratio of 530:470 in an grace smart RP 18, 250x4.6 mm , 5 micrometer column at a ambient temperature and the flow rate1.0ml/min.

B.I*n-vitro* Drug Release Studies

In-vitro drug release studies were carried out using a USP type II dissolution apparatus. The pellets were placed in 900ml of 0.1N HCl at paddle speed 75 rpm maintained at 37 °C ± 0.5 °c for 2hrs. One ml of sample was taken and analyzed using UV spectrophotometer at 263nm. The dissolution medium was replaced with P^H 6.8 phosphate buffer 900 ml and tested for drug release for further 12hrs. 1ml sample was withdrawn after every hour and was replaced by an equal volume of fresh dissolution medium of same P^H Collected samples were analyzed at 283 nm.

C.Accelerated Stability Studies

Stability study is used to predict the shelf life of the product by accelerating the rate of decomposition, preferably by increasing the temperature of reaction conditions. The pellets were packed in aluminum pouch and charged for accelerated stability study at 40 °c /75 RH for 3 months in accelerated stability chamber At the end of 1,2 and 3 months the formulation were evaluated for the drug content.

D.Scanning Electronic Microscopy:

Scanning electronic microscopy was used to test the surface morphology of pellets. The pellets were coated with gold and observed under scanning electron microscopy for surface characteristics

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Fig 5: SEM Study

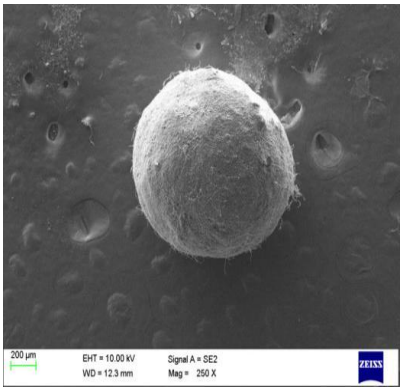
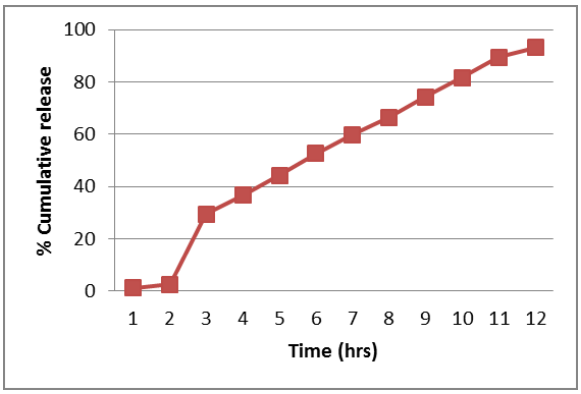


Fig 6: % Cumulative Release of Optimized formulation



III RESULTS

FT-IR studies revealed that there was no drug polymer interaction. SEM studies revealed that the pellets were smooth and spherical shape. Micrometrics properties indicating good flow characteristics of the pellets suitable for handling and filling into capsules. The *in-vitro d*issolution drug profile of optimized formulation in phosphate buffer P^H 6.8 shows prolonged drug release. The dissolution profile in 0.1N HCl shows that the pellets were enclosed in a enteric coated capsule, would prevent drug release in acidic medium of the stomach. So that intestinal absorption of the drug would be improved, leading to increased bio availability.

IV CONCLUSION

It can be concluded that the controlled release matrix pellets prepared by 1:1 ratio of (Drug: polymer) HPMC shows extended release profile having better bioavailability.

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