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Original Research Article

# Formulation and Evaluation of Esomeprazole Delayed-Release Tablets Using Multiple Unit Pellet System

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**Abstract:**
Esomeprazole belongs to the Proton-pump inhibitors class of drugs (azoles) that may be taken orally and is used to treat Gastroesophageal reflux disease, Peptic ulcers, Heartburns, Duodenal ulcers, Zollinger-Ellison syndrome. The main goal of this study was to formulate and evaluate Esomeprazole Delayed-Release MUPS Tablets. MUPS was designed as delayed-release particles firstly to resist the gastric-acid secretion and secondly to avoid dose dumping. MUPS were formulated by using one of the pelletization techniques i.e., solution-dispersion layering method using Wurster technology. The formulated Multiple Unit Pellets contain four successive coating layers of pre-coating, drug-loading, seal-coating, and enteric-coating onto the inert core (sugar spheres #45-60). These coatings contain inactive ingredients such as Hypromellose AN3, Talc, PEG 6000, Magnesium stearate, Eudragit L30 D, and Titanium dioxide. Eudragit L30 D was used as an enteric-coating polymer on the seal-coated pellets to protect the drug from acidic pH 1.2-3.5 and release it in alkaline pH 6.8. Esomeprazole has a biological half-life of about 1-1.5 hours. MUPS were evaluated for flow properties and in-vitro drug release. MUPS along with Tableting excipients (MCC Ph 102, PEG 6000, Colloidal silicon dioxide, LHPC-LH 11, Crospovidone, and Magnesium stearate) were evaluated for pre- compression parameters. These delayed-release MUPS containing 40mg Esomeprazole were compressed into tablets using the Direct-Compression method then post-compression parameters and %Assay were evaluated. The dissolution studies (in-vitro) were carried out in an acidic medium (0.1 N HCl) for 2hrs and then followed by an alkaline medium (pH 6.8 phosphate buffer) for 1 hr. These tablets were blister-packed and subjected to accelerated stability studies (40ºC±2ºC/75%±5%RH) for 1,2, and 3 months and compared with the %assay,
%acid resistance, and in-vitro dissolution studies of the initial and innovator results. Based on the results, a formulation whose %assay, % acid resistance, and in-vitro dissolution profile similar to the innovator has been selected as an ideal formulation for developing Esomeprazole delayed-release MUPS tablets.
**Keywords:** Proton-Pump Inhibitors (PPI's), Esomeprazole, Gastroesophageal reflux disease, Zollinger-Ellison syndrome, Wurster, Eudragit L30 D, LHPC LH-11, PEG 6000.

## Introduction

Initially, a novel drug product is protected by a patent when it is produced and commercialized in order to prevent other companies from producing a comparable product that is based on bioequivalence. Such drugs are commonly known as ―branded‖ or ―originator‖ drugs. When that protection period expires, other manufacturers can obtain FDA approval for their own formulations of the drug. The term ―generic‖ or ―multiple sources refer to medications whose initial patent protection of active ingredient has ended. Generic manufacturers may challenge patents before they expire in order to provide patients with more affordable medicines as soon as possible[1].

In order to encourage generics to undertake the extreme risk and expense of such patent challenges, Congress has granted the first pharmaceutical company to challenge such patents with the possibility for 180 days[2]. Generics are extremely important in healthcare. As branded drug expires, then the introduction of multiple generic manufacturers competes directly, resulting in considerable cost reductions for the healthcare system. According to Food and Drug Administration, a generic medicine is one that compares to the pioneer or reference, product (usually a branded drug) in strength, dosage form, route of administration, quality, safety and performance[3].

Gastro-resistant tablets are delayed-release tablets that are intended to withstand gastro-fluids and thereby deliver the drug into the intestinal fluid. These tablets are often composed of granules (or) particulates treated with a gastro-resistant coating (or) in some situations, tablets themselves are coated with a gastro-resistant coating[4].

The modified drug delivery system requires advancements in protein and peptide delivery techniques. Homeostasis is the process that keeps human metabolism functioning by releasing several bioactive components. Fluid pH ranges provide environmental triggers for responsive medication release in different segments of the gastrointestinal system[4,5].

A DR dosage forms are systems that are designed to release the active ingredient at a time other than immediately after administration. Dosage forms can be designed to alter the drug release over a period of time (or) after the dosage form reaches the desired site[6].

Delayed-release oral dosage forms have the ability to control the drug release until it reaches the targeted site, for example, when the dosage form reaches the small intestine (enteric-coated dosage forms) or the drug after a predetermined time in a predetermined location, i.e., they do not release the drug immediately after ingestion, such as enteric-coated tablets and pulsatile release capsules. The oral route of drug administration is generally considered as the most preferred patient- convenient approach of drug administration. The drug release from an oral dosage form may be consciously delayed until it reaches the intestine. So, polymers are often used to achieve this goal. A suitable polymer can be coated on the dosage form (for example, a tablet (or) the granules (or) pellets before tableting)[7].

Because the polymer dissolves as a function of pH when the dosage form passes from the low pH environment of the stomach to the higher pH environment of the small intestine, the polymer coat dissolves and the drug is released. When this takes place, the release is immediate again, and the resulting plasma concentration versus time curve is similar to that of the immediate release dosage form[8].

The proper selection and balance of excipients and processes in solid dosage

formulations are intended to improve the micrometric (or) macrometric properties of materials during manufacturing and /or to provide the desired drug delivery system. Tablets, capsules, granules and pellets are the most commonly used pharmaceutical delayed release solid oral dosage forms today[9,10].

The aim of the present study is to formulate Esomeprazole Multiple Unit Particulate System (MUPS) tablets as a delayed-release dosage form and study the in-vitro release pattern.

**Materials and Methods:**

**Determination of Absorption Maxima of Esomeprazole Magnesium Trihydrate by using UV-Spectrophotometer:**

**Preparation of Standard Stock Solution for UV- Spectrophotometric analysis[11]:**

- 10mg of Esomeprazole magnesium trihydrate was weighed accurately and transferred into a 20mL volumetric flask.

- Dissolve and dilute to 20mL with ethanol to produce a stock solution containing 500µg/mL of Esomeprazole.

- 10mL of standard solution is taken and diluted with pH6.8 phosphate buffer up to 50mL to produce a solution containing 100µg/mL of Esomeprazole.

- From the working standard solution, a series of solutions containing 20, 30, 40, 50, and 60µg/mL of Esomeprazole were prepared and scanned in a UV- Spectrophotometer.

- Thus, the absorption maxima (λmax) of Esomeprazole Mg. trihydrate were observed at a wavelength of 302nm.

**Calibration Curve /Standard graph of Esomeprazole Magnesium Trihydrate:**

**Instrument[12]:**
High-Performance Liquid Chromatography equipped with PDA/UV-Detector and data handling system.

**Table 1: List of Chromatographic Parameters of Calibration Curve**

| Chromatographic Parameters | | |
|---|---|---|
| 1. | Column | Inertsil ODS-3V 4.6-mm x 150-mm; 5-µm (or) equivalent column |
| 2. | Column Temperature | 25ºC |
| 3. | Wavelength | 302nm |
| 4. | Injection Volume | 20µL |
| 5. | Flow Rate | 1.0mL/minute |
| 6. | Elution | Gradient |

**Preparation of Mobile Phase[13]:**

A mixture of Buffer, Acetonitrile, and Methanol (50:40:10) was added with 0.1% v/v triethylamine and finally adjusted with glacial acetic acid to a pH of 6.8.

**Preparation of Buffer:**

Dibasic sodium phosphate (1.42 mg/mL) and Monobasic potassium phosphate (1.36 mg/mL) was added in HPLC grade water.

**Preparation of Diluent:**

A 50:50 mixture of 0.1 M Sodium hydroxide and Methanol was prepared.

**Preparation of Standard Stock Solution[14]:**

- Weigh accurately 25mg of Esomeprazole magnesium trihydrate and transfer into 50mL volumetric flask then add diluent and sonicate until the content dissolves completely.

- The solution was kept aside for a few minutes to cool the content at room temperature and made volume up to the mark with diluent.

- Transfer 10mL standard stock solution of Esomeprazole magnesium trihydrate into 50mL volumetric flask and made the

volume up to the mark with mobile phase, from which 2,5,10,15,20 µg/mL of working standard solutions was prepared and analyzed by using HPLC.

- From this data, the standard curve of Esomeprazole was obtained by plotting Peak Area on Y-axis against Concentration (µg/ml) on X-axis.

- Thus, the Correlation coefficient ($R^2$) of Esomeprazole was found to be 0.999.

**Drug–Excipient Compatibility Studies:**

**By Physical Method[15]:**

The drug and excipient compatibility studies were carried out using the physical method. In physical studies, the drug and each excipient, the drug and all excipients, were stored in glass vials at 25º±2ºC / 60±5%RH and 40º±2ºC / 75±5%RH for up to 4 weeks. The samples were examined for any colour changes during the period of storage.

**By FT-IR Studies[16]:**

Drug-excipient compatibility studies were carried out to determine the compatibility of the active ingredient and other excipients in order to produce a stable, safe, and therapeutically effective product. The KBr pellet technique was used to prepare samples by combining an accurately weighed amount of drug and other excipients was mixed, and one milligram of the sample was taken and mixed with 20mg of potassium bromide using mortar and pestle. These quantities are usually enough to make a disc with a diameter of 10-15mm and a pellet with a suitable intensity using a hydraulic press to make a transparent pellet. The pellet was placed in the diffuse reflectance sampler, and the spectrum was recorded in an FT-IR Spectrophotometer by scanning in the wavelength region of IR 4000-400 $cm^{-1}$. To check for any drug-excipient interactions, the IR spectrum of the drug was compared to that of the mixture.

**Characterization of Flow Properties[17-23]:**

**Pre-Compression Parameters of the Blend (Pellets+Tableting Excipients):**

This is an extremely important parameter to measure because it affects the mass of uniformity of the dose, which is usually predicted in terms of bulk density, tapped density, etc.,

**Bulk Density:** The apparent bulk density ($\rho b$) of the blend was determined by pouring the blend into a graduated cylinder. The bulk volume ($V_b$) of the powder and weight

(M) of the powder was calculated. The bulk density was determined by using the formula below;

$$\rho_b = M / V_b$$

Where,

$\rho b$ = Bulk Density

M = Sample weight in grams $V_b$ = Final blend volume in $cm^3$.

**Tapped Density:** This is the ratio of total powder mass to tapped powder volume. By

tapping the powder 500 times, the volume was determined. The tapping was then repeated 750 times and the tapped volume was recorded. The tapped density was determined using the formula below;

$$\rho_t = M / V_t$$

Where,

$P_t$ = Tapped Density

M = Sample weight in grams

$V_t$ = Tapped blend volume in $cm^3$.

**Compressibility Index and Hausner's Ratio:** The compressibility index and Hausner's ratio of a powder were calculated by measuring both its bulk density and its tapped density.

***Basic methods for determining the Compressibility Index and Hausner's***

***Ratio:*** While the method of determining the compressibility index and Hausner's ratio differs, the basic procedure is to measure the unsettled apparent volume (Vo) and final tapped volume (Vf) of the powder after tapping the material until there are no more volume changes. Thus, the compressibility index and Hausner's ratio were determined as follows:

Compressibility Index = Tapped Density – Bulk Density / Tapped Density x 100

Hausner's Ratio = Tapped Density / Bulk Density

**Compression of Coated Pellets:**

Compaction of coated multi particulates into tablets could result in either disintegrating tablet that provides a multi particulates system during GI transit (or) intact tablets due to the fusion of the multi particulates in a larger compact. Ideally, the compacted pellets should disintegrate quickly in the individual pellets in gastrointestinal fluids. During compaction, the pellets must not fuse into a non-disintegrating matrix. The compaction process should not affect drug release.

**Assay**

**Instrument:**

High-Performance Liquid Chromatography equipped with PDA/UV- Detector and data handling system.

**Table 2: List of Chromatographic parameters of Assay**

| Chromatographic Parameters | | |
|---|---|---|
| 1. | Column | Inertsil ODS–3V 4.6-mm x 150-mm; 5-µm or equivalent column |
| 2. | Column Temperature | 25ºC |
| 3. | Wavelength | 302nm |
| 4. | Injection Volume | 20µL |
| 5. | Flow Rate | 1.0mL/minute |
| 6. | Run Time | 10 min |
| 7. | Elution | Gradient |

**Preparation of 1.0 M Monobasic Sodium Phosphate Buffer solution:**

Accurately weigh and transfer 13.79g of sodium dihydrogen phosphate monohydrate into a 100mL volumetric flask then add 70mL of purified water to dissolve and dilute to volume with purified water.

**Preparation of 0.5 M Dibasic Sodium Phosphate Buffer solution[23]:**

Accurately weigh and transfer 7.10g of disodium hydrogen phosphate anhydrous into a 100mL volumetric flask then add 70mL of purified water to dissolve and dilute to volume with purified water.

**Preparation of Mobile phase Buffer solution:**

Mix 10.5mL of 1.0 M Monobasic sodium phosphate buffer and 60mL of 0.5 M Dibasic sodium phosphate buffer and dilute with water to 1000mL.

**Preparation of Mobile phase:**

Mix 350mL of Acetonitrile and 500mL of the mobile phase buffer, dilute with water to 1000mL.

**Preparation of Diluent buffer solution:**

Dissolve 5.24g of Tribasic sodium phosphate dodecahydrate in 500mL of water, add 110mL of 0.5 M Dibasic sodium phosphate solution and dilute with water to 1000mL.

**Preparation of Standard solution:**

Weigh accurately about 50mg of Esomeprazole working standard and transfer into 100mL volumetric flask, dissolve in about 20mL of methanol, add 40mL of diluent and dilute with diluent to volume. Further, dilute the Standard stock solution into a 50mL volumetric flask and dilute with

water to obtain a solution of concentration 0.04mg/mL of Omeprazole.

**Preparation of Sample solution[24]:**

Accurately weigh the pellets equivalent to 40mg of Esomeprazole into a 100mL volumetric flask, add 60mL of diluent and keep for rotary shaking for 10 minutes to dissolve the pellets, sonicate for 5 minutes. Add 20mL of alcohol and sonicate for 15 minutes, cool and dilute with diluent to volume. Filter the solution through a 0.45µ nylon filter. Further, dilute 5mL of the above sample stock solution into a 50mL volumetric flask and dilute with water to obtain a solution of concentration 0.04mg/mL.

**Note:** Use amber-colored volumetric flasks for the preparation of solutions.

**Procedure:**

Separately inject 20µL of Blank, five replicate injections of standard solutions, one injection for each sample solution prepared and one injection of standard as bracketing at the end (or) every six sample injections into the chromatography. Record the chromatograms and measure the peak responses.

**Assay Calculation:**

$$\%Assay = \frac{A_T}{A_S} \times \frac{Wt_{std}}{100} \times \frac{4}{50} \times \frac{100}{A_W} \times \frac{50}{5} \times \frac{P}{LC} \times 100$$

Where,

$A_T$ = Peak area of Esomeprazole in Sample solution

$A_S$ = Average peak area of Omeprazole in Standard solution $Wt_{std}$ = Weight of Omeprazole working Standard taken in mg

$A_W$ = Weight of Sample taken in mg

LC = Label Claim

P = Purity of Omeprazole working standard

**Acceptance Criteria:** NLT 90.0% and NMT 110.0% of label claim.

**Evaluation of Post-Compression Parameters of Tablets[25,26]:**

**Shape and Colour of Tablets:**

Uncoated tablets were examined under a lens for shape and colour by keeping the tablets in the light.

**%Weight Variation:**

To determine %weight variation, 20 tablets were chosen at random from each formulation and weighed individually. The US Pharmacopeia allows for little variation in tablet weight.

**Table 3: %Weight variation limits for Tablets (USP)**

| Average weight of a Tablet (USP Standards) | Percentage deviation |
|---|---|
| 130mg (or) less | 10 |
| More than 130mg and less than 324mg | 7.5 |
| 324mg (or) more | 5 |

The %deviation was calculated as;

$$\%Deviation = (Individual\ weight - Average\ weight / Average\ weight) * 100$$

**Uniformity of Thickness:**

Six tablets were chosen at random from each formulation and their thickness was measured in PharmaG automatic thickness tester. It was measured in milli-meters and the standard deviation was computed.

**Hardness:**

The ability of a tablet to withstand mechanical shocks while handling is indicated by its hardness. A PharmaG Automatic Hardness tester was used to determine the hardness of the tablets. It is measured in Kp. Six tablets were chosen at random, and the hardness of the same tablets from each formulation was measured.

**Friability:**

The Roche friabilator was used to determine the friability of tablets. It is expressed in percentage (%). Tablets weighing less than 650mg are taken as whole tablets, which were initially weighed (Winitial) to

be nearly 6.5g and transferred into the friabilator, according to USP. The friabilator was operated at 25rpm for 4 minutes about 100 revolutions. Then the final weight of tablets was noted (Wfinal).

The percentage friability was then determined as;

$$\%Friability = Winitial - Wfinal / Winitial * 100$$

**Disintegration Time:**

Disintegration is the process of breaking down a tablet into smaller particles. The in-vitro disintegration time of a tablet was determined using an I.P- specified disintegration test apparatus. Place one tablet in each of the basket's six tubes. Fill each tube with a disc and run the apparatus with a pH 6.8 phosphate buffer kept at 37±2ºC as the immersion liquid. The assembly should be iii. raised and lowered 30 times per minute in a pH 6.8 phosphate buffer kept at 37±2ºC. The time in seconds required for the tablet to completely disintegrate with no palpable mass remaining in the apparatus was measured and recorded.

**In-Vitro Dissolution Studies[27]:**

The tablet dissolution test apparatus USP II was used for in-vitro release studies. The development of in-vitro dissolution tests has two goals:

i. To demonstrate that the drug is released from the tablet as close to 100% as possible, and

ii. To demonstrate that the rate of drug release is consistent from batch to batch and is the same as the release rate from batches proven to be bioavailable and clinically effective.

**Table 4: Dissolution Parameters for Acid Stage**

| **Medium** | 0.1N HCl |
|---|---|
| **Volume** | 300mL |
| **Apparatus** | USP Type II (Paddle) |
| **RPM** | 100 |
| **Time** | 120 minutes |
| **Temperature** | 37ºC±0.5ºC |
| **Medium** | 0.1N HCl |
| **Volume** | 300mL |
| **Apparatus** | USP Type II (Paddle) |
| **RPM** | 100 |
| **Time** | 120 minutes |
| **Temperature** | 37ºC±0.5ºC |

**Table 5: Dissolution Parameters for Buffer Stage**

| **Medium** | Dibasic Sodium phosphate, Buffer, pH 6.8 |
|---|---|
| **Volume** | To 300mL of 0.1N HCl add 700mL of Buffer medium |
| **Apparatus** | USP Type II (Paddle) |
| **RPM** | 100 |
| **Time** | 60 minutes |
| **Temperature** | 37ºC±0.5ºC |

**STABILITY STUDIES[28]:**

It is crucial to determine the stability of all pharmaceutical dosage forms. This includes storage at both normal and extreme temperature ranges, with the necessary extrapolations to ensure that the product will provide the drug for absorption at the same rate as when it was first formulated over its

intended shelf life. The design of formal stability studies for the drug product should be based on knowledge of the drug substance behavior and properties, as well as formal stability studies on the drug substance.

**Storage Conditions:**

A drug product should be evaluated in general under storage conditions that test its stability and, if applicable, its sensitivity to moisture (or) potential for solvent loss. At the time of submission, the long-term testing should cover a minimum of 12 months of research (or) at least three batches, and it should be continued for a sufficient period of time until it covers the proposed shelf life. The following are the accelerated, intermediate storage conditions for pharmaceutical products.

**Table 6: Storage conditions for Stability samples**

| | |
|---|---|
| Accelerated | 40 ± 2ºC / 75 ± 5%RH |
| Intermediate | 30 ± 2ºC / 65 ± 5%RH |
| Long term | 25 ± 2ºC / 60 ± 5%RH |

**Table 7: Testing intervals for Stability samples**

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

When a significant change occurs at any point of time during the 6-month testing period at the accelerated storage condition, additional testing at intermediate storage, the condition should be carried out and evaluated against the criteria for significant change.

**Preparation of MUPS Tablets include the following steps:**

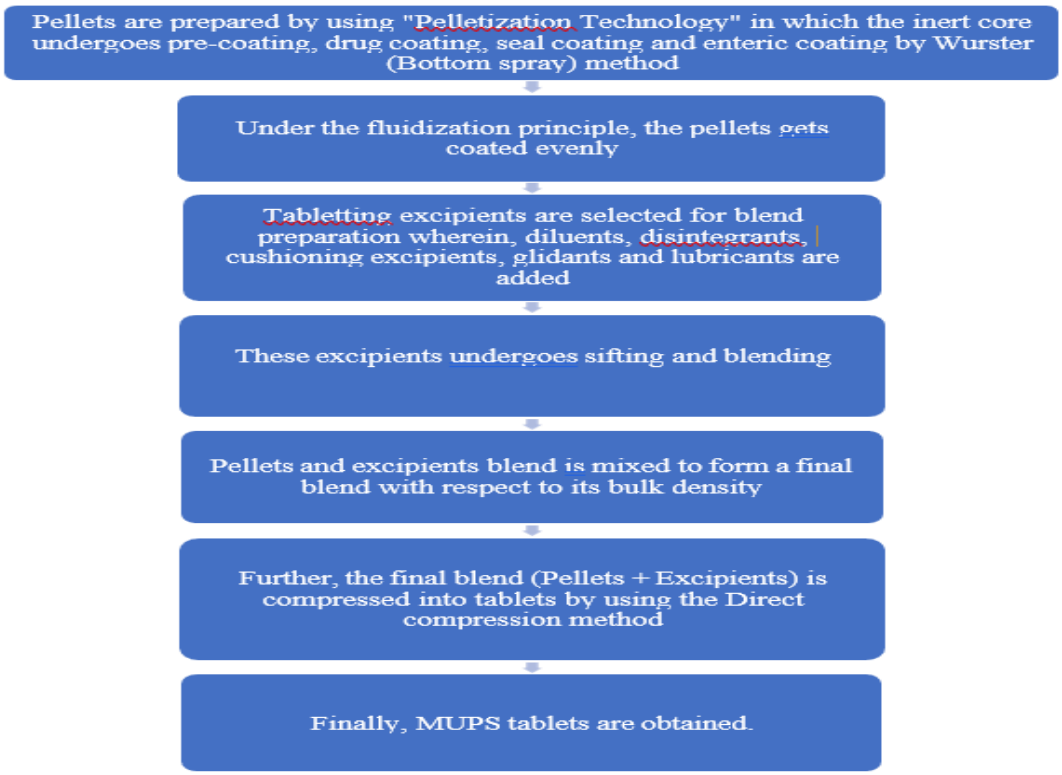


**Figure 1: Outline Procedure of MUPS Tablets Manufacturing**

## MUPS PROCESS FLOWCHART:

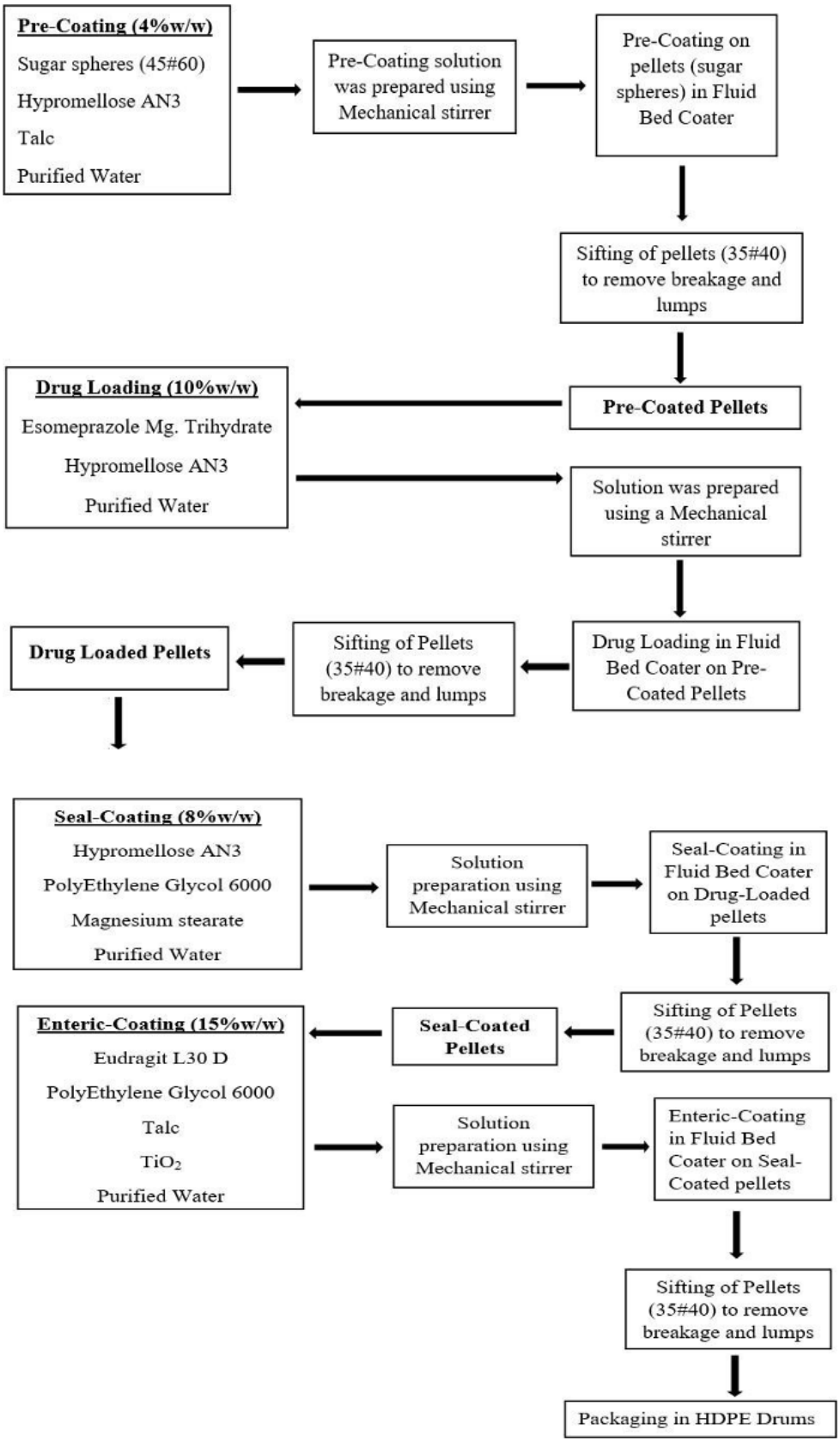


**Figure 2: Flowchart of MUPS preparation**

## *TABLETING PROCESS FLOWCHART:*

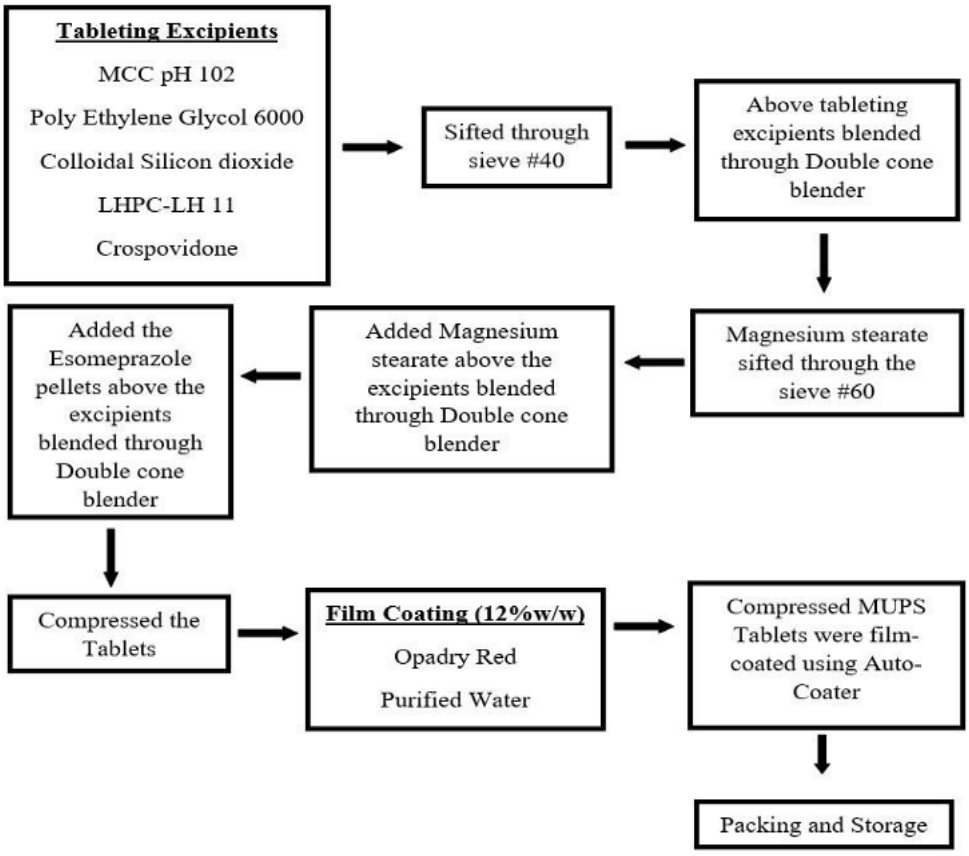


**Figure 3: Flowchart of Tableting and Film-coating**

## Formulation Development Trials:

**Table 8: Formulation Trials of MUPS**

| *Esomeprazole Mg. trihydrate DR Pellets 22.5%w/w* | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **A.** | **PreCoating (4 %w/w)** | **F1** | | **F2** | | **F3** | | **F4** | | **F5** | |
| **S.No** | **Ingredients** | **%w/w** | **mg/tab** | **%w/w** | **mg/tab** | **%w/w** | **mg/tab** | **%w/w** | **mg/tab** | **%w/w** | **mg/tab** |
| 1 | Sugar Spheres | 32.94 | 58.56 | 29.94 | 53.23 | 27.04 | 48.07 | 23.84 | 42.38 | 21.87 | 38.88 |
| 2 | Hypromellose AN3 | 2.00 | 3.56 | 1.00 | 1.78 | 2.00 | 3.56 | 2.00 | 3.56 | 2.00 | 3.56 |
| 3 | Talc | 0.50 | 0.89 | 0.50 | 0.89 | 0.50 | 0.89 | 0.50 | 0.89 | 0.50 | 0.89 |
| 4 | Purified Water | q. s | q. s | q. s | q. s | q. s | q. s | q. s | q. s | q. s | q. s |
| **B.** | **Drug loading (10%w/w)** | | | | | | | | | | |
| 5 | Esomeprazole Mg. Trihydrate | 25.06 | 44.55 | 25.06 | 44.55 | 25.06 | 44.55 | 25.06 | 44.55 | 25.06 | 44.55 |
| 6 | Hypromellose AN3 | 4.00 | 7.11 | 4.70 | 8.36 | 5.00 | 8.89 | 6.00 | 10.67 | 6.27 | 11.15 |
| 7 | Purified Water | q. s | q. s | q. s | q. s | q. s | q. s | q. s | q. s | q. s | q. s |
| **C.** | **Seal Coating (8%w/w)** | | | | | | | | | | |
| 8 | Hypromellose AN3 | 5.00 | 8.89 | 6.00 | 10.67 | 6.50 | 11.56 | 7.00 | 12.44 | 8.00 | 14.22 |
| 9 | PEG 6000 | 0.50 | 0.89 | 0.60 | 1.07 | 0.60 | 1.07 | 0.70 | 1.24 | 0.80 | 1.42 |
| 10 | Magnesium Stearate | 1.00 | 1.78 | 1.00 | 1.78 | 1.00 | 1.78 | 1.00 | 1.78 | 1.00 | 1.78 |
| 11 | Purified Water | q. s | q. s | q. s | q. s | q. s | q. s | q. s | q. s | q. s | q. s |
| **D.** | **Enteric Coating (15%w/w)** | | | | | | | | | | |
| 12 | Eudragit L30 D | 25.00 | 44.45 | 27.00 | 48.00 | 28.00 | 49.78 | 29.50 | 52.45 | 30.00 | 53.33 |
| 13 | PEG 6000 | 2.50 | 4.44 | 2.70 | 4.80 | 2.80 | 4.98 | 2.90 | 5.16 | 3.00 | 5.33 |
| 14 | Talc | 1.00 | 1.78 | 1.00 | 1.78 | 1.00 | 1.78 | 1.00 | 1.78 | 1.00 | 1.78 |
| 15 | Titanium dioxide | 0.50 | 0.89 | 0.50 | 0.89 | 0.50 | 0.89 | 0.50 | 0.89 | 0.50 | 0.889 |
| 16 | Purified Water | q. s | q. s | q. s | q. s | q. s | q. s | q. s | q. s | q. s | q. s |
| **l weight of Pellets** | | **100.00** | **177.78** | **100.00** | **177.78** | **100.00** | **177.78** | **100.00** | **177.78** | **100.00** | **177.78** |

**Table 9: Formulation Trials of Esomeprazole Mg. trihydrate MUPS Tablets**

| *Compression of MUPS Tablets and Coating* | | | | | | |
|---|---|---|---|---|---|---|
| **E.** | **Tableting ( for 40mg Strength)** | **F1** | **F2** | **F3** | **F4** | **F5** |
| **S.No** | **Ingredients** | **mg/unit** | **mg/unit** | **mg/unit** | **mg/unit** | **mg/unit** |
| 1 | Esomeprazole Pellets | 177.78 | 177.78 | 177.78 | 177.78 | 177.78 |
| 2 | Microcrystalline cellulose PH 102 | 305.72 | 328.56 | 317.52 | 329.90 | 313.62 |
| 3 | PEG 6000 | 58.50 | 36.00 | 40.00 | 42.00 | 46.00 |
| 4 | Colloidal Silicon dioxide (Aerosil) | 2.00 | 1.46 | 3.00 | 3.00 | 3.00 |
| 5 | LHPC LH 11 | 17.00 | 16.00 | 15.70 | 14.00 | 18.00 |
| 6 | Crosspovidone | 22.00 | 23.20 | 27.00 | 14.62 | 24.00 |
| 7 | Magnesium Stearate | 2.00 | 2.00 | 4.00 | 3.70 | 2.60 |
| **Tablet Core Weight** | | **585** | **585** | **585** | **585** | **585** |
| **F.** | **Film Coating (12%w/w)** | | | | | |
| 8 | Opadry Red | 15.00 | 15.00 | 15.00 | 15.00 | 15.00 |
| 9 | Purified Water | q. s | q. s | q. s | q. s | q. s |
| **Total Tablet Weight** | | **600** | **600** | **600** | **600** | **600** |

## Results & Discussion:

The present study was to formulate and evaluate Esomeprazole delayed-release MUPS tablets 40mg. Initially, the MUPS were prepared by coating the sugar spheres with pre-coating, drug- loading, seal coating and then followed by enteric coating. Finally, these MUPS along with tableting excipients were blended and compressed into tablets by direct compression method.

### Pre-formulation Studies

### API Characterization:

**Figure 4: Appearance of Esomeprazole Mg. trihydrate (API)**

**Table 10: Description of API**

| S. No | Test | Result |
|---|---|---|
| 1. | Color | White to Off-white color |
| 2. | Nature | Crystalline powder |
| 3. | Odor | Odorless |

### Solubility:

**Table 11: Solubility analysis of API in various solvents**

| S. No | Solvents | Results |
|---|---|---|
| 1. | Methanol | Soluble |
| 2. | Ethanol | Soluble |
| 3. | Water | Slightly soluble |
| 4. | Heptane | Insoluble |
| 5. | Acetone | Insoluble |

**Melting Point determination:**

The melting point of the drug was found to be 185ºC, which was within the range mentioned in the literature review i.e., 182-191ºC. Thus, the API was confirmed as the ―Esomeprazole Magnesium trihydrate‖.

**Partition Coefficient (log P):**

The partition coefficient of the drug was found to be 2.43.

**Analytical Method Development**

**Absorption Maxima of the API:** The absorption maxima ($\lambda_{max}$) of Esomeprazole Magnesium trihydrate were observed at a wavelength of 302nm.

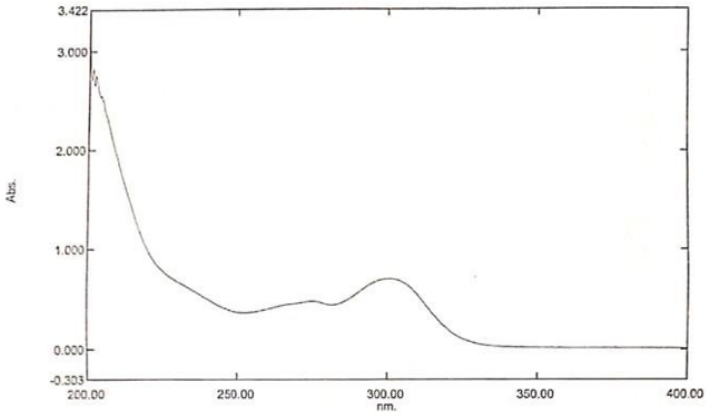


**Figure 5: Absorption Maxima Spectra of Esomeprazole Mg. Trihydrate**

**Calibration curve / Standard Graph of Esomeprazole Magnesium trihydrate:**

**Table 12: Standard Graph Data**

| Esomeprazole Mg. trihydrate | Concentration (µg / mL) | Peak Area |
|---|---|---|
| Standard 1 | 2 | 65424 |
| Standard 2 | 5 | 160784 |
| Standard 3 | 10 | 310801 |
| Standard 4 | 15 | 471820 |
| Standard 5 | 20 | 625618 |

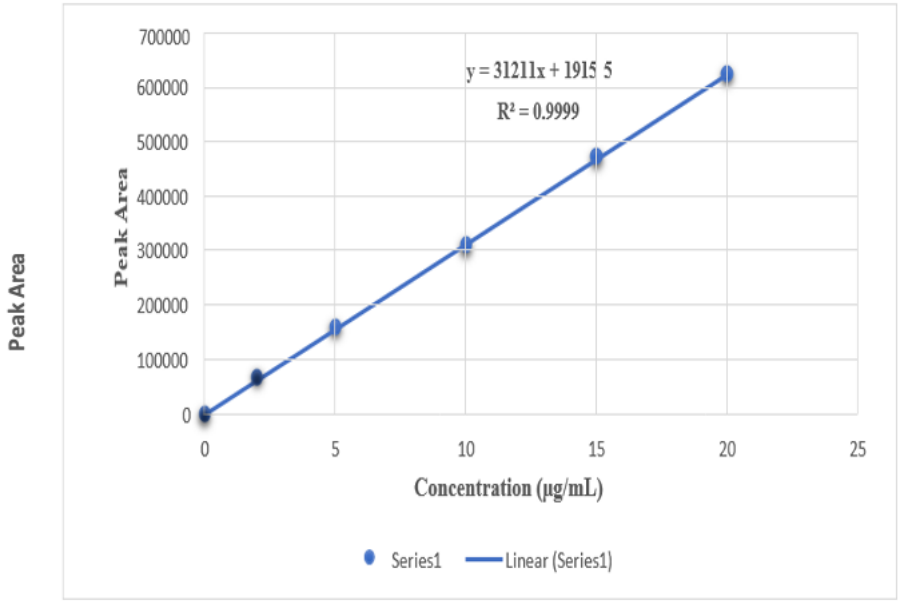


**Figure 6: Standard graph of Esomeprazole Magnesium trihydrate by using HPLC**

## Drug – Excipient Compatibility Studies:

**Table 13: Drug-Excipient Compatibility Studies- Physical appearance**

| S. No | Material | Ratio (D:E) | Physical ap-pearance | (25 ±2ºC/ 60±5%RH) & (40±2ºC/ 75±5%RH) | | |
|---|---|---|---|---|---|---|
| | | | | Week 1 | Week 2 | Week 4 |
| 1. | Esomeprazole Mg. trihydrate | 1:00 | # | □ | □ | □ |
| 2. | API+ Hypromellose AN3 | 1:1 | # | □ | □ | □ |
| 3. | API+ Talc | 1:1 | # | □ | □ | □ |
| 4. | API+ PEG 6000 | 1:1 | # | □ | □ | □ |
| 5. | API+ Magnesium stearate | 1:1 | # | □ | □ | □ |
| 6. | API+ Eudragit L 30D | 1:1 | # | □ | □ | □ |
| 7. | API+ Titanium dioxide | 1:1 | # | □ | □ | □ |
| 8. | API+ Opadry red | 1:1 | # | □ | □ | □ |
| 9. | API+ MCC PH 102 | 1:1 | # | □ | □ | □ |
| 10. | API+ Silicon dioxide | 1:1 | # | □ | □ | □ |
| 11. | API+ LHPC-LH 11 | 1:1 | # | □ | □ | □ |
| 12. | API+ Crosspovidone | 1:1 | # | □ | □ | □ |

**# is White to off-white color powder** **□ No Color change**

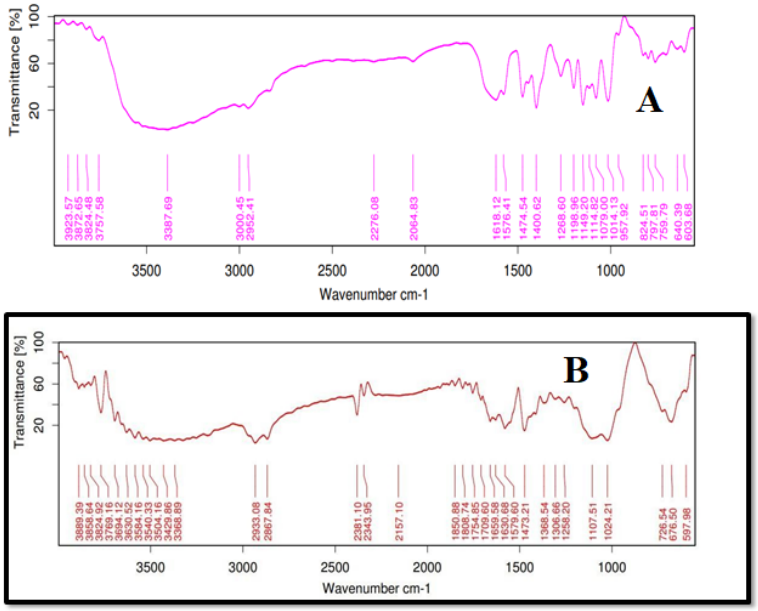


**Figure 7: FT-IR spectra of A. Pure Esomeprazole Mg. trihydrate and Drug + All Excipients**

**Table 14: Drug-Excipient Compatibility Studies – FT-IR Spectrum Interpretation**

| Functional Groups | Esomeprazole Mg. trihydrate (Drug) Wave numbers $cm^{-1}$ | Esomeprazole Mg. trihydrate (Drug) + All Excipients Wave numbers $cm^{-1}$ |
|---|---|---|
| C-H (Stretching) | 2952.41 | 2933.08 |
| C=N (Stretching) | 1618.12 | 1630.68 |
| C=C (Stretching) | 1576.41 | 1579.60 |
| C-N (Stretching) | 1268.60 | 1258.20 |
| C-O-C (Stretching) | 1079.00 | 1075.02 |
| S=O | 1014.13 | 1024.21 |

**Discussion:**

In the Drug-Excipient compatibility experiments, we can see that there are no interactions between the pure drug (Esomeprazole) and the drug and all excipients mixture (Esomeprazole: Excipients), indicating that there are no physical changes.

**Pre-Compression Parameters:**

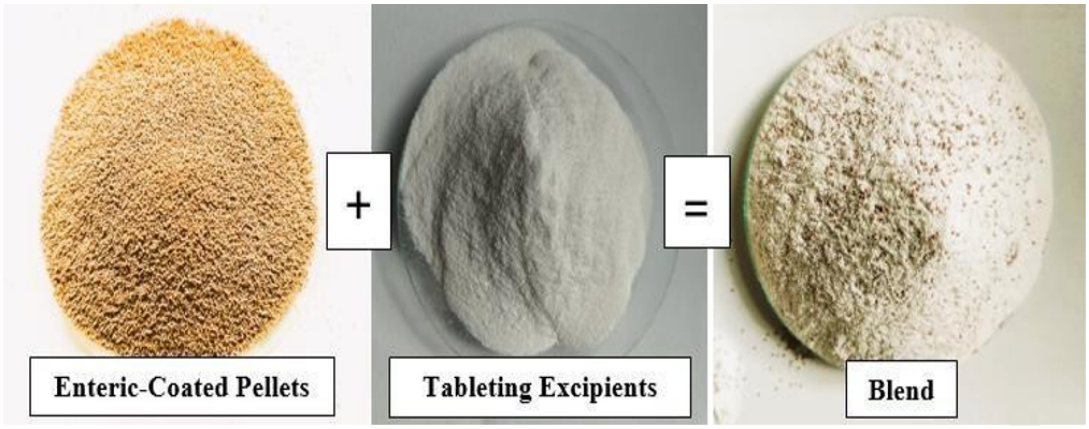


**Figure 8: Representation of the Pre-compression Blend**

**Table 15: Evaluation of Pre-Compression parameters of the Blend**

| S. No | Formulation | Bulk Density (g/mL) * | Tapped Density (g/mL) * | Carr's Index (%) * | Hausner's Ratio* |
|---|---|---|---|---|---|
| 1. | F1 | 0.923±0.26 | 0.989±0.21 | 6.67±0.31 | 1.07±0.25 |
| 2. | F2 | 0.937±0.29 | 1.005±0.34 | 6.77±0.37 | 1.07±0.26 |
| 3. | F3 | 0.921±0.17 | 0.988±0.26 | 6.78±0.41 | 1.07±0.24 |
| 4. | F4 | 0.934±0.14 | 0.991±0.35 | 5.75±0.27 | 1.06±0.26 |
| 5. | F5 | 0.915±0.36 | 0.959±0.15 | 4.59±0.26 | 1.05±0.13 |

*All values expressed as mean±standard deviation (n=3)

The bulk density of the blend was found between 0.915g/mL to 0.937g/mL. Tapped density was found between 0.959g/mL to 1.005g/mL. From these values, Carr's index and Hausner's ratio were calculated respectively.

Carr's index for all the formulations was found to be between 4.59% to 6.78% and Hausner's ratio was found to be between 1.05 to 1.07 which shows that the blend has Excellent‖ flow properties. So, it was confirmed that the flow property of the blend (pellets+excipients) was free-flowing.

**Post-Compression Parameters:**

**Shape and Color of the Tablets:**

Shape of the Tablets: Capsule-shaped

Color of the Tablets: Off-White.

**%Weight Variation:**

**Table 16: %Weight Variation values of all Formulations**

| S. No | Formulation Code | Weight Variation (%) * |
|---|---|---|
| 1. | F1 | 0.06±0.28 |
| 2. | F2 | 0.37±0.94 |
| 3. | F3 | 1.43±1.33 |
| 4. | F4 | 1.71±1.26 |
| 5. | F5 | 0.10±0.44 |

*All values expressed in mean ± standard deviation(n=20)

**Discussion:** All formulations passed the weight variation test as the % weight variation was within the USP specifications of ±5% as the total tablet weight was 600mg.

**Hardness:**

**Discussion:** The hardness of the tablets was acceptable and uniform from batch-to-batch variation, and was found to be 8.00-8.54 Kp.

**Thickness:**

**Discussion:** The thickness of the tablets was found to be 5.15-5.80(mm) in the formulation trials carried out which have shown batch-to-batch variation.

**Friability:**

**Discussion:** Friability values were found to be less than 1 in all the formulations F1-F5 which was considered to be satisfactory and mechanically stable.

**Disintegration Time:**

**Discussion:**

Disintegration time was found to be less than 5mins in all the formulations F1-F5 and was considered to be satisfactory because all the formulations were disintegrating within the specifications due to super disintegrants in the formulation.

**Assay:**

The assay results show that the drug is within the acceptance criteria in all the above-mentioned formulations.

**Table 18: Thickness values of all Formulations**

| S. No | Formulation Code | Thickness (mm) * | Friability (%) * | Hardness (Kp) * | Disintegration Time (mins)* | Assay (%) * |
|---|---|---|---|---|---|---|
| 1. | F1 | 5.60±0.14 | 0.617±0.16 | 8.12±0.54 | 4±0.42 | 100.2 ± 1.08 |
| 2. | F2 | 5.65±0.20 | 0.125±0.25 | 8.25±0.32 | 4±0.14 | 98.4 ± 2.18 |
| 3. | F3 | 5.15±0.18 | 0.592±0.27 | 8.54±0.26 | 3±0.54 | 97.7 ± 2.45 |
| 4. | F4 | 5.32±0.24 | 0.244±0.19 | 8.15±0.52 | 2±0.35 | 102.2 ± 1.15 |
| 5. | F5 | 5.80±0.30 | 0.187±0.29 | 8.00±0.22 | 1±0.44 | 101.2 ± 1.20 |

*All values expressed in mean ± standard deviation(n=6)

**Dissolution:**

**Evaluation of MUPS (Enteric Coated Pellets):**

**Table 19: In-vitro Dissolution Profile of all MUPS formulations**

| Time | % Cumulative Drug Release | | | | | |
|---|---|---|---|---|---|---|
| (mins) | Innovator | F1 | F2 | F3 | F4 | F5 |
| **0.1N HCl** | | | | | | |
| **0** | 0 | 0 | 0 | 0 | 0 | 0 |
| **30** | 0 | 1.2±0.25 | 0 | 0 | 0 | 0 |
| **60** | 0 | 3.0±0.50 | 2.4±0.15 | 1.4±0.05 | 0 | 0 |
| **90** | 0 | 5.3±0.62 | 6.1±0.29 | 2.1±0.12 | 1.3±0.10 | 0 |
| **120** | 0 | 8.2±0.78 | 7.2±0.42 | 5.4±0.46 | 2.5±0.29 | 1.4±0.50 |
| **pH 6.8 Phosphate Buffer** | | | | | | |
| **5** | 17.2±1.24 | 38.3±1.25 | 40.1±0.84 | 27.2±0.85 | 58.4±0.87 | 25.5±0.44 |
| **10** | 29.5±1.60 | 54.2±1.72 | 51.3±1.21 | 28.3±1.56 | 62.3±0.66 | 39.4±0.84 |
| **15** | 43.2±1.42 | 69.4±1.96 | 67.2±0.69 | 30.5±1.40 | 64.5±0.34 | 49.3±1.36 |
| **20** | 52.4±1.23 | 75.2±1.26 | 71.4±1.22 | 33.7±1.98 | 68.2±1.87 | 59.6±1.93 |
| **30** | 81.3±1.36 | 81.6±1.34 | 80.5±1.05 | 34.3±1.52 | 72.3±1.62 | 82.3±0.77 |
| **45** | 97.2±1.19 | 83.5±1.07 | 87.2±1.64 | 46.2±0.61 | 76.2±1.49 | 97.1±0.59 |
| **60** | 98.9±1.26 | 85.8±1.23 | 89.6±1.27 | 60.6±1.48 | 80.8±1.54 | 98.8±1.72 |

*All values expressed in mean ± standard deviation (n=6)

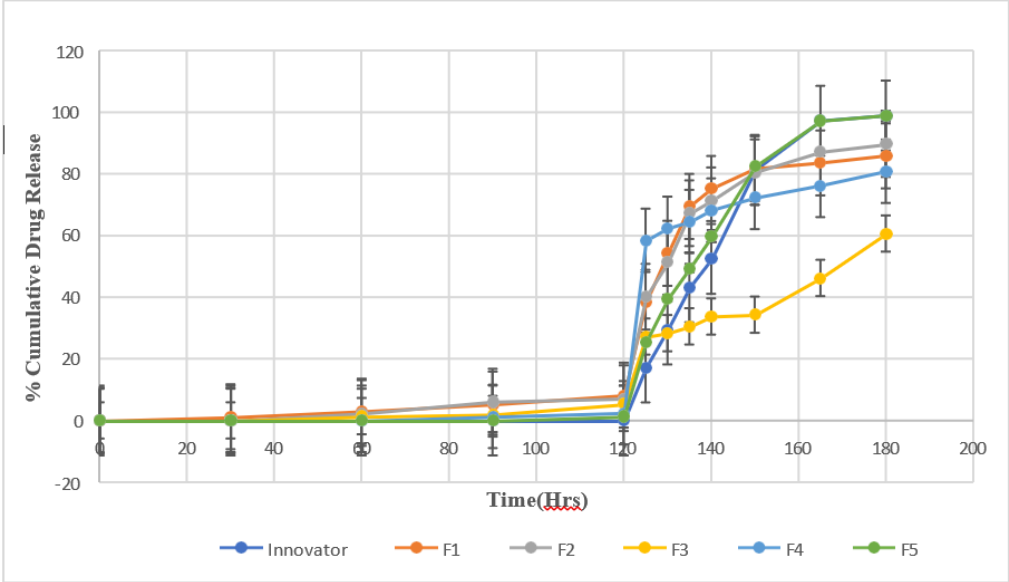


**Fig-55: Graphical representation showing comparative In-Vitro drug release studies of all MUPS (Enteric-coated pellets) Formulations (F1-F5) to Innovator**

**Discussion:**

**Enteric-Coating:**

According to the literature review, Eudragit forms a very harder film. For tablets, flexible film formation is required. By Eudragit L 30D polymer we can achieve flexible films. The enteric- coating was done by using 30% aqueous dispersion of the dry polymer. Optimization of the enteric-coating was done by comparing the parameters like assay, acid release, and dissolution of the enteric-coated pellets with the Innovator.

F1, F2, F3, and F4 formulations do not comply with USP limits for the % drug released in 0.1N HCl.

F4 formulation complies with USP limits and Innovator for the % drug released in 0.1N HCl but the dissolution is very slow compared with the innovator. So, further trials were planned with increased enteric-coating concentration(F5).

F5 formulation was found to have zero percent drug release in the acid stage which complies with USP limits.

**Conclusion:**

The F1 to F5 formulations were prepared by using Eudragit L30 D as an enteric coating polymer in different formulations. As a result, in this study Esomeprazole Mg. trihydrate delayed-release MUPS Tablets were developed. All the physical parameters of the pure drug were evaluated and the In-Vitro drug release profile was compared with the innovator's product. Both innovator's product and the formulation F5 showed almost identical cumulative drug release profiles. Hence, both of them were considered ad pharmaceutically equivalent. Stability studies were carried out for optimized formulation for 1, 2, and 3 months at 40ºC±2ºC/ 75% ± 5% RH and according to ICH guidelines, the formulation F5 was found to be stable. Based on the drug release kinetics, it was concluded that the optimized formulation F5 follows the zero-order release kinetics where the regression value was found to be 0.9172. It was found that the drug was released by diffusion mechanism as the regression in the Higuchi plot was 0.9542 and also, it followed the Korsmeyers-Peppas model where the regression value was found to be 0.9449.

**References:**

1. Hornecker, J. R. (2009). Generic drugs: history, approval process, and current challenges. US Pharm, 34(6), 26-30.

2. Patel.H., Solanki N.S. (2017). Gastro-resistant drug delivery system: A review. International Journal of Drug Development & Research, 4(4):1-8.
3. Abdul, S., Chandewar, A. V., & Jaiswal, S. B. (2010). A flexible technology for modified-release drugs: multiple-unit pellet system (MUPS). Journal of controlled release, 147(1), 2-16.
4. Kandukuri, J. M., Allenki, V., Eaga, C. M., Keshetty, V., & Jannu, K. K. (2009). Pelletization techniques for oral drug delivery. International Journal of Pharmaceutical Sciences and Drug Research, 1(2), 63-70.
5. Hirjau, M., Nicoara, A. C., Hirjau, V., & Lupuleasa, D. (2011). Pelletization techniques used in pharmaceutical fields. Farma, 4(3), 4.
6. Kulkarni, P. A., Kulkarni, A. D., Gandhi, J. A., Shirolkar, S. V., & Kasture, P. V. (2010). Pelletization techniques as a pharmaceutical tool in the multiparticulate drug delivery system: a review. Int J Drug Formul Res, 1(1), 89-118.
7. Engelmann, C., & Kragl, U. (2018). Spray congealing as innovative technique for enzyme encapsulation. Journal of Chemical Technology & Biotechnology, 93(1), 191- 197.
8. Young, C. R., Koleng, J. J., & McGinity, J. W. (2002). Production of spherical pellets by a hot-melt extrusion and spheronization process. International journal of pharmaceutics, 242(1-2), 87-92.
9. Tun, T. Y. (2016). Melt spheronization-Direct rotary shaping process for hot melt extrudates.
10. Pusapati, R. T., & Rao, T. V. (2014). Fluidized bed processing: A review. Indian Journal of Research in Pharmacy and Biotechnology, 2(4), 1360.
11. Zakowiecki, D., Szczepanska, M., Hess, T., Cal, K., Mikolaszek, B., Paszkowska, J & Garbacz, G. (2020). Preparation of delayed-release multiparticulate formulations of diclofenac sodium and evaluation of their dissolution characteristics using biorelevant dissolution methods. Journal of Drug Delivery Science and Technology, 60, 101986.
12. Maderuelo, C., Lanao, J. M., & Zarzuelo, A. (2019). Enteric coating of oral solid dosage forms as a tool to improve drug bioavailability. European Journal of Pharmaceutical Sciences, 138, 105019.
13. Chatap, V. K., & Joshi, D. (2018). Recent Advanced of Multiple Unite Pellet System (MUPS) Technology in Formulation of Pharmaceutical Products: A Review. International Journal of Contemporary Research and Review, 9(10), 20202- 20214.
14. Kokate, S., & Rachh, P. R. (2018). Microparticulate hot melt pallets technology: a review. Journal of Drug Delivery and Therapeutics, 8(6-s), 377-383.
15. Al-Hashimi, N., Begg, N., Alany, R. G., Hassanin, H., & Elshaer, A. (2018). Oral modified release multiple-unit particulate systems: compressed pellets, microparticles and nanoparticles. Pharmaceutics, 10(4), 176.
16. Barmpalexis, P., & Grypioti, A. (2018). Development of a new esomeprazole delayed release gastro-resistant pellet formulation with improved storage stability. Drug Development and Industrial Pharmacy, 44(6), 942-952.
17. Liu, J. Y., Zhang, X. X., Huang, H. Y., Lee, B. J., Cui, J. H., & Cao, Q. R. (2018). Esomeprazole magnesium enteric-coated pellet-based tablets with high acid tolerance and good compressibility. Journal of Pharmaceutical Investigation, 48(3), 341-350.
18. Borra, S. P., Eswaraiah, M. C., & Reddy, G. K. (2018). Effect of Polysorbate 80 and Particle Size of Budesonide API on In-vitro Dissolution Profiles of Budesonide MUPS Tablets 9 mg. Research Journal of Pharmacy and Technology, 11(10), 4285-4295.
19. Reddy, M. S., Eddagiri, R., Haq, S., Hl, M. F., & Venkateswarlu, V. (2017). Design and in-vitro characterization of delayed release multi unit particulates using wurster technology. Indo American

Journal of Pharmaceutical Sciences, 4(12), 4315-4324.
20. Patel, S. A., Patel, N. G., & Joshi, A. B. (2017). Multiple Unit Pellet System (mups) based fast disintegrating delayed-release tablets for pantoprazole delivery. Int J Pharm Sci, 10, 77-84.
21. Chen, T., Li, J., Chen, T., Sun, C. C., & Zheng, Y. (2017). Tablets of multi-unit pellet system for controlled drug delivery. Journal of Controlled Release, 262, 222-231.
22. Sawant, K, Patel, M, Patel, J., & Mundada, P. (2017). Formulation, optimization, characterization and in vivo antiulcer activity of esomeprazole magnesium trihydrate gastro resistant microspheres. Int J Pharm Sci, 9(1), 273.
23. Blanco, D., Antikainen, O., Räikkönen, H., Yliruusi, J., & Juppo, A. M. (2021). Effect of colloidal silicon dioxide and moisture on powder flow properties: Predicting in- process performance using image-based analysis. International Journal of Pharmaceutics, 597, 120344.
24. Mishra, S. M., & Sauer, A. (2022). Effect of Physical Properties and Chemical Substitution of Excipient on Compaction and Disintegration Behavior of Tablet: A Case Study of Low-Substituted Hydroxypropyl Cellulose (L-HPC). Macromol, 2(1), 113-130.
25. Di Martino, P., Malaj, L., Censi, R., Martelli, S., Joiris, E., & BarthélémyASZ., , C. (2007). The role of several L-HPCs in preventing tablet capping during direct compression of metronidazole. Drug development and industrial pharmacy, 33(12), 1308-1317.
26. Bennett, J. M., Pelletier, E., Albrand, G., Borgogno, J. P., Lazarides, B., Carniglia, C. K & Saxer, A. (1989). Comparison of the properties of titanium dioxide films prepared by various techniques. Applied optics, 28(16), 3303-3317.
27. Bui, V. K. H., Tran, V. V., Moon, J. Y., Park, D., & Lee, Y. C. (2020). Titanium dioxide microscale and macroscale structures: a mini-review. Nanomaterials, 10(6), 1190.
28. Sumaiyah, S., Mentari, J., & Suryanto, S. (2019). The Effect of Crospovidone on the Dissolution Profile of Amlodipine Besylate from Fast Orally Dissolving Film. Open Access Macedonian Journal of Medical Sciences, 7(22), 3811