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# DEVELOPMENT AND EVALUATION OF ENTERIC COATED OMEPRAZOLE PELLETS 22.5% W/W

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**Abstract:**
*The objective of the present study is to formulate and evaluate enteric coated delayed release pellets of Omeprazole. The formulations of Omeprazole delayed release pellets of were developed by enteric film coating process varying the compositions of drug loading, barrier coating and enteric coating. HPMC E5 was used as enteric polymer. The process variables were standardized and the different batches prepared were evaluated for assay/drug content, water content, acid resistance and dissolution rate. The drug dissolution profiles of Omeprazole delayed release formulations developed were compared with that of innovators product. Based on the results formulation containing enteric coating polymer and plasticizers has been selected as the best formulation developed for Omeprazole delayed release pellets.*

**Keywords:** *Enteric coating, Delayed release, Omeprazole, Pellets*

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## INTRODUCTION:

Oral route is the most widely used route for drug administration because of its convenience. Different types of dosage forms of delayed release, controlled and sustained release are administered through this route [1]. After admistration, the drug present in the dosage form enters into the stomach and thereby intestine. Some drugs are unstable in the gastric environment of the stomach, that type of drugs are administered by giving coating to release the drug only in the intestine, which are called as enteric coated formulations [2,3]. The primary aim of using delayed release products is to protect the drug from gastric fluids, to reduce gastric distress caused by drugs particularly irritating to the stomach or to facilitate gastrointestinal transit for drugs that are better absorbed from intestine[4]. Enteric polymers are becoming very popular due to their property of intact in the stomach, but will dissolve and release of the contents once it reaches the small intestine, their prime intension is to delay the release of drugs, which are inactivated by the stomach contents or may cause bleeding or nausea by the irritation of gastric mucosa [5,6].

Omeprazole is a proton pump inhibitor used for short-term treatment of acid peptic disease, gastro esophageal reflux, gastric ulcer, duodenal ulcer. Omeprazole degrades in water but is readily soluble in alkaline conditions [7,8]. The stability of omeprazole decreases in acidic medium, when it comes in contact of acidic medium leads a significant degradation of the drug and hence reduced bioavailability [9]. Due to its low bioavailability, short biological half life and hepatic first pass metabolism, omeprazole enteric-coated pellets were developed [10]. hence, attempts have been made to develop enteric coated delayed release product which increase residence time due to attachment with the intestinal mucosa for prolong time and may give local effect in duodenal ulcer, reduced drug loss and also reduced dosing frequency [11,12].

## MATERIALS AND METHODS:

Omeprazole pure drug obtained from Everest Organics private Limited, HPMC E5 polymer and PEG 5000, tween 80 were obtained form viswaat chemicals ltd. starch, potassium di hydrogen o-phosphate was purchased from srinor laboratories, acryl coat L30, talc, titanium dioxide were purchased from Corel pharma chem.

**Formulation of Pellets:**

**Table 1: Formulation of Pellets**

| **Ingredient** | Quantity Required | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **F1** | **F2** | **F3** | **F4** | **F5** | **F6** | **F7** | **F8** | **F9** |
| Omeprazole | 11.80 | 11.80 | 11.80 | 11.80 | 11.80 | 11.80 | 11.80 | 11.80 | 11.80 |
| Sucrose | 3.54 | 4.54 | 4.54 | 4.54 | 4.54 | 4.54 | 4.54 | 4.54 | 4.54 |
| Starch | 5.24 | 5.24 | 5.24 | 5.24 | 5.24 | 5.24 | 5.24 | 5.24 | 5.24 |
| SLS | ----- | 1.54 | 1.54 | ---- | 1.54 | 1.54 | 1.60 | 1.54 | 1.54 |
| DSHP | 2.90 | 2.90 | 2.90 | 2.90 | 2.90 | 2.90 | 3.00 | 2.90 | 2.90 |
| HPMC E5 | 1.500 | 2.00 | 3.00 | 3.500 | 4.00 | 4.00 | 5.00 | 4.00 | 4.00 |
| Sugar | 3.64 | 3.64 | 3.64 | 3.64 | 3.64 | 3.64 | 3.64 | 3.64 | 3.64 |
| Methacrylic acid | 20.00 | 250.00 | 30.00 | 350.00 | 40.00 | 50.00 | 55.00 | 50.00 | 650.00 |
| PEG | ---- | 1.00 | ---- | 1.16 | --- | 1.16 | 1.16 | 1.16 | 1.16 |
| Talc | 0.82 | 0.82 | 0.82 | 0.82 | 0.82 | 0.82 | 0.82 | 0.82 | 0.82 |
| Titanium Dioxide | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Tween 80 | ----- | ----- | 0.12 | 0.12 | 0.12 | 0.12 | 0.12 | 0.12 | 0.12 |
| Methyl Parabane | ------ | 0.002 | 0.004 | 0.006 | 0.008 | 0.008 | 0.008 | 0.008 | 0.008 |
| Propyl Parabane | ----- | ------ | 0.0004 | ----- | 0.0006 | 0.0008 | 0.0008 | 0.0008 | 0.0008 |

Series of sieves were arranged in the order of their decreasing pore diameter (increasing sieve number) i.e. sieve no. ASTM 40, 60, 80, 100 with 40 grams of drug were weighed accurately and transferred to sieve 40 which were kept on top. The sieves were shaken for about 5-10 minutes[13] .Then the drug retained on each sieves were taken, Weighted separately and expressed in terms of percentage. 69.4% Omeprazole powder pass through sieve 100 (NLT 65% should pass through 100 mesh) similarly all the formulations were passed through the sieves to prepare powder [14,15].

**Method of Preparation of Core Pellets:** Core pellets was prepared by drug; loading on seed pellets. The required quantity of Omeprazole was weighted and sifted through sieve 30, starch, sodium lauryl sulphate, seed pellets, DHSP were weighted accurately and sifted through sieve, and blend was prepared [16]. Sugar, Hydroxyl propyl methyl cellulose was dissolved in purified water and it is used as granulating fluid for granulation. Seed pellets loaded into conventional coating pan equipment parameters set as determined and spraying of binder solution has started, while spraying drug mix was sprayed on the seed pellets bed. The same procedure continued up to completion of core pellets processing core pellets has dried for 8 hours [17,18].

**Parameters-** LOD of wet pellets- 27 % · LOD of dried pellets- 1.5 %

**Seal Coating on Core Pellets:** The required quantity of Hydroxyl propyl methyl cellulose and plasticizer were weighed and dispersed in purified water with the help of overhead stirrer for over a period of 10 min. Pigment suspension was prepared by dissolving titanium dioxide, color, in a sufficient volume of purified water by using homogenizer [19]. The pigment suspension was added in HPMC solution then specified volume of sufficient sugar syrup was added and continuous stirring for another 5 minutes. Prepared coating suspension was sprayed on core pellets in fluid bed processor. The coating was carried out with the help of bottom spray. The coating was continuous until 5% build up was achieved [20,21].

**Fluidized Bed Processor Was Operated with Following Conditions [22,23]** ·
Inlet temperature - 40-42$^0$ C ·
Bed temperature – 35-40$^0$ C ·
Exhaust (blower) - 3000 RPM ·
Spray rate- 7 RPM ·
Air pressure- 15 kg\cm$^2$

**EVALUATION OF ENTERIC COATED PELLETS:** Procedure provided in this document is limited for chemical tests only (i.e., identification, assay and dissolution tests) All physical quality attributes shall be tested as per the procedure laid in general testing procedure for pellets.

**1. Moisture content by KF [24]** Taken about 15 – 20 ml of methanol in titration vessel and neutralized the solvent with Karl Fischer Reagent. Weighed accurately about 1.0gm of omeprazole, transferred to the pre – neutralized KF titration vessel, carried out the titration and noted the titer value and calculated the moisture content from the following formula.

$$\text{Moisture Content} = \frac{\text{Titer value X KF factor}}{\text{Weight of sample taken for titration}}$$

Determined the moisture content on 0.1 g of the sample.

2. **Bulk Density [25,26]:** Taken about 10g of pellets in to a dried in a 25ml measuring cylinder and measured the volume. Calculated the Bulk Density in g per ml.

**Calculation:** $\text{Bulk Density} = \frac{\text{Wt of the sample in g}}{\text{Volume in ml}}$

**3. Pellets mesh size:** Placed 10g of sample in required standard sieves and sieved it for 10 minutes. Calculated the % retention by passing the pellets through the sieves**.**

$$\%\text{Retention from ASTM \# 14v} = \frac{\text{Wt.of retained pellets } \mathbf{X\ 100}}{\text{Wt.of sample taken}}$$

$$\%\text{Passing through ASTM \# 18} = \frac{\text{Wt. of passed through sieve X 100}}{\text{Wt of sample taken}}$$

**4. Identification: (By HPLC) [26]:** The principal peak in the chromatogram obtained with test preparation should have the same retention time as that of the peak in the chromatogram obtained with standard solution.

**Assay:**

**Chromatographic Conditions: Column-** : C18, 150 × 4.6, 5µ **Make-** : Thermo Scientific, ODS Hypersil or equivalent **Wavelength:** 305nm. **Flow rate**: 1.2 ml/min. **Injection Volume**: 10µl. **Column Temperature**: Ambient

**Chemicals and Reagents:** Sodium borate decahydrate AR grade Water HPLC grade or equivalent Sodium hydroxide AR grade Alcohol Di-sodium edentate AR grade Glycine AR grade Methanol Acetonitrile **Preparation of Diluents** Dissolved 7.6 g of sodium borate decahydrate in about 800ml of water. Added 1.0 g of Edetate disodium and adjusted with 50% sodium hydroxide solution to a pH of 11.0 ± 0.1. Transferred the solution to a 2000ml volumetric flask, added 400ml of dehydrated alcohol and diluted with water to

volume. **Preparation of Solution A** Prepared a filtered and degassed solution of 6.0 g of glycine in 1500 ml of water. Adjusted with 50% sodium hydroxide solution to a pH of 9.0 and diluted with water to 2000ml.

**Preparation of Solution B** Used a filtered and degassed mixture of Acetonitrile and Methanol (85:15).

**The chromatograph is programmed as follows:**

| Time (minute) | Solution A % | Solution B% | Elution |
|---|---|---|---|
| 0-20 | 88-40 | 12-60 | Linear Gradient |
| 20-21 | 40-88 | 60-12 | Linear Gradient |
| 21-25 | 88 | 12 | Isocratic |

**5. Dissolution Test [27]:** Acid medium: 0.1N HCL Apparatus: USP Apparatus II (Paddle) Speed: 100 RPM Temperature: 37°c ±0.5°c Dissolution volume: 500 ml Time: 120 Minutes (2 hours)

**Dissolution Procedure**: Weighed the pellets to be examined equivalent to 20mg of Omeprazole (Calculated based on label claim) and transferred it to the individual dissolution jars Run the dissolution for 2 hours at 1oo rpm.

**Test Solution:** After 2 hours; removed sample from each jar and collected the pellets on the sieve. Rinsed the pellets carefully with water. Quantitatively transfered the washed pellets into separate 100ml volumetric flask. Added 60ml of 0.01M Sodium borate solution. Sonicated on a sonicator to dissolve and added 20ml of alcohol to the flask and mixed. Diluted to volume with 0.01M sodium borate solution and mixed. Transfered 1.0ml of this solution in to a 10ml volumetric flask and diluted with 0.01M b Sodium borate solution to volume and mixed. (0.02mg /ml).

**Acid Standard solution (Duplicate):** Transferred about 20mg of Omeprazole WS, accurately weighed, to a 100ml volumetric flask. Added 60ml of 0.01M Sodium borate solution Sonicated on a sonicator to dissolve and added 20ml of alcohol to the flask and mixed. Diluted to volume with 0.01M Sodium borate solution and mixed. Transfered 1.0ml of this solution in to a 10ml volumetric flask and dilute with 0.01M Sodium borate solution to volume and mix. (0.02mg per ml).

**pH 6.8 phosphate buffer:** Added 400ml of 0.1N Hydrochloric acid to 320ml of 0.235M Dibasic sodium phosphate pH 10.4 adjusted pH of the solution with 2N sodium hydroxide or 2N Hydrochloric acid to a pH of 6.8±0.05.

**Dissolution Apparatus parameters:** Dissolution Medium: pH 6.8 phosphate buffer Apparatus : USP Apparatus II (Paddles) Speed : 100 RPM Temperature : 37°c±0.5°c Dissolution volume : 900ml Time : 30 Minute

**Dissolution Procedure:** Weighed the pellets to be examined equivalent to 20mg (calculated based on label claimed) and transferred it to the Dissolution jar and proceed as directed for Gastric resistance stage with a new set of samples from the same batch. After 2 hours, added 400ml of 0.235M Dibasic sodium phosphate pH 10.4 to the acidic medium. adjusted pH of the solution with 2N Sodium hydroxide solution or 2N Hydrochloric acid solution to a pH of 6.8± 0.05. Continued the dissolution test for 45 minutes.

**Test Solution:** After 45 minutes, withdrawn 5.0ml sample and transferred it in a test tube containing 1.0ml of 0.25M sodium hydroxide solution and mix. Filtered through a 0.45µ filter paper or fine porosity (Whatman No.41) and collected the filterate.

6. **Desciption [28]** – For checking the appearance of pellets 20 gm of pellets taken From respective batch and observed for the color, shape of pellets

7. **Dimension [29]** – The size of pellets was determined by using mitutoyo absolute Verniar caliper from the respective sample.

8. **Hardness [30]** – Hardness tester was used to determine the hardness of pellets. The test pellet was held between the edge of the fixed and movable part of the instrument and holds the pellets between the edges and the nozzle in edgewise position .the scale was adjusted by sliding so that the zero on the scale coincides with the pointer. The adjustable knob slowly moved till the pellet breaks. The pressure indicated on the dial was in N. Also hardness test was performed by Dr. Schieuniger hardness tester. Kept the pellets in between the two edges. After breaking of pellets reading displayed.

## RESULTS AND DISCUSSION:

Table 2:0.1N HCL % Drug Release

| Formula/Time | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|
| 20Min | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 40Min | 2.89 | 3.18 | 2.65 | 2.25 | 3.12 | 1.05 | 0.85 | 1.15 | 2.35 |
| 60Min | 3.00 | 3.42 | 3.30 | 3.0 | 3.60 | 1.50 | 1.20 | 2.0 | 3.0 |
| 80min | 4.20 | 4.58 | 4.60 | 3.50 | 4.20 | 2.10 | 2.20 | 2.6 | 4.2 |
| 100Min | 4.80 | 5.08 | 4.80 | 4.00 | 4.80 | 2.30 | 2.40 | 3.0 | 4.8 |
| 120Min | 5.56 | 5.98 | 5.65 | 4.25 | 5.05 | 2.55 | 2.85 | 3.45 | 6.35 |

Table 3: pH 6.8 phosphate buffer % Drug Release

| Formula/Time | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|
| 5Min | 69.12 | 72.80 | 69.69 | 80.95 | 78.68 | 91.69 | 90.69 | 89.95 | 86.95 |
| 10Min | 72.05 | 73.50 | 72.08 | 81.05 | 79.05 | 92.05 | 90.95 | 90.05 | 87.05 |
| 15Min | 73.86 | 76.20 | 73.88 | 82.86 | 81.86 | 93.86 | 91.86 | 91.86 | 87.86 |
| 20min | 75.08 | 79.08 | 75.02 | 83.08 | 83.08 | 95.08 | 95.08 | 93.08 | 88.08 |
| 25Min | 78.90 | 80.90 | 76.10 | 83.90 | 85.90 | 96.20 | 96.90 | 95.90 | 89.90 |
| 30Min | 80.15 | 82.26 | 77.00 | 84.25 | 86.72 | 97.00 | 98.00 | 96.25 | 90.25 |

**Evaluation:**

Stability data of the three commercial scale batches of the drug product Omeprazole Pellets 22.5% w/w been studied up to 06 months at $40^{O}C + 2^{O}C$ & 75 % + 5% (accelerated stability conditions) & and up to 42 months (i.e., shelf life + additional six months) at $30^{O}C + 2^{O}C$ & 60 % + 5% (Long term storage conditions) Test results obtained from periodical testing has been demonstrated in tabulated and graphical representations and been evaluated against the pre defined specification. It is found, No significant changed observed with respect to the appearance/description of the product, LOD, dissolution and assay results. The container closure system found to be faultless and confirmed to be competent & resistant to that of storage conditions provided during the accelerated stability study With reference to the study results, a commitment has also made for ongoing stability studies. As per the commitment every first batch of the year is proposed to be kept for stability under long term storage conditions.

Table 4: Evaluation of formulations

| **Batch NO** | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|
| **Test parameter** | **Results** | **Results** | **Results** | **Results** | **Results** | **Results** | **Results** | **Resuls** | **Results** |
| Description | Confirms | Confirms | Confirms | Confirms | Confirms | Confirms | Confirms | Confirms | Confirms |
| Identification | Confirms | Confirms | Confirms | Confirms | Confirms | Confirms | Confirms | Confirms | Confirms |
| Moisture content by KF | 1.02 % | 0.98 % | 0.78 % | 1.15 % | 1.21 % | 1.06 % | 0.78 % | 1.02 % | 1.15 % |
| Bulk Density | 0.85 g/ml | 0.84 g/ml | 0.86 g/ml | 0.85 g/ml | 0.84 g/ml | 0.86 g/ml | 0.86 g/ml | 0.85 g/ml | 0.85 g/ml |
| Assay For Omeprazole 22.5 % w/w (Labeled claim) | 93.25 % | 95.63 % | 94.86 % | 97.56% | 99.12% | 100.12 % | 99.86 % | 100.35% | 99.56% |
| Retention on #14 | 10.22 % | 8.02 | 5.8 | 0.45 % | 0.98 % | 1.12 % | Nil | 1.02 % | 0.45 % |
| Passing through # 18 | 1.12 % | 0.48 % | 1.02 % | 1.36 % | 1.00 % | 0.56 % | 1.02 % | 1.12 % | 1.36 % |
| %DR in acid | 80.15 % | 82.36 % | 77.00 % | 84.25 % | 86.72 % | 97.00 % | 98.00 % | 96.25 % | 87.25 % |
| % DR in Buffer | 69.12 | 72.8 | 69.69 | 80.95 | 78.68 | 91.69 | 90.69 | 89.95 | 90.25 |
| Total impurity | 0.3 % | 0.45 % | 0.3 % | 0.45 % | 0.35 % | 0.25 % | 0.3 % | 0.3 % | 0.45 % |

## CONCLUSION:

As evaluated above, test results ( of both accelerated and long term stability study ) with the three commercial batches it is confirmed that the formulation being used for Omeprazole Pellets are a stable formulation no changes has been observed during storage. No significant change took place in the Appearance, LOD, assay and dissolution testes. In both accelerated storage conditions Viewing that stability of product quality parameters, it can be concluded that product within the defined container closure system withstand successfully, against the accelerated term storage condition.

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