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# Design, Development, And Evaluation Of Esomeprazole Gastroretentive Tablets Using Co-Processed Excipients

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***Abstract:*** Esomeprazole is a proton pump inhibitor used in the treatment of Gastroesophageal Reflux Disease (GERD), peptic or duodenal ulcers, *Helicobacter pylori* infection, hyperchlorhydria, and in conjunction with other medications that have propensity to cause gastric ulcers. The biological half-life of esomeprazole is 1 to 1.5 hours with an oral bioavailability of 50-60%. It is known that gastroretentive drug delivery system (GRDDS) can increase gastric residence time and thus can improve the bioavailability. In this study, co-processed excipient (Xanthan-Guar gum prepared by solvent evaporation technique) in different ratios is used to reap the combined physico-chemical benefits of the individual excipients. Esomeprazole GRDDS tablets are thus developed to overcome the shortcomings of the drug and provide better therapeutic efficacy. The prepared tablets are evaluated for various quality control parameters such as diameter, thickness, hardness, friability, weight variation test, disintegration test, buoyancy, in vitro drug dissolution behavior, and drug release kinetics. It is observed that the formulation F5 containing 1:3 ratio of Xanthan and Guar Gum co-processed excipient has desirable properties of fastest floating lag time (4.42 $\pm$ 0.29 min) with a sustained drug release of up to 7 hours. This study proved that co-processed excipients can be used to provide hybrid benefits by providing additive effects on the overall drug performance in the body.

***Keywords*** **– Gastroretentive drug delivery, Co-processed excipients, GERD, *H. pylori*, Esomeprazole.**

## I. INTRODUCTION

Gastroretentive drug delivery systems (GRDDS) have unique advantages in the sense that they offer improved bioavailability to the drugs having poor absorption, they increase the gastric residence time, they provide a local effect, and lessen the adverse effects as the drug is localized to the gastric region only (BADONI *ET AL.*, 2012). Esomeprazole is chosen as an ideal candidate for this study due to its poor oral bioavailability (50-60%), low elimination half-life (1 to 1.5 hours), apart from its intended therapeutic action which is also said to be in the gastric region. GRDDS can overcome these disadvantages of the drug by promoting the gastric residence time (GRT), providing sustained action, and escalating the bioavailability (PRINDERRE *ET AL.*, 2011).

Use of co-processed excipients in the pharmaceutical industry has increased drastically in the recent years due to their versatility of offering the combined benefits of the excipients with single entity. These are prepared using spray drying, solvent evaporation, crystallization, melt extrusion or agglomeration techniques in which the excipients undergo sufficient stress such that the physicochemical properties of the excipients are modified and synergistic effect is obtained on the overall performance (Saha and Shahiwala, 2009). Past works on the co-processed excipients have revealed that usage of this technology not only provides decreased excipient usage but also overcomes the shortfalls of the drug with superior release characteristics (Wang *et al.*, 2015).

A thorough literature review revealed that there is very little work with Esomeprazole and co-processed excipients. The main aim of this research work is to develop Esomeprazole GRDDS tablets that can overcome the shortfalls of the drug and provide better therapeutic efficiency. The second objective is to evaluate the superiority of the co-processed excipients and compare their effect on individual polymers on the drug release. Esomeprazole is a BCS Class II drug (low solubility, and high permeability) and used in the management of gastroesophageal reflux disease (GERD), *H. pylori* infection, gastritis, hyperchlorhydria (Scott *et al.*, 2002). The pKa (4.78) of the drug favors its release in the gastric region and the development of GRDDS system provides extra mileage to the therapeutic effect of the drug (Spencer and Faulds, 2000).

## II. MATERIALS

Esomeprazole is obtained as a gift sample from Sainor Laboratories, Hyderabad. Sodium bicarbonate, Citric acid, Polyvinyl pyrrolidone PVP K25, Xanthan Gum, Guar gum are procured from Molychem Pvt Ltd, Hyderabad. All the chemicals and excipients used in the research work are of analytical grade to ensure homogeneity and avoid any error due to source variation.

## III. METHODOLOGY

### 3.1. Preformulation studies

Preformulation studies are carried out to ensure whether the physicochemical property of the Active Pharmaceutical Ingredient (API) is matching with the official monograph and to identify any deviations (Chaurasia, 2016).

#### 3.1.1. Analytical studies

Esomeprazole can be estimated by using Gas chromatography (Reddy *et al.*, 2010), Liquid Chromatography-Mass Spectrophotometer (Cheng *et al.*, 2010), UV-Visible spectroscopy (Manoharan, 2019). In this study, Esomeprazole is estimated by using UV-visible spectroscopy as it is found to be effective, and economical with more reproducibility that suits the current work. The absorption maxima of esomeprazole in 0.1 N HCl is found to be 276 nm. 0.1 N HCl is used as a buffer to simulate the gastric environment where the drug is released. 100 mg of the drug is dissolved in 100 ml of 0.1N HCl. From this stock solution, 1-5 mL aliquots are transferred to 10 ml volumetric flasks to obtain 10-50 µg/mL solutions and the absorbance of each of the dilutions were determined by using double beam UV-visible spectrophotometer (Lab India UV-3200)

#### 3.1.2. Drug-excipient compatibility studies using Fourier-Transform Infrared Spectroscopy (FTIR)

Drug Excipient incompatibility studies are carried out by FTIR spectroscopy (Shimadzu FT-IR 8400S) in the range of 400-4000 cm-1 with a resolution of 4 cm-1 using potassium bromide disc method (Reddy *et al.*, n.d.). The pure drug and excipient mixture (1:1 w/w) were stored at 40 ± $2^0$C and 75 ± 5 % RH for 1 month. The powder sample is mixed thoroughly with potassium bromide for 3-5mins in a mortar and compressed into the disc. The pellets were placed in the sample chamber and the FTIR spectrum is analyzed for evidence of any interactions

### 3.2. Formulation of Esomeprazole floating tablets

#### 3.2.1. Preparation of co-processed excipient

The floating tablets of Esomeprazole are prepared using a co-processed excipient of Xanthan gum and guar gum. Coprocessed excipient of xanthan and guar gum was prepared by using the solvent evaporation method (Bhatia *et al.*, 2022). Co-processed excipients for different formulations like (F1-F5) were prepared in the ratios of (1:1, 1:2, 2:1, 1:3, 3:1). Required quantities of xanthan and guar gum was weighed and dissolved in 10ml of petroleum ether. Then it was heated by using magnetic stirrer until all the solvent has been evaporated. Thus formed residue has to be dried in an oven and then dried sample was collected and the same procedure was carried out for all the formulations i.e, (F1-F5). The formulation F6 is prepared by taking the simple admixture of Xanthan and guar gum at a ratio of 1:1 to compare the differences between the individual excipient and coprocessed excipient.

#### 3.2.2. Preparation of tablets

Floating tablets of esomeprazole were prepared by direct compression technique (Jaimini *et al.*, 2007). Required amounts of all ingredients like drug, coprocessed excipient of Xanthan and Guar gum, Sodium bicarbonate, citric acid, Microcrystalline cellulose, Magnesium Stearate and Talc were accurately weighed according to the quantities shown in Table 1 and passed through the sieve # 60. All the ingredients except magnesium stearate and talc were further mixed for additional 2-3min and various precompression parameters for the powder blend were carried out to determine the flow property of different formulations, and drug excipient compatibility studies were carried out. Then the powder blend was compressed using a tablet punching machine. Weights of all the tablets were kept constant in all formulations. Sodium bicarbonate and citric acid were used to produce the effervescence by the release of carbon dioxide, so the dosage form can easily float on within the stomach after tablet compression formulations were evaluated for the various compression parameters.

Table 1: Formulation of floating tablets of Esomeprazole

| Sl. No. | Ingredients | Functional Category | Quantity (mg)/ 1 tablet | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | F1 (1:1) | F2 (1:2) | F3 (2:1) | F4 (1:3) | F5 (3:1) | F6 (Simple admixture) |
| 1. | Esomeprazole | API | 20 | 20 | 20 | 20 | 20 | 20 |
| 2. | Sodium bicarbonate | Effervescing agent | 25 | 25 | 25 | 25 | 25 | 25 |
| 3. | Citric acid | Effervescing agent | 12.5 | 12.5 | 12.5 | 12.5 | 12.5 | 12.5 |
| 4. | PVP K 25 | Binding agent | 12.5 | 12.5 | 12.5 | 12.5 | 12.5 | 12.5 |
| 5. | Xanthan & Guar gum | Co-processed excipient | 20 | 20 | 20 | 20 | 20 | 20 |
| 6. | MCC | Diluent | 150 | 150 | 150 | 150 | 150 | 150 |
| 7. | Talc | Glidant | 5 | 5 | 5 | 5 | 5 | 5 |
| 8. | Magnesium stearate | Lubricant | 5 | 5 | 5 | 5 | 5 | 5 |
| 9. | Total weight (mg) | | 250 | 250 | 250 | 250 | 250 | 250 |

### 3.3. Evaluation of pre-compression parameters

The powder blends of the drug and excipients are evaluated for various precompression parameters like Bulk density, tapped density, angle of repose, Carr's index, and Hausner's ratio to determine the flow properties and accordingly adjust the concentration of glidants and lubricants in the final formulation before compression (Gunda, 2015).

#### 3.3.1. Bulk and Tapped density

5gm of powder blend of each formulation was accurately weighed and was transferred into a 100 ml measuring cylinder. Then the initial volume of the powder blend will be the bulk volume and it was repeated for three times and the mean of the values were taken and the final volume was taken as bulk volume and then the cylinder was tapped continuously for 100 tappings and recorded the final volume of powder, it will be the tapped volume *(Gunda, 2015)*. Same procedure was carried out for all the formulations. Then bulk and tapped density were calculated by using the given equation:

$$Bulk\ density\ = \frac{Weight\ of\ powder}{Bulk\ volume} \quad (3.1)$$

$$\text{Tapped}\ density\ = \frac{Weight\ of\ powder}{\text{Tapped}\ volume} \quad (3.2)$$

#### 3.3.2. Angle of repose

Angle of repose is the angle between the slope of a powder pile and horizontal plane. It is determined by using static funnel method where a funnel was secured with its tip at a given height h, above graph paper that was placed on a flat horizontal surface. Granules were carefully poured through the funnel until the apex of the conical pile just touches the tip of the funnel. Thus, with r being the radius of the base of the conical pile angle, h being the height of the pile, angle of repose can be calculated using the equation 3.3. Angle of Repose value of less than 25 is considered as excellent flow property, 25 to 30 is regarded as good flow, 30 to 40 –moderate while angle of repose >40 is assumed as poor flow property.

$$\text{Tan}\ \theta\ = \frac{\text{Height of the powder pile (h)}}{\text{Radius of the powder pile (r)}} \quad (3.3)$$

#### 3.3.3. Carr's index

It is also called Carr's compressibility index, is an indication of compressibility of a powder. It is calculated from the equation 3.4. Carr's index less than 16% is regarded as excellent flow while a value of 16-20% and value above 20% are regarded as good and poor flow respectively.

$$Carr's\ index\ = \frac{Tapped\ density - Bulk\ Density}{Bulk\ Density} * 100 \quad (3.4)$$

#### 3.3.4. Hausner's ratio

It is the ratio of tapped density to untapped density. It is calculated by using the equation 3.5. A Hausner's ratio of less than 1.11 indicates excellent flow property.

$$\text{Hausner's ratio}\ = \frac{Tapped\ density}{Bulk\ Density} \quad (3.5)$$

### 3.4. Post compression studies

#### 3.4.1 Diameter and thickness

Three tablets from each batch of formulation were collected and diameter of tablets was measured with the help of Vernier calipers and the average diameter was calculated. Similarly thickness of tablet (in mm) was also determined with the help of Vernier caliper *(Pare* et al., *2008)*. The measurements were taken in triplicate

#### 3.4.2 Hardness

The hardness of the tablet is a official Test for the tablets as per IP and it was determined for all the formulations by using Monsanto type hardness testers (Padmavathy *et al.*, 2011). The hardness of the tablets can be measured by using monsanto hardness tester. This test was used to check whether the tablet has sufficient hardness to resist breaking during the normal handling and transportation. For each formulation, the hardness of three tablets was determined and the average is calculated. It is measured in kg/cm$^2$. A hardness of 4-6 kg/cm$^2$ is considered to be ideal.

#### 3.4.3 Friability

It is carried out by using Roche Friabilator. 10 tablets were weighed initially ($W_{initial}$) and transferred into the friabilator operating at 25 rpm for 4 minutes. Then the tablets were weighed again after friabilation ($W_{final}$). The % friability was then calculated using the equation 3.6. The friability value should not be more than 1%.

$$\text{Friability} = \frac{(\text{Weight}_{initial}) - (\text{Weight}_{final})}{(\text{Weight}_{initial})} \quad (3.6)$$

### 3.4.4 Weight variation test

The weight variation test was carried out using 20 tablets by taking the individual weight and Average weight of 20 tablets. Weight variation is calculated by using the equation 3.7. The weight variation limit for a tablet weighing 250 mg or more is ± 5%.

$$\%\ Weight\ variation = \frac{Individual\ weight\ of\ the\ tablet}{Average\ weight\ of\ the\ 20\ tablets} * 100 \qquad (3.7)$$

### 3.4.5 Disintegration time

The disintegration time for floating tablets was determined by using USP disintegration test apparatus. Disintegration time for the prepared floating tablets can be determined by using USP disintegration apparatus (Jagdale *et al.*, 2009). The test involves usage of 6 glass tubes that are 3inches long, open at the top and 10 mesh screen at the bottom end. One tablet is placed in each tube and the basket rack is positioned in a 1-L beaker of water. Move the basket containing the tablets up and down through a distance of 5-6cm at a frequency of 28-32cycles per minute. Note down the time taken to disintegration of tablet and repeat the same procedure for all the formulations (F1-F5). The official limit of disintegration time is not more than 30 minute for uncoated tablets

### 3.4.6 Buoyancy studies

Buoyancy studies for the prepared floating tablets can be performed by using HCl. The prepared tablets from each of the formulations were placed in a beaker containing 100ml 0.1N HCl. Then the time taken for the tablet to emerge on the surface of the medium was noted and this will be the floating lag time. And the total duration of time by which tablet remained buoyant on the surface of the medium will be taken as the Total floating time *(Pare* et al., *2008)*. Same procedure is carried out for all the formulations

### 3.4.7 In vitro dissolution studies

The in vitro release of esomeprazole from the tablets was determined using a dissolution apparatus according to USP method II (paddle). This apparatus is placed in a water bath thermostatically maintained at $37^0$C (+/-) $0.5^0$C and stirred at a rate of 50 rpm. Sink conditions were maintained throughout the study. The dissolution medium is 900ml of 0.1N HCl pH 1.2. At pre-determined time intervals 5ml samples were withdrawn and replaced with fresh buffer solution *(Reddy* et al., *n.d.)*. Samples were filtered and analyzed using a UV-spectrophotometer at 276 nm. Released drug contents were determined from the calibration curve

### 3.4.8 Drug release kinetics

Mathematical models are used to evaluate the kinetics and mechanism of drug release from the tablets *(Nur and Zhang, 2000)*. The model that best fits the release data is selected based on the correlation coefficient (R) value in various models. The model with high '$R^2$' value is considered as the best fit on the release data

#### *3.4.8.1 Zero order release*

The equation for zero order release is represented as

$$Qt = Q_0 + K_0 t \qquad (3.8)$$

Where: Qt = amount of drug released in time (t), $Q_0$ = initial amount of drug in the solution $K_0$ = Zero order release constant

#### *3.4.8.2 First order release*

The equation for zero order release is represented as

$$Log\ C = Log\ C_0 - \frac{K_t}{2.303} \qquad (3.8)$$

Where, C = amount of drug remaining unreleased at time (t)

$C_0$ = initial amount of drug in solution

K = first order rate constant

### 3.4.9 Statistical analysis

All the statistical analysis such as descriptive statistics, One-way ANOVA are carried out using JMP trial version 13.0. All the parametric tests are carried out at 5% level of significance

## IV. RESULTS

### 4.1. Preformulation studies

Preformulation studies were carried out to identify and confirm the purity of the obtained sample of Esomeprazole. The results obtained were shown in the table 2

Table 2: Preformulation analysis of Esomeprazole

| Sl. No. | Tests | Requirements | Results |
|---|---|---|---|
| 1. | Description | White to off white, crystalline powder | Complies |
| 2. | Solubility | Insoluble in water;<br>sparingly soluble in alcohol<br>freely soluble in chloroform | Complies |
| 3. | Identification | by Melting Point Determination<br>169°C - 175°C | 174$^0$C<br>Complies |
| 4. | Loss on drying | Not more than 0.5% t 105$^0$C for 4 hrs | 0.37% |
| 5. | Sulphated ash | Not more than 0.1% | Nil |
| 6. | Assay | Esomeprazole sample contains not less than 90% and not more than 110% of the labeled claim. | 99.84% |

### 4.1.1. Analytical studies

UV spectrum of Esomeprazole in 1.2 pH HCl buffer solution shows that the drug has $\lambda_{max}$ of 276 nm. The data for calibration curve of Esomeprazole in 1.2 pH HCl buffer solution is shown in table 3 and figure 1. The calibration curve was constructed over a concentration range of 2µg/ml to 10µg/ml and was found to be linear with $r^2$=0.990 and slope of 0.076 and intercept of 0.084

Table 3: Data for calibration curve of Esomeprazole

| Concentration (µg/ml) | Absorbance | | | |
|---|---|---|---|---|
| | Trial –I | Trial –II | Trial –III | Average± S.D |
| 2 | 0.157 | 0.162 | 0.164 | 0.161±0.003 |
| 4 | 0.235 | 0.253 | 0.244 | 0.244±0.009 |
| 6 | 0.312 | 0.298 | 0.324 | 0.311±0.013 |
| 8 | 0.378 | 0.347 | 0.386 | 0.370±0.020 |
| 10 | 0.469 | 0.479 | 0.486 | 0.478±0.008 |

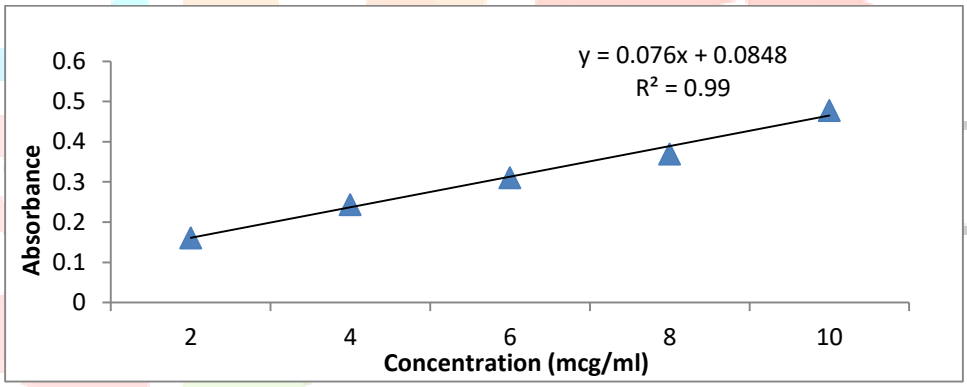



Fig 1: Calibration curve of Esomeprazole at 276 nm

### 4.1.2. Drug excipient studies using Fourier-Transform Infrared Spectroscopy (FTIR)

The results of drug excipient incompatibility by FTIR spectroscopy are shown in the fig 2 and table 4.

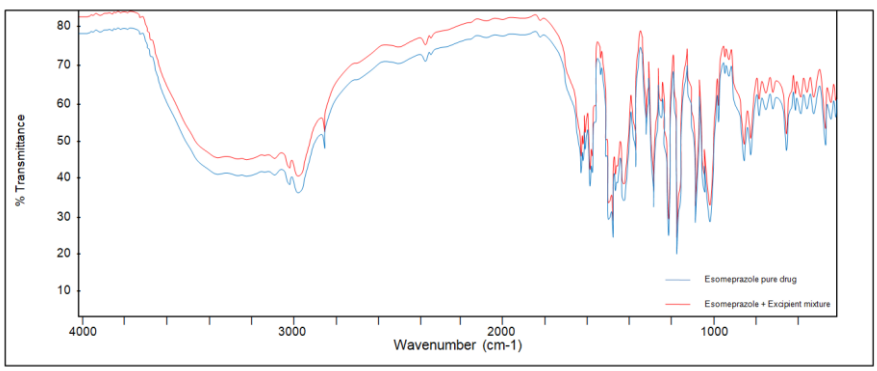



Figure 2: Drug-Excipient incompatibility studies by FTIR

Table 8: Drug Excipient incompatibility studies by FTIR

| Sl. No. | Functional group | Pure drug (Absorption frequency $cm^{-1}$) | Pure drug + Excipients mixture (Absorption frequency $cm^{-1}$) |
|---|---|---|---|
| 01 | S=O stretching | 1078 | 1081 |
| 02 | C-O stretching | 1230 | 1225 |
| 03 | NH bending | 1410 | 1412 |
| 04 | C=N stretching | 1620 | 1611 |
| 05 | C=C-H asymmetric stretching | 2880 | 2872 |

### 4.1.3 Solubility profile

The solubility profile of Esomeprazole is analyzed to determine buffers and the solvents required during formulation development. The results are shown in the table 9

Table 9: Solubility of Esomeprazole in Different Solvents

| S.No. | Solvents | Solubility |
|---|---|---|
| 1. | Distilled water | - |
| 2. | 6.8 pH Sorenson's buffer | - |
| 3. | 0.1 N HCl | + |
| 4. | 0.1 N NaOH | + |
| 5. | Ethanol | ++ |
| 6. | Methanol | ++ |

Practically insoluble (-) slightly soluble (+) soluble (++)

### 4.2. Formulation of Esomeprazole floating tablets

The prepared tablets appear white in color, round in shape with smooth edges and no signs of chipping or capping or tearing. The obtained tablets are shown in the figure 3. The tablets are subjected to post-compression tests for determining the integrity of the tablets produced


Fig 3: Different formulations of Esomeprazole floating tablets prepared with co-processed excipients

### 4.3. Evaluation of precompression parameters

Before compressing into tablets, the precompression parameters are assessed to determine the extent of glidants and lubricants required so as to obtain uniform flow into the die cavity of the compression machine. The results of the pre-compression parameters are shown in the table 10

Table 10: Results of various precompression parameters

| Formulations | Bulk density* (gm/cc) | Tapped density* (gm/cc) | Carr's index (%) | Hausner's ratio (%) | Angle of repose |
|---|---|---|---|---|---|
| F1 | 0.55±0.004 | 0.67±0.023 | 17.91 | 1.21 | 29±2.645 |
| F2 | 0.54±0.012 | 0.66±0.005 | 18.18 | 1.22 | 30±1.439 |
| F3 | 0.58±0.011 | 0.74±0.015 | 21.62 | 1.27 | 31±2.872 |
| F4 | 0.59±0.006 | 0.71±0.017 | 16.90 | 1.20 | 28±0.225 |
| F5 | 0.62±0.008 | 0.75±0.006 | 17.33 | 1.20 | 29±2.169 |
| F6 | 0.64±0.015 | 0.78±0.005 | 17.94 | 1.21 | 27±1.752 |

* The values represent mean SD, n = 3

**4.4. Post compression studies**

The post compression properties of the gastro-retentive floating tablets of Esomeprazole like thickness, hardness and friability, for the formulations F1 to F6 were determined and the results are reported in table 11, 12

Table 11: Results for Thickness, Hardness, Friability

| Formulations | Thickness* (mm) | Hardness** (Kg/cm2) | Friability (%) |
|---|---|---|---|
| F1 | 4.12±0.06 | 4.3 ±0.084 | 0.618±0.0002 |
| F2 | 4.81±0.05 | 5.2 ±0.163 | 0.440±0.0002 |
| F3 | 4.34±0.03 | 5.7 ±0.126 | 0.492±0.0002 |
| F4 | 4.60±0.08 | 4.8 ±0.103 | 0.548±0.0004 |
| F5 | 5.05±0.02 | 5.0 ±0.084 | 0.421±0.0003 |
| F6 | 4.94±0.03 | 5.4 ±0.103 | 0.639±0.0002 |

* = Average of 3 readings SD, n=3. ** = Average of 3 readings SD, n=3.

**Table 12: Results for weight variation, I*n vitro* disintegration time, FLT, TFT and drug content**

| Formulation | Weight variation (%) | *In-vitro* disintegration time (seconds)* | Floating Lag time (FLT) (min) | Total Floating Time (TFT) hrs | Drug content (%) |
|---|---|---|---|---|---|
| F1 | 2.29 | 34.33±0.57 | 11.32±0.81 | 24 | 98.68±0.678 |
| F2 | 1.73 | 39.33±1.52 | 10.41±0.16 | 24 | 97.76±0.880 |
| F3 | 0.87 | 45.00±1.00 | 6.21±0.63 | 24 | 98.13±0.660 |
| F4 | 2.56 | 32.33±0.57 | 7.54±0.24 | 24 | 98.93±0.797 |
| F5 | 1.01 | 15.36±1.52 | 4.42±0.29 | 24 | 99.18±0.354 |
| F6 | 2.94 | 19.00±1.00 | 12.7±0.21 | 24 | 98.85±0.776 |

* = Average of 3 readings SD

Fig 4: Floating tablets of Esomeprazole in 0.1 N HCl

**4.5 *In vitro* dissolution studies**

**In vitro drug release:** The *in-vitro* drug release pattern of all the formulations F1 to F6 are given in the table 13 below and displayed in figure no. 5

**Table 12: In vitro drug release studies**

| Sl. No. | Time (Hrs) | % Cumulative drug release | | | | | |
|---|---|---|---|---|---|---|---|
| | | F1 | F2 | F3 | F4 | F5 | F6 |
| 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2 | 0.25 | 10.33 | 11.46 | 9.98 | 11.20 | 9.46 | 11.03 |
| 3 | 0.5 | 20.92 | 25.09 | 19.01 | 19.19 | 21.01 | 21.79 |
| 4 | 0.75 | 29.86 | 40.89 | 27.26 | 27.69 | 30.47 | 30.91 |
| 5 | 1 | 49.83 | 56.78 | 38.29 | 45.23 | 50.01 | 46.19 |
| 6 | 1.5 | 67.98 | 63.55 | 56.95 | 58.51 | 58.86 | 64.77 |
| 7 | 2 | 75.62 | 76.40 | 64.68 | 69.28 | 64.33 | 77.96 |
| 8 | 4 | 86.38 | 87.25 | 80.74 | 81.17 | 82.91 | 98.54 |
| 9 | 5 | 96.80 | 98.54 | 88.55 | 90.72 | 91.16 | -- |
| 10 | 6 | -- | -- | 97.23 | 98.06 | 95.84 | |
| 11 | 7 | -- | -- | -- | -- | 99.14 | |

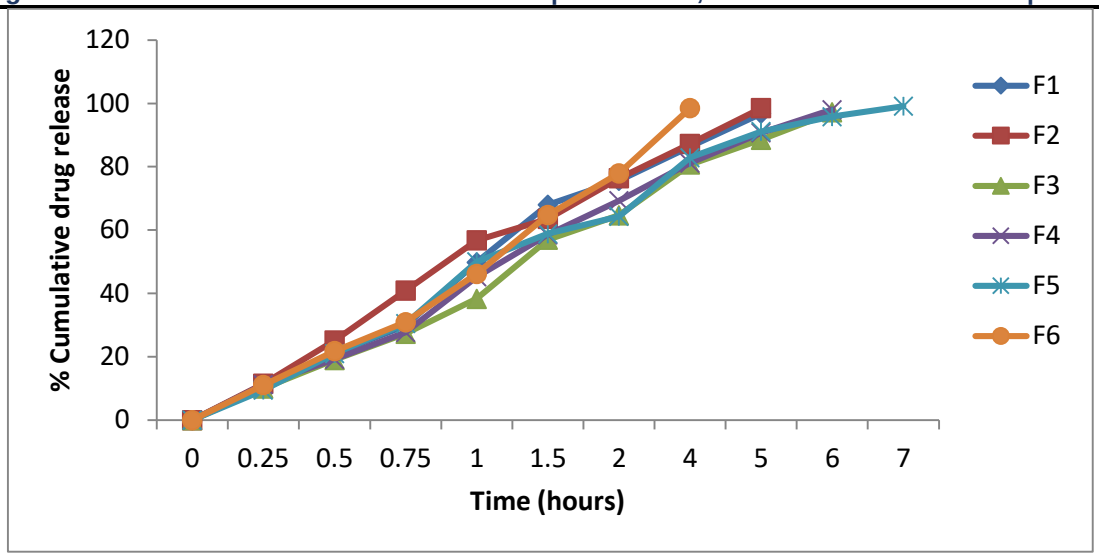



**Fig 5: In vitro drug release of Esomeprazole gastroretentive floating tablets F1-F6**

### 4.6 Drug release kinetics

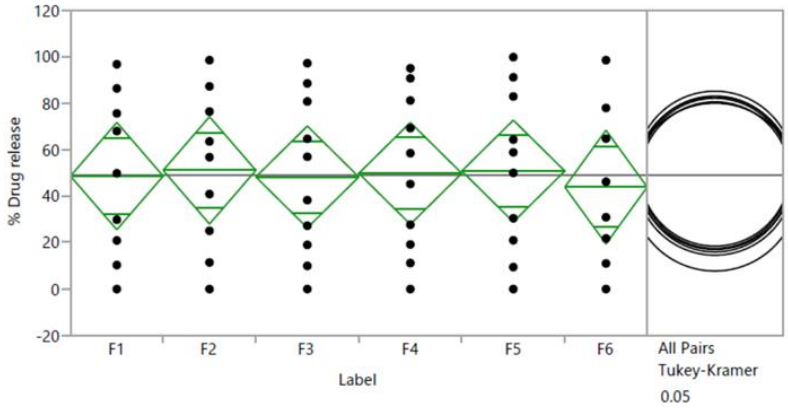
The data from the *in vitro* drug release is fitted into zero order and first order plots to determine the drug release kinetics. The results are shown in the table 13.

Table 13: Drug release kinetics of Formulations F1-F6

| Formulations | Zero Order | | First Order | | | Best fit model |
|---|---|---|---|---|---|---|
| | Slope (K) | $R^2$ | Slope | K | $R^2$ | |
| **F1** | 12.71 | **0.989** | -0.163 | 0.375 | 0.846 | **Zero Order** |
| **F2** | 12.44 | **0.994** | -0.184 | 0.423 | 0.775 | **Zero Order** |
| **F3** | 12.03 | **0.986** | -0.153 | 0.352 | 0.729 | **Zero Order** |
| **F4** | 12.01 | **0.994** | -0.139 | 0.320 | 0.824 | **Zero Order** |
| **F5** | 12.44 | **0.989** | -0.238 | 0.548 | 0.558 | **Zero Order** |
| **F6** | 13.91 | **0.985** | -0.100 | 0.230 | 0.915 | **Zero Order** |

### 4.7 Statistical analysis

A one-way ANOVA test is performed to find out the difference between the treatment groups in terms of drug release at 5% confidence. The results are shown in the fig 6




**Analysis of Variance**

| Source | DF | Sum of Squares | Mean Square | F Ratio | Prob > F |
|---|---|---|---|---|---|
| Label | 5 | 293.006 | 58.60 | 0.0492 | 0.9984 |
| Error | 50 | 59496.096 | 1189.92 | | |
| C. Total | 55 | 59789.102 | | | |

Fig 6: One-way ANOVA of drug release profiles of formulations F1-F6

## V. DISCUSSION

Esomeprazole is a proton pump inhibitor used in the management of gastro-oesophageal reflux disease (GERD), erosive esophagitis, and H.pylori eradication to reduce the risk of duodenal ulcer recurrence. However, it is known to have **elimination half life of 1 to 1.5 hrs** and **low oral bioavailability (50-60%)** (Spencer and Faulds, 2000)**.** Formulation of such a drug requires a technique to increase the gastric residence time so as to improve the bioavailability of the drug. Formulating a proton pump inhibitor as gastroretentive system also provides intended action without systemic adverse effects. As esomeprazole is a BCS class II drug (low solubility and high permeability) and owing to its low bioavailability, the present study attempts to improve the bioavailability and dissolution of the drug using gastroretentive floating drug delivery system in order to improve the gastric residence time.

The drug was estimated by UV spectroscopy. Esomeprazole exhibited $\lambda_{max}$ of 276 nm and its calibration curve in 1.2 pH HCl buffer was found to be linear over a concentration range of 2-10 µg/ml with $r^2$=0.990. The melting point of Esomeprazole was found to be 174ºC. It complies with standards and the solubility, assay, loss on drying, sulphated ash confirms the purity and authenticity of drug sample. Before choosing the excipients, a drug-excipient incompatibility study is carried out using FTIR spectroscopy which revealed that all the functional groups of the pure drug remained intact in the physical mixture thus paving the way for formulation of the gastroretentive floating drug delivery system with the intended excipients. Coprocessed excipient of xanthan and guar gum was prepared by using solvent evaporation method. Co-processed excipients for different formulations like (F1-F5) were prepared in the ratios of 1:1, 1:2, 2:1, 1:3, 3:1 respectively. The formulation F6 is prepared by taking the admixture of Xanthan and guar gum at a ratio of 1:1 to compare the differences between the individual excipient and coprocessed excipient (Wang *et al.*, 2015).

Precompression studies indicated that the drug has fair to good flow property, necessitating the need for addition of glidants and lubricants to have adequate flow property. The pre compressional parameters like flow properties of liquisolid mixtures were found to be satisfactory as indicated by Carr's index (16.90-21.62 %), Hausner's ratio (1.20-1.27%) and angle of repose (28.0-31.0). Direct compression method is used to prepare the gastroretentive floating tablets. Average hardness of the tablet ranges from 4.12 to 5.05 kg/cm$^2$ which was within the limits. Friability values are in the range of 0.44% to 0.639%. This indicates that acceptable resistance is shown by the tablets to withstand handling. Weight variation was found to be in the range of 0.87% to 2.94% for all the formulations, indicating that all formulations passed the test (Chaurasia, 2016).

Disintegration time was found to be in the range of 34.33 ± 0.57 sec to 45.0 ± 1.00 sec. Faster disintegration time indicate rapid release rates. The floating lag time of the formulations is in the range of 24 min to 60 mins. Drug dissolution studies indicated that the formulations containing higher proportion of xanthan gum have a better controlled drug release when compared to guar gum. The order of drug release from the formulations is in the order of F5>F3>F4>F2>F1>F6. The formulations F5, F3 has higher proportion of xanthan gum and lower proportion of guar gum (3:1 and 2:1 respectively) indicating that xanthan gum has a more sustained action on the drug release.

Curve fitting analysis revealed that the drug release from the formulations followed zero order kinetics as evident from the higher $r^2$ values. This is consistent with theoretical assumptions that sustained release dosage forms follow zero order (concentration independent) kinetics. Statistical analysis is carried out to determine the differences in the drug release pattern from the formulations. It can be seen from the One-way ANOVA analysis that there is no significant difference ($p>0.05$) in drug release between the formulations indicating that Xanthan gum and Guar gum are good either as coprocessed excipients or when used alone. However, the drug release from F6 that contains compound mixture of Xanthan gum and Guar gum is significantly lower than all the other formulations (F1-F5) which contains the coprocessed excipient indicating its superiority. Basing on the post-compression parameters, drug release, and floating lag time **F5 containing 3:1 ratio of Xanthan gum and guar gum is chosen as the best formulation**.

## VI. CONCLUSION

Formulation F5 which contained 1:3 ratio of Xanthan gum and guar gum as co-processed excipient had a better floating time among the six formulae at 4.42±0.29 min, with consistent drug release for a period of up to 7 hours. Thus, formulation F5 is chosen as the best formulation among others. From this study it can be concluded that co-processed excipients can breathe new life to the existing excipients combing the desirable properties to achieve a hybrid excipient that possesses the individual advantages of both the excipients and alter the therapeutic performance of the drugs

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