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# Preparation and evaluation of delayed release pantoprazol sodium sesquihydrate pellets by extrusion and spheronization technique

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## ABSTRACT

The present invention concerns the development of delayed release pellets of Pantoprazole sodium sesquihydrate which are designed to modify the drug release followed by delay of release of action. The use of multiparticulate systems to provide modified release formulations is ever increasing and it is an ideal way of delivering drugs that are acid sensitive and it also aids in effective local delivery. The two most common approaches to pellet formulation are extrusion/spheronization and coating of non-pareil seeds. Pantoprazole core pellets were formulated by using extrusion and spheronization process by polysorbate- 80 as binder. The core pellets were seal coated by HPMC 5CPS as first coating material. To seal coated pellets were again coated by using eudragit L-30 D-55 as enteric coating material to delay the drug release (Eudragit L-30 D-55 concentration is raised to get delayed release of drug). The coated pellets size and shape was observed during processing. The coated pellets were evaluated for surface morphology, assay, *in vitro* drug release to attain the aim of delayed release. Compatibility studies performed using FTIR revealed no deleterious interactions between drug and excipients. The optimized Formulation (F5) was kept under stability conditions at for 3 months as per ICH guidelines which revealed that the formulation was stable through period of storage.

**Keywords:** Extrusion, Spheronization, Delayed release, FTIR

## INTRODUCTION

The proton pump inhibitors are extensively used in the management of gastroesophageal reflux disease, gastric ulcer, duodenal ulcer, Zollinger-Ellison syndrome. *H. pylori* infection is the main cause of gastritis, gastroduodenal ulcer disease and gastric cancer.[1] At present, the treatment of choice for *H. pylori* infection is triple therapy containing a proton pump inhibitor and two antibiotics.[2,3,4.] The PPIs are superior to the $H_2$-receptor antagonists in healing, symptom relief and maintenance therapy of erosive and nonerosive gastroesophageal reflux disorder (GERD). [(4)] Although there are some differences in pharmacokinetics and binding affinity for the pump, all PPIs are comparatively similar in their efficacy in treatment of gastric diseases. There are numerous side effects of proton pump

inhibitors but they occur infrequently. .[5] The side effects are headache, diarrhea, abdominal pain, dizziness, rash and constipation. Oral administration of drugs has been the most common and preferred route for delivery of most therapeutic agents. The popularity of the oral route is attributed to patient acceptance and ease of administration. [6]. In oral drug delivery system, there are many types of dosage forms available to deliver the drugs such as tablets, capsules, liquids etc. However, tablet dosage forms are preferred due to their accurate dose, good physical and chemical stability, competitive unit production costs and an elegant distinctive appearance resulting in a high level of patient acceptability[7, 8, 9.] Orally administered drug must be absorbed through the gut which depends on various factors such as gastric emptying, intestinal motility, mucosal surface area, degradation of drug in the stomach and first pass effect.[10, 11.] The absorption rate varies from the stomach to the intestine owing to the increased surface area (about 4500 cm2), the intestinal mucosa and greater blood flow (1000 ml/min) through the intestinal capillaries compared to the gastric capillaries. It is also known that some drugs possessing pH dependent stability which are not stable in acidic environment (in the stomach).[12,13] Various techniques have been developed to overcome this stability problem. One out of them is development of enteric coated products. These enteric-coated dosage forms resist the acidic environment of the stomach and allow disintegration in the higher pH environment of the intestinal fluid. The enteric coating on a solid dosage form can also be used for site-specific drug delivery of a therapeutic agent to the intestinal region[14,15]

## MATERIALS AND METHODS

Pantoprazole sodium sesquihydrate was a gift sample from nifty labs, India.MCC PH 101 was a gift sample form FMC biopolymers. sodium carbonate was supplied by canton labs, polysorbate 80 and Eudragit L-30-D55 was a gift sample from evonik labs and triethyl citrate was supplied by Lezenzc pharma.

### Formulation of pellets

First we have to sieve all the ingredients like pantaprozole sodium and microcrystalline cellulose (avicel PH 101), cross povidone (kollidon CL), HPMC 3CPS,Sodium carbonate independently. After sieving mix all the above ingredients in rapid mix granulater for 10 minutes. The binder solution was prepared by dissolving the polysorbate 80 in water in stirring conditions then prepared binder solution was added to the drug mixture. Finally it becomes like wet mass. This wet mass was passed through the extruder, rod shaped extrudates were formed. The extrudates were placed in spheronizer to get spherical shaped pellets. The spherical shaped pellets were dried in fluidized bed processer. These pellets were seal coated with HPMC-5. Finally these pellets were enteric coated with mixture of eudragit L-30 D-55 and talc, tri ethyl citrate. The coating was carried out until enteric coating was achieved.

### Note

The coating suspension was kept under the continuous overhead stirrer because the settlement of talc may take place and lead to blockage of nozzle and inefficient coating.

### Formulation Chart

| S no. | Ingredients | Qty/cap F1 | F2 | F3 | F4 | F5 |
|---|---|---|---|---|---|---|
| 1. | Pantoprozole sodium sesquihydrate | 40 | 40 | 40 | 40 | 40 |
| 2. | Micro crystalline cellulose(Avicel PH101) | 35.74 | 35.74 | 35.74 | 35.74 | 35.74 |
| 3. | Cross povidone | 15 | 15 | 15 | 15 | 15 |
| 4. | Hpmc 3CPS | 1 | 1 | 1 | 1 | 1 |
| 5. | Sodium carbonate | 6.5 | 6.5 | 6.5 | 6.5 | 6.5 |
| **Binder addition** | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| 6. | Polysorbate 80 | 5 | 5 | 5 | 5 | 5 |
| 7. | Purified water | q.s | q.s | q.s | q.s | q.s |
| **Seal coating** | | | | | | |
| 8. | Hpmc 5CPS | 4.130 | 6.194 | 6.194 | 6.194 | 6.194 |
| 9. | Purified water | q.s | q.s | q.s | q.s | q.s |
| **Enteric coating** | | | | | | |
| 10. | Eudragit L-30 D-55 | 20.132 | 20.519 | 33.553 | 47.877 | 53.685 |
| 11. | Triethyl citrate | 2.01318 | 2.052 | 3.355 | 4.787 | 5.369 |
| 12. | Talc | 10.0659 | 10.259 | 16.777 | 23.939 | 26.843 |
| 13. | Purified water | q.s | q.s | q.s | q.s | q.s |
| | Total weight (mg) | **139.581** | **142.265** | **163.119** | **186.037** | **195.330** |

**All quantities are in mg**

## EVALUATION OF PELLETS

### Bulk Density

Funnel and measure the volume and weight as is given Bulk density of a compound varies significantly with the method of crystallization, milling or formulation. Bulk density is determined by pouring pre-sieved blend into a graduated cylinder via a large by

**Bulk Density** = Weight of the blend / Bulk Volume of the Blend.

### Tapped density

Tapped density is determined by placing a graduated cylinder containing known mass of blends on a mechanical tapped apparatus, which is operated for a fixed number of taps until the powder bed volume has reached a minimum volume. Using the weight of the drug in the cylinder and this minimum volume, the tapped density may be computed.

**Tapped Density** = Weight of Blends /Tapped Volume of Blends

### Determination of Sieve analysis (%)

Arrange the sample collector, 20ASTM sieve, 16ASTM sieve, Weigh and transfer around 100g of the sample into 16 ASTM sieve and shake for 5 minutes. Collect the 16 ASTM retains ($W_{16}$) from 16 mesh and 20 ASTM passes ($W_{20}$) from the sample collector.

Calculation: Calculation the % retains and passing's as follows.

% Retains on 16 ASTM = ($W_{16}$ in g/ Weight of sample in g) X 100

% Passing through 20 ASTM = ($W_{20}$ in g/ Weight of sample in g) X100

### Determination of Assay by UV - Vis (% w/w)

Accurately weighed quantity of the pellets equivalent to about 40.0mg of pantoprazole sodium sesquihydrate in a 50 mL volumetric flask add 50mL of 0.1N Hcl and take 1mL of above solution in 100mL volumetric flask and dilute to the volume with 0.1N Hcl. Absorbance was read at 284 nm against the reagent blank, and the concentrations of pantoprazole sodium sesquihydrate in µg/ ml was determined by using the regression equation.

**Y = 0.0507X + 0.021**

**Drug content in mg = conc. µg/ml * dilution factor**

**% Drug content = (drug content in mg /label claim X100**

### Determination of drug release by UV -Vis (% w/w)

Carefully transfer the pellets individually in each of the 6 dissolution flasks, containing 900 mL of 0.1N Hcl, which has been equilibrated to the temperature of 37± 0.5°C. Immediately start the Apparatus , after specified interval withdraw sample from a zone midway between the surface of the medium and top of the rotating blade and not less than 1 cm from the vessel wall and filter through 0.45µ membrane filter by discarding the first 5 mL and take 5.0mL of filter solution.

| Medium | 0.1N HCL, 900ml, PH 6.8 |
|---|---|
| Buffer. Apparatus | USP Apparatus II |
| RPM | 50 |

### Sampling Interval

1st, 2nd hours in 0.1 Hcl and remaining in pH 6.8 Buffer

### Procedure

Determine the amount of Pantoprazole sodium sesquihydrate release in UV absorption at the wavelength of maximum absorbance at about 284nm in for first 2 hours and 291 for the remaining duration on filtered portions of the solution under test, suitably diluted with Dissolution medium.

### Stability study

For all the pharmaceutical dosage forms it is important to determine the stability of the dosage form. This will include storage at both normal and exaggerated temperature conditions, with the necessary extrapolations to ensure the product will, over its designed shelf life, provide medication for absorption at the same rate as when originally formulated. The design of the formal stability studies for the drug product should be based on the knowledge of the behavior and properties of the drug substance and formal stability studies on the drug substance. Specification which is list of tests, reference to the analytical procedures and proposed acceptance criteria, including the concept of different acceptable criteria for release and shelf life specifications, is addressed in ICH guidelines.

## STORAGE CONDITIONS

### Stability samples are stored at

Accelerated : 40±2°C/75±5% RH
Intermediate: 30±2°C/65±5% RH
Long term : 25±2°C/60±5% RH

### Testing Intervals for

Accelerated: Initial, 1, 2, 3 & 6 months
Intermediate: Initial, 3, 6, 9 & 12 months.
Long term: Initial, 3, 6, 9, 12, 18, 24 & 36 months.

### In general significant change for a drug product is defined as

- A 5% change in assay from its initial value or failure to meet the acceptance criteria for when using biological or immunological procedures.
- Any degradation products exceeding its acceptance criterion.
- Failure to meet the acceptance criterion for appearance, physical attributes, and functionality test. e.g. size, shape and dose delivery per activation however some changes in physical attributes may be accepted under accelerated condition and as appropriate for the dosage form.
- Failure to meet the acceptance criterion for pH.
- Failure to meet the acceptance criterion for dissolution for 12 dosage units.
- Studies like assay, dissolution studies were carried out for a period of 3 months. Initial stage, at the end of first month, second month and third month the above said parameters were carried out at 25$^{O}$C/60%RH, 30$^{O}$C/65% RH and 40$^{O}$C/75%RH.

## RESULTS AND DISCUSSION

The present work was an attempt to formulate and evaluate oral delayed release formulation for 40mg dose. It has been explored to prevent ulcers.

### Preformulation characteristics of Drug

### Physical characterization

Preformulation studies of drug were performed to characterize pantoprazole sodium sesqui hydrate. The results are shown in the table 5.1; the above results mentioned in tables shows that API complies with the standard limits.

### Analytical studies

Determination of $\lambda_{max}$ of pantoprazole sodium sesqui hydrate:
After scanning 10 µg/ml solution of pantoprazole, the $\lambda_{max}$ of pantoprazole was found to be 284nm in

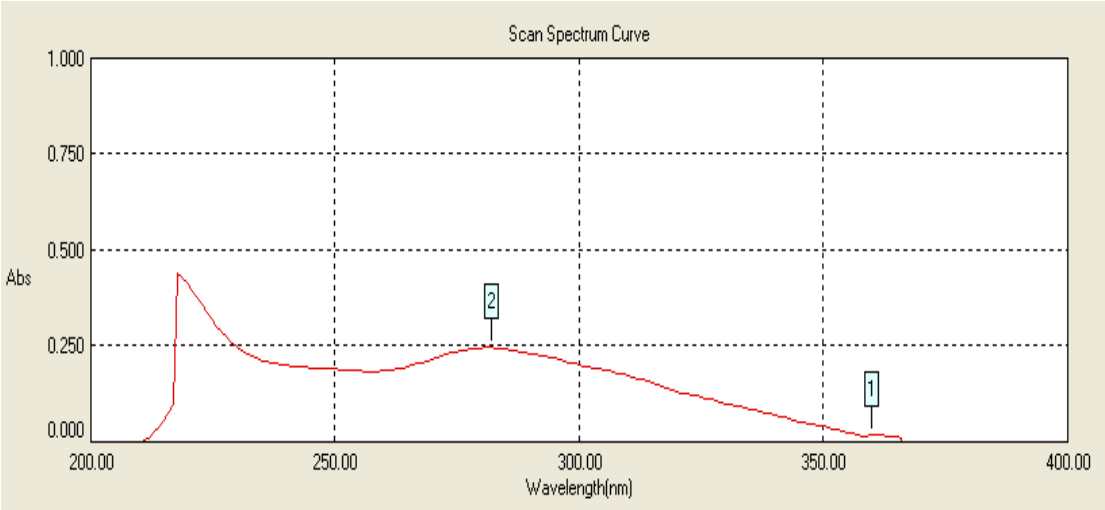
0.1N Hcl solution and 291 nm in pH 6.8 Buffer solution as shown in Fig: 5.1 and 5.2 respectively

## Standard Graph of Pantoprazole sodium sesqui hydrate

## Standard Graph in 0.1 N Hcl solutions

The scanning of the volumetric solution of pantoprazole sodium sesqui hydrate in the ultraviolet range (200-400nm) against 0.1 N HCl blank gave the $\lambda_{max}$ as 284 nm. The standard concentrations of drug (5-20 µg/ml) prepared in 0.1N HCl showed good linearity with $R^2$ value of 0.999, which suggests that it obeys the Beer--Lamberts law.

## Determination of $\lambda_{max}$ of Pantoprazole Sodium sesqui Hydrate in 0.1N HCl




**Standard Graph of Pantoprazole Sodium sesqui Hydrate in 0.1N HCl**

**Table: 5.2. Observations for Calibration Curve of Pantoprazole Sodium sesqui Hydrate in 0.1 N HCl**

| Sno | CONC(mcg/ml) | ABSORBANCE |
|---|---|---|
| 1 | 0 | 0 |
| 2 | 5 | 0.270 |
| 3 | 10 | 0.538 |
| 4 | 15 | 0.821 |
| 5 | 20 | 1.051 |

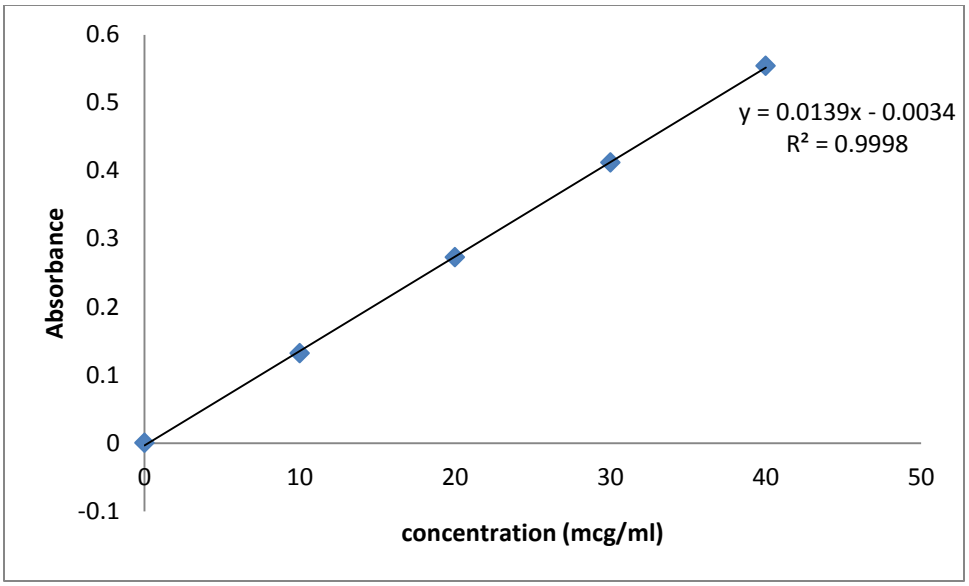



**Fig: 5.2. Standard Calibration Curve of Pantoprazole Sodium sesqui Hydrate in 0.1N HCl at 284 nm**

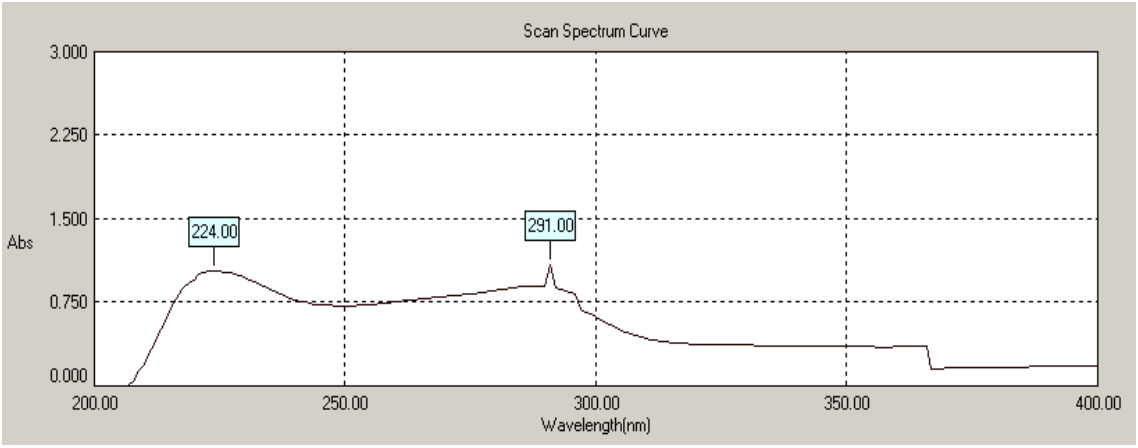


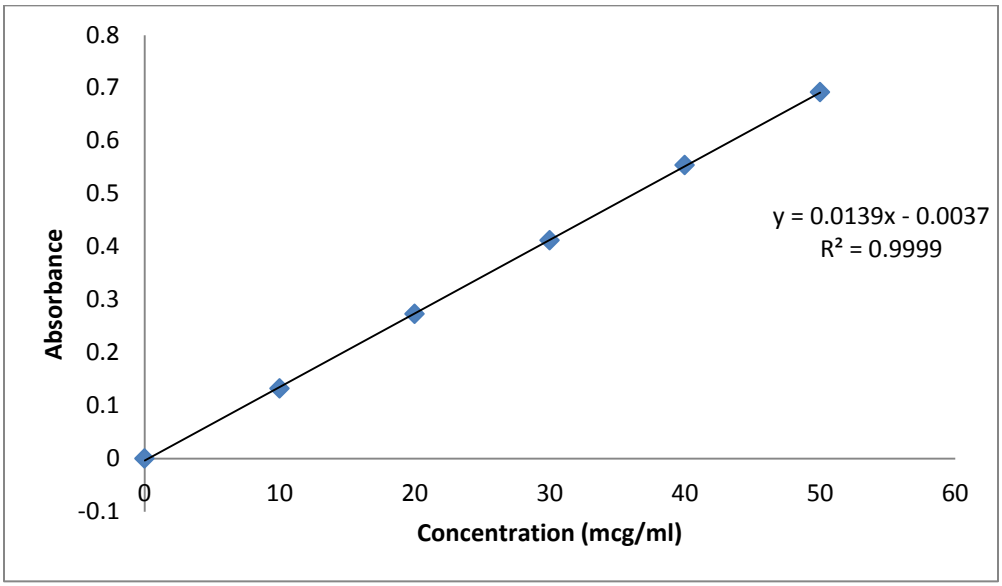

**Fig: 5.3. Determination of $\lambda_{max}$ of Pantoprazole Sodium sesqui Hydrate in pH 6.8 Phosphate Buffer:**

**Table: 5.3. Observations for Calibration Curve of Pantoprazole Sodium sesqui Hydrate in pH 6.8 Phosphate Buffer at 291 nm**

| Sno | CONCENTRATION | ABSORBANCE |
|---|---|---|
| 1 | 0 | 0 |
| 2 | 10 | 0.132 |
| 3 | 20 | 0.273 |
| 4 | 30 | 0.412 |
| 5 | 40 | 0.554 |
| 6 | 50 | 0.692 |

**Fig: 5.4.** Standard Graph of Pantoprazole Sodium sesqui Hydrate in pH 6.8 Phosphate Buffer: 6.2.2.2. Standard Graph in pH 6.8 Phosphate Buffer solution. The scanning of the volumetric solution of pantoprazole sodium sesqui hydrate in the ultraviolet range (200-400nm) against pH 6.8

Phosphate Buffer blank gave the $\lambda_{max}$ as 291 nm. The standard concentrations of drug (10-50 µg/ml) prepared in pH 6.8 Buffer l showed good linearity with $R^2$ value of 0.999, which suggests that it obeys the Beer-Lamberts law.




## Drug - Excipients Compatibility Studies

Compatibility studies by accelerated stability testing showed that there was no physical change or interaction between drug and selected excipients. The FTIR spectrum of the Formulation showed drug in its active form without any alteration of chemical structure .Based on the compatibility results and composition of the excipients were selected for formulation development.

| S. No. | Drug and Excipients | Initial Physical Description | 25°C / 60% RH & 40°C / 75% RH (Closed) | | |
|---|---|---|---|---|---|
| | | | 1st Week | 2nd Week | 4th Week |
| 1 | Pantoprazole | White powder | * | * | * |
| 2 | Pantoprazole + MCC PH 101 | white powder | * | * | * |
| 3 | Pantoprazole + Cross povidone | White powder | * | * | * |
| 4 | Pantoprazole + HPMC 3 cps | White powder | * | * | * |
| 5 | Pantoprazole + HPMC 6 cps | White powder | * | * | * |
| 6 | Pantoprazole + Eudragit L 30 D 55 | White powder | * | * | * |
| 7 | Pantoprazole + Sodium carbonate | White powder | * | * | * |
| 8 | Pantoprazole + Polysorbate 80 | White powder | * | * | * |
| 9 | Pantoprazole + MCC PH 101 + Cross povidone +HPMC 3 cps+ HPMC 6 cps + Eudragit L 30 D 55+ sodium carbonate | White powder .containing lumps | * | * | * |

## Note

Star mark (Y) indicates that there is interaction between drug and excipients at 25° C/60% RH, 40°C/75% RH ,(*) indicates that there is no interaction between drug and excipients at 25° C/60% RH, 40°C/75% RH.

## FTIR

### FTIR Spectrum of Pantoprazole Pure Drug

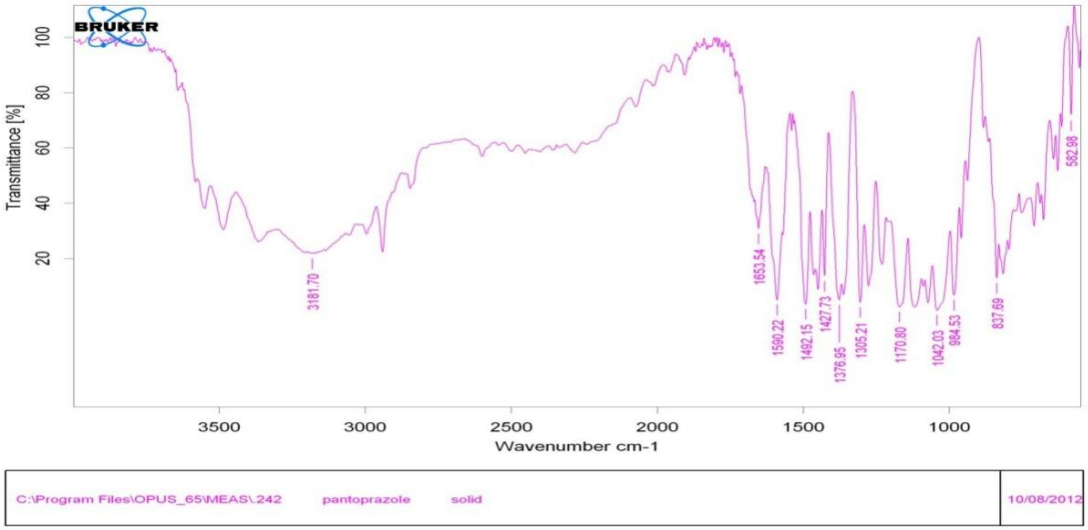



**Fig 5.6: FTIR SPECTRUM OF PANTOPRAZOLE ENTERIC COATED PELLETS**

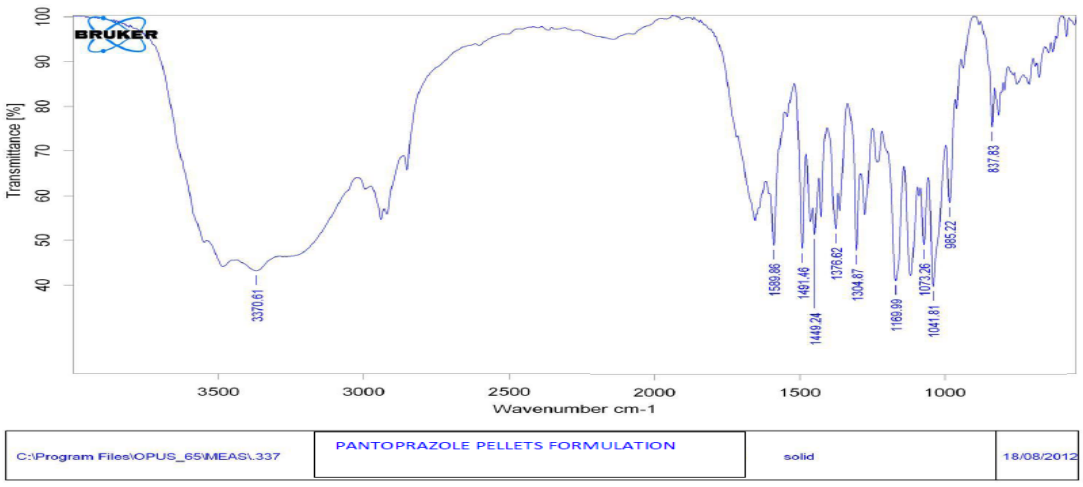



**Table: 5.5. FTIR Peak Positions ($cm^{-1}$) and Assignments for Pantoprazole Sodium sesqui Hydrate Drug and its Combinations with Excipients in the Delayed enteric coated pellets**

| S.NO | Wave number in formulation ($cm^{-1}$) | | Bond nature and bond attributed |
|---|---|---|---|
| | Pure drug | Optimized Formulation | |
| 1 | 3181.70 | 3370.61 | N-H stretching |
| 2 | 2984.15 | 2975.16 | C-H stretching ($-CH_2$) |
| 3 | 1590.22 | 1580.96 | C=N stretching |
| 4 | 1427.73 | 1449.24 | $CH_2$ bending |
| 5 | 1170.80 | 1169.99 | CO- aromatic ether stretch |
| 6 | 837.69 | 837.83 | C-H plane bending |

## EVALUATION OF PELLETS

The bulk densities of the formulations ranged between 0.512 ±0.08 to 0.583 ±0.06 gm/$cm^3$. The optimized formulation f5 showed bulk density value of 0.512 ±0.08 gm/$cm^3$. The tapped densities of the formulations ranged between 0.597 ± 0.04 to 0.651 ± 0.06 gm/ $cm^3$. The optimized formulation f5 showed bulk density value of 0.598 ± 0.08 gm/$cm^3$. The values of all formulations indicate existence of good flow property. All the formulations were subjected to sieve analysis, it was noted that all of them passed the limits. (not more than 5 should retain on 16 mesh and not more than 5 should pass through 20 mesh) the formulations were assayed for the drug content by uv method, the results revealed that the drug content was in the range of 98.10 ± 0.03 % to 98.17 ± 0.02 %.

| FC | Bulk density (gm/$cm^3$) | Tapped density (gm/$cm^3$) | Sieve Analysis % retained on 16 ASTM | % Passed through 20 ASTM | Assay (%) |
|---|---|---|---|---|---|
| F1 | 0.512 ±0.08 | 0.598 ± 0.05 | 2.7 | 3.1 | 98.17 ± 0.02 |
| F2 | 0.583 ±0.06 | 0.650 ± 0.06 | 2.0 | 1.5 | 98.10 ± 0.03 |
| F3 | 0.576 ±0.04 | 0.651 ± 0.06 | 2.3 | 1.30 | 99.13 ± 0.08 |
| F4 | 0.529 ±0.06 | 0.597 ± 0.04 | 3.1 | 2.3 | 99.12 ± 0.09 |
| F5 | 0.512 ±0.08 | 0.598 ± 0.08 | 3.2 | 2.1 | 99.15 ± 0.06 |

## DISSOLUTION PROFILES

### Invitro drug release studies

The invitro drug release was inversely proportional to the amount of enteric coating on the pellets. Formulation F1 that had only 4 % seal coating released 94.11% drug within 1 hour of the study. Formulation F2 that had 6 % seal coating and 30% enteric coat could not resist the acidic medium and released 18 % of drug within 15 min of study at the end of 2 hours complete drug was released. Formulation F3 that had 6 % seal coating and 50% enteric coat could not resist the acidic medium and released 28 % of drug within 30 min of study at the end of 2 hours 15 min complete drug was released. Formulation F4 that had 6 % seal coating and 70% enteric coat could not resist the acidic medium and released 16 % of drug within 1 hour of study at the end of 2 hours 45 min complete drug was released. Formulation F5 that had 6 % seal coating and 80% enteric coat could resist the acidic medium and released 4.68 % of drug within 90 min of study at the end of 2 hours 45 min complete drug was released

**Table no.18: *In vitro* dissolution studies of enteric coated pellets**

| Time(min) | % Drug Release | | | | |
|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 |
| 15 | 43.34 | 18.63 | ---- | ---- | ---- |
| 30 | 87.12 | 43.25 | 28.14 | ---- | ---- |
| 60 | 94.11 | 53.42 | 41.02 | 16.16 | ---- |
| 90 | | 74.03 | 52.33 | 29.35 | 4.68 |
| 120 | | 94.33 | 72.15 | 38.52 | 13.14 |
| 135 | | | 96.07 | 52.13 | 51.13 |
| 150 | | | | 70.15 | 69.15 |
| 165 | | | | 96.54 | 95.07 |

## CONCLUSION

The present study was to formulate and evaluate delayed release pellets of Pantoprazole sodium sesqui hydrate. The formulation process was carried out in FBP by Extrusion & Speronization technique. Pantoprazole sodium sesqui hydrate is an acid liable drug; it degrades at acid pH of the stomach. To bypass stomach, the formulation has to delay the release and give the release in proximal small intestine. This can be achieved by enteric coating. The work was carried out to delay the release of drug by using enteric coating polymer Eudragit L-30-D55. The study includes preformulation of drug and excipients, formulation and evaluation, and stability studies of pellets. Enteric coated pellets were evaluated for compatibility, assay, dissolution and surface morphology, the results were found to be optimum. Accelerated stability studies were conducted for 3 months. Based on the assay, dissolution release profile, a stability value the optimized enteric coated formulation (F5) was to be stable and is optimized.

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