Controlled porosity osmotic pump tablets packed with esomeprazole double walled microspheres

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Abstract

The current investigation objective was to fabricate osmotic tablets embedded with double walled microspheres of esomeprazole for the treatment of peptic ulcer. The microspheres were prepared by an ionotropic gelation technique using calcium chloride (5%) as cross-linking agent, sodium alginate, gelatin and pectin as mucoadhesive polymers. Total six batches of microspheres were prepared among this F1-F3 contains gelatin as a mucoadhesive polymer together sodium alginate that was added to produce calcium-alginate beads in an ionotropic gelation also act as a second mucoadhesive polymer. The next set of microspheres from F4-F6 contains pectin as first and sodium alginate as second polymer. The formulated microspheres were evaluated based on the parameters- particle size, percentage yield (%), drug incorporation efficiency (%), swelling index (%), drug content (%) and in vitro drug release (%). The best batches of microspheres were selected for fabrication of osmotic tablets by adding osmotic agents and finally polishing with coating solution containing pore former and plasticizer makes the controlled porosity osmotic pump tablets. The data obtained after evaluation of the tablets suggest that a micro particulate system can be successfully designed for sustained delivery of esomeprazole and to improve its bioavailability.

Key words: Muco adhesive microspheres, Opop tablets, Pore formers, Controlled drug delivery.

INTRODUCTION

Microspheres are potential drug carriers for oral controlled release. Microspheres had significant importance in biomedical applications [1]. Microspheres can be produced by using sodium alginate as polymer and calcium chloride as crosslinking agent. Drug administration in the form of microspheres had significant importance in biomedical applications [2]. The mucoadhesive dosage forms one of the promising delivery system in which drug delivery system adheres to the mucous layer at particular sites of action for a longer period of time and intensified contact with the mucosa increasing the drug concentration gradient. Hence, uptake and consequently bioavailability of the drug may be increased, frequency of dosing reduced and patient compliance improved [3]. Present microsphere delivery system technology consisting of a single drug dispersed within a polymer matrix has several drawbacks. One of the problems is called “burst effect” [4]. To overcome this initial bursting effect a double walled drug delivery system can be fabricated with the aid of two types of polymers. Controlled porosity osmotic pump tablet; which is an extension of an elementary osmotic tablet, utilizes the principle of osmotic pressure for the delivery of drugs and avoids the expensive laser drilling for creation of delivery orifice on the tablet coat. They do not have any aperture to release the drugs; drug release is achieved through the pores, which are formed in the semi permeable wall in situ during the operation. The advantages of controlled porosity osmotic pump tablet are mainly driven by the capacity to deliver drugs in a sustained manner, independent of the drug chemical properties, patient’s physiological factors or concomitant food intake [5].

Esomeprazole is Anti-Ulcer Agent, Proton-pump Inhibitors and Antihistamines. It is absorbed completely (90%) after oral administration and the protein binding of esomeprazole is 97%.
Esomeprazole is extensively metabolized in the liver by the cytochrome P450 (CYP) enzyme system and approximately 80% of an oral dose of esomeprazole is excreted as inactive metabolites in the urine and the remainder is found as inactive metabolites in the feces [6]. But it is an acid liable drug can’t remain stable in the acidic condition of the stomach. So controlled porosity osmotic pump tablets packed with encapsulated Esomeprazole can overcome the limitations such as:- it can protect the drug from low pH of the stomach and can target the drug action into the intestine through the process of encapsulation, mucoadhesive characteristics can enhance the bioavailability and finally the CPOP tablets releases the drug in a sustained manner, irrespective of the pH.

MATERIALS AND METHODS
Materials
Esomeprazole, gelatin, mannitol, colloidal silicone dioxide was purchased from Yarrow Chem, Mumbai. Pectin, Sodium Alginate, Micro Crystalline Cellulose, Cellulose acetate phthalate, PEG400&Sorbitol was purchased from Nice Chemicals Pvt Ltd, Cochin and Calcium chloride was purchased from Spectrum reagents & chemicals Pvt Ltd Edayar, Cochin.

Methods
Preformulation study
Recording of the FTIR spectra of drug and excipients
The compatibility study of drug and excipients can be analysed by the significant changes in the shape and position of the absorbance bands in an IR Spectrum. In this method individual samples as well as the mixture of the drug and excipients are ground and mixed thoroughly with potassium bromide (1:100) for 3-5 minutes in a mortar and compressed into the disc by applying pressure of 5 tons for 2 mins in a hydraulic press. The diffusion reflectance spectroscopy technique was utilized in the mid-IR (400–4000 cm−1) spectral region. The prepared pellet was placed in the light path (sample holder) and scanned, Then the characteristic peaks of all samples as well as mixtures are obtained [7].

Preparation of Alginate–Gelatin Microspheres
Three batches of drug loaded Microspheres (F1, F2, and F3) were prepared using a combination of sodium alginate (1%) and gelatin (1, 2, & 3% respectively). To 100ml of deionized water, gelatin was added and stirred with the electric stirrer to form mucilage. Then sodium alginate was added to form uniform dispersion. Weighed quantity of Esomeprazole was added and homogenized for 5 min. The resulting dispersion was dropped through a syringe with a needle into 100ml of 5%w/v aqueous calcium chloride solution and stirred at 100rpm. After stirring for 1 hour, the formed microspheres were separated by filtration, washed with distilled water, dried at 50°C in hot air oven [8].

Preparation of Alginate-Pectin Microspheres
Three batches of drug loaded microspheres (F4, F5, and F6) were prepared using a combination of sodium alginate (1%) and pectin (1, 2, & 3%) respectively. To 1000ml of deionized water, Pectin was added and stirred with the electric stirrer to form mucilage. Then sodium alginate was added to form uniform dispersion. Weighed quantity of Esomeprazole was added and homogenized for 5 min. The resulting dispersion was dropped through a syringe with a needle into 100ml of 5%w/v aqueous calcium chloride solution and stirred at 100rpm. After stirring for 1 hour, the formed microspheres were separated by filtration, washed with distilled water, dried at 50°C in an oven. Different concentrations and ratios of polymers used in the formulation of microspheres are mentioned in Table 1.

Evaluation of mucoadhesive microspheres
Percentage Yield
The Percentage yield of microspheres containing a drug was determined by the weight ratio of the dried microspheres to the loading amount of the drug and Polymer. The yield of each batch was calculated in terms of percentage yield as per following formula [4].

\[
\text{Percentage yield} = \left( \frac{\text{Percentage yield}}{\text{Microspheres yield}} \right) \times 100
\]

Drug incorporation efficiency (%)
To determine the %EE, microspheres (10mg) were weighed, carefully crushed, triturated and suspended in a required quantity of buffer for dissolving microspheres shell coat. The suspension was suitably diluted with the same buffer and filtered to separate shell fragments. The drug content was analysed after suitable dilution spectrophotometrically at 302nm [9]. The amount of drug incorporated in microspheres was calculated by the following formula
% Drug entrapment = \frac{\text{Experimental drug loading} \times 100}{\text{Theoretical drug loading}}

\text{Experimental drug loading} = \frac{\text{Concentration of drug loaded microspheres}}{1000} \times 100

\text{Theoretical drug loading} = \frac{\text{Amount of drug added}}{\text{Amount of drug added}} \times 100

Swelling index studies
The capacity of the microspheres to absorb water and swell was determined in terms of swelling index. For determining swelling index, the microspheres were weighed initially, then suspended in pH 1.2. After 1h microspheres were transferred onto blotting paper to remove the excess moisture, then weighed the swollen microspheres using a microbalance. After that swollen microspheres were dried in oven at 60°C for 5h until showed the constant weight [10]. The difference in weight of microspheres was used to calculate the swelling index

Swelling index (%) = \frac{\text{Final weight - Initial weight}}{\text{Initial weight}} \times 100

Determination of drug content (%)
100mg of drug loaded microspheres were added to 100ml of 6.8pH phosphate buffer. Stir the dispersion using a magnetic stirrer for 3hrs. Filter the dispersion using whatmann filter paper and dilute it according to need (take 1ml dilute to 100ml) and measure the absorbance at 302nm. The following equation can be used for drug content determination.

Drug content (%) = \frac{\text{Concentration of drug loaded microspheres}}{1000} \times 100

Particle size analysis
The size distributions in terms of average diameter of the microspheres were determined by the optical microscope method. A minute quantity of dried microspheres was suspended in glycerin and the particle size of 100 microspheres was determined in each batch and final the particle size was calculated [11-12].

In vitro drug release studies
In the current study, drug release from microspheres was studied using USP Type2 (paddle) dissolution apparatus at 50rpm in 0.1N HCl (pH 1.2) and 6.8 pH phosphate buffer as dissolution fluids (900ml) maintained at 37 \pm 0.5°C. The samples were withdrawn at predetermined time intervals such as 1, 2, 4, 6, 8, 10 and 12h simultaneously. Same volume replenished each time to maintain the sink condition [13]. The samples were analyzed spectrophotometrically at 302nm for the estimation of Esomeprazole concentrations in the test samples.

Amount of drug release = \frac{\text{Amount of drug released until time factor}}{1000} \text{ mg/ml}
Percentage drug release = \frac{\text{Amount of drug released until time factor}}{\text{Amount of drug loaded}} \times 100

Kinetic modeling of drug release
The formulations were treated with the different release kinetic equations include Zero order, First order, Higuchi’s model and Korsmeyer-Peppas. Analysis of drug release from microspheres was determined by calculating the correlation coefficient (r^2) [14].

In vitro mucoadhesiveness
The mucoadhesive properties of the microspheres were evaluated by the in vitro wash-off test. A 1 cm x 1 cm piece of chicken ileum was tied onto a glass slide (3 inch x 1 inch) using a thread. Microspheres were spread onto the wet, rinsed, tissue specimen, and the prepared slide was hung onto one of the groves of a USP tablet disintegrating test apparatus. The disintegrating test apparatus was operated such that the tissue specimen was given regular up and down movements in a beaker containing 6.8 phosphate buffer. At the end of every time interval, the number of microspheres still adhering on to the tissue was counted and their adhesive strength was determined using the following formula [15].

Mucoadhesion (%) = \frac{\text{Weight of adhered microsphere}}{\text{Weight of applied microspheres}} \times 100

Fabrication of controlled porosity osmotic pump tablets embedded with Esomeprazole microspheres
The optimized batch of microspheres were tableted by direct compression using directly compressible excipients.

Core formulation
Direct compression method
The controlled porosity osmotic pump tablets were prepared by direct compression technique. Required quantities of drug (Esomeprazole)
containing microspheres and directly compressible diluent MCC were mixed thoroughly, passed through 60 meshes. Then the blend was lubricated with magnesium stearate and Aerosil was used as glidant. In this formulation mannitol was used as osmogent. Finally, the powder mix was subjected to compression on a ten station rotary punch tablet machine using 8 mm convex punch. The composition of CPOP tablets was given in table 2 [16].

Coating Process
Preparation of Coating Solution
The coating solution containing cellulose acetate, polyethylene glycol 400 & sorbitol (pore formers), Dibutyl phthalate (flux regulator) was prepared as per the formula given in the Table 3. Accurately weighed quantity of cellulose acetate phthalate (20 % w/w), PEG 400 (2 % w/v), sorbitol (2%) were mixed continuously for 30 minutes with solvent mixture acetone and alcohol in 8:2 ratio. The mixture was stirred continuously for 30 minutes.

Dip Coating
The tablets were coated by dip coating process 6.3 % w/w cellulose acetate solution was used for coating [17]. The coating of core tablet was done manually by holding each tablet with the help of forceps. The coated tablets were dried by keeping them at room temperature for 24 hours. The coating composition for the preparation controlled porosity osmotic pump tablets was shown in table 3.

Friability test
The friability of tablets was determined using Roche Friabilator. It is expressed in percentage (%). 10 tablets were initially weighed (W) and transferred into friabilator and was operated at 25 rpm for 4 min or run up to 100 revaluations [20]. Then the tablets were weighed again (Wi). The percentage friability was then calculated by

\[
\% \text{ friability (F)} = \left( \frac{\text{initial weight (W)} - \text{final weight (Wi)}}{\text{Initial weight} \times 100} \right)
\]

Percentage friability of tablet less than 1% are considered acceptable

Dissolution for Osmotic tablet of Esomeprazole
The dissolution studies for the prepared Esomeprazole tablets were carried out using dissolution test apparatus USP II paddle type. The dissolution medium is 900 ml of phosphate buffer of pH 6.8 for 60 min. The temperature of the medium was maintained at 37±0.5°C. The speed of rotation of the paddle was kept at 50 rpm. Aliquots of 1ml were withdrawn after every 1 hour. These samples were diluted to make up the volume of 10ml with pH 6.8 buffer. The samples so withdrawn were replaced with the fresh dissolution medium equilibrated at the same temperature. The drug released at the different time intervals from the dosage form is measured by UV visible spectrophotometer, by measuring the absorbance of the sample solutions at 302nm [21].

RESULTS AND DISCUSSION
Preformulation study
FTIR Studies
The results of FTIR studies of the drug and excipient mixture were shown in the table 5. FT-IR spectrum of Drug and excipients did not differed with major peaks of esomeprazole.ie, similar peaks were observed with minor differences indicate that there is no possible interaction between drug and excipients.

Micromeritics properties
The Micromeritics properties were evaluated for the preliminary batch of microspheres and the results were depicted in the table 6. The angle of repose of the microspheres ranged from 25.45° to 30.11°. The bulk and tapped density values of the microspheres ranged from 0.247 to 0.302g/cm3 and 0.318 to 0.368 g/cm3 respectively. The % compressibility index (Carr’s index) ranged between 11.94% and 17.93%. The Housner’s ratio of themicrospheres
The values of Carr’s index and the angle of repose indicate good flow properties. Also, higher Housner’s ratio indicates greater cohesion between particles. The better flow property indicates that the microspheres produced are unaggregated. Thus, it is an added advantage while processing the formulation using high-speed packaging equipments. Moreover, the process scale-up is also facilitated because of the excellent flow properties.

**Evaluation study for microspheres**

The evaluation studies such as determination of percentage yield, entrapment efficiency, swelling index, drug content, *in vitro* drug release, Mucoadhesion studies and particle size analysis were carried out and the table 7 gives the results of the study.

**Kinetic modeling of drug release**

The release kinetics obtained were fitted to zero order, first order, Higuchi and Koresmeyer- Peppas equation to determine the corresponding release rate and mechanism of drug release from the microspheres. The corresponding plot for Korsmeyer-Peppas equation indicated a good linearity. The $r^2$ value of Higuchi ranges from 0.769-0.994. The mechanism of drug release from formulations was determined by Korsmeyer-Peppas equation where exponent ‘n’ indicated mechanism of drug release. All the formulations, except F1 follows first order release kinetics. Korsmeyer-Peppas plots ‘value ranges from 1.058-1.539 for four batches, indicating that the Esomeprazole release mechanism followed diffusion and erosion. From all the above studies, it results that F3 formulation containing gelatin and pectin as the mucoadhesive polymers are found to be the best one. So it can be selected for the fabrication of osmotic tablets by adding osmogens and pore former polishing.

**Evaluation of CPOP tablets**

**Hardness**

The hardness of tablets was determined by using a Monsanto hardness tester. The average hardness of osmotic tablets of Esomeprazole was found to be 5.21Kg/cm².

**Friability**

Friability test is used to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping. The IP limit for friability is <1%. The prepared tablet has friability 0.38%. So it passes the test for friability.

**Weight variation**

The weight variation study for prepared tablets was carried out and all the tablets from the particular batch fall within the IP limit. So it passes the weight variation test.

**In-vitro drug release study for CPOP tablet**

The dissolution studies of osmotic tablets were conducted in 6.8 pH phosphate buffer for 12hrs. The dissolution profile was shown in table 8.

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**Table 1. Composition of bioadhesive microspheres of Esomeprazole**

<table>
<thead>
<tr>
<th>S.No</th>
<th>Ingredients</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Esomeprazole LP (g)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>Gelatin (g)</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Pectin (g)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>Sodium alginate (g)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>Calcium chloride (%w/v)</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
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</table>

**Table 2. Composition of CPOP tablets**

<table>
<thead>
<tr>
<th>S.No</th>
<th>Ingredients</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Esomeprazole microspheres</td>
<td>Weight equivalent to 14 mg</td>
</tr>
<tr>
<td>2</td>
<td>Micro Crystalline cellulose</td>
<td>67mg</td>
</tr>
<tr>
<td>3</td>
<td>Mannitol</td>
<td>25mg</td>
</tr>
<tr>
<td>4</td>
<td>Magnesium stearate</td>
<td>4mg</td>
</tr>
<tr>
<td>5</td>
<td>Aerosil</td>
<td>6mg</td>
</tr>
<tr>
<td>6</td>
<td>Talc</td>
<td>4mg</td>
</tr>
</tbody>
</table>
**Table 3. Coating composition of osmotic tablets**

<table>
<thead>
<tr>
<th>S. No</th>
<th>Ingredients</th>
<th>Quantity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cellulose acetate phthalate</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>PEG 400</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>Sorbitol</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>Acetone: Isopropyl alcohol</td>
<td>8.2</td>
</tr>
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</table>

**Table 4. Specification for weight variation of tablets as per IP**

<table>
<thead>
<tr>
<th>Average weight of tablets</th>
<th>Percentage difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>125 or less</td>
<td>10</td>
</tr>
<tr>
<td>125-250</td>
<td>7.5</td>
</tr>
<tr>
<td>More than 250</td>
<td>5</td>
</tr>
</tbody>
</table>

**Table 5. FTIR studies of drug and drug excipient mixtures**

<table>
<thead>
<tr>
<th>S.No</th>
<th>Interpretation</th>
<th>Esomeprazole</th>
<th>Esomeprazole Gelatin+sodium alginate + Pectin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>S=O</td>
<td>1076.28</td>
<td>1076.28</td>
</tr>
<tr>
<td>2</td>
<td>C-H</td>
<td>2935.66</td>
<td>2993.52</td>
</tr>
<tr>
<td>3</td>
<td>C-O</td>
<td>1153.43</td>
<td>1153.43</td>
</tr>
<tr>
<td>4</td>
<td>C-N</td>
<td>1269.16</td>
<td>1269.16</td>
</tr>
</tbody>
</table>

**Table 6. Bulk characterization of Preliminary Trail Batch**

<table>
<thead>
<tr>
<th>Batch code</th>
<th>Angle of repose (°)</th>
<th>Bulk density (gm/cc)</th>
<th>Tapped density(g/cc)</th>
<th>Carr’s index(%)</th>
<th>Hausner’s ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>26.56</td>
<td>0.280</td>
<td>0.318</td>
<td>11.94</td>
<td>1.13</td>
</tr>
<tr>
<td>F2</td>
<td>25.96</td>
<td>0.247</td>
<td>0.327</td>
<td>16.20</td>
<td>1.19</td>
</tr>
<tr>
<td>F3</td>
<td>25.45</td>
<td>0.302</td>
<td>0.357</td>
<td>14.42</td>
<td>1.13</td>
</tr>
<tr>
<td>F4</td>
<td>30.11</td>
<td>0.287</td>
<td>0.337</td>
<td>14.83</td>
<td>1.17</td>
</tr>
<tr>
<td>F5</td>
<td>28.05</td>
<td>0.302</td>
<td>0.368</td>
<td>17.93</td>
<td>1.21</td>
</tr>
<tr>
<td>F6</td>
<td>27.47</td>
<td>0.295</td>
<td>0.347</td>
<td>14.98</td>
<td>1.17</td>
</tr>
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</table>

**Table 7. Evaluation study for microspheres**

<table>
<thead>
<tr>
<th>Batch code</th>
<th>Percentage yield (%)</th>
<th>Mean Diameter (µM)</th>
<th>Entrapment Efficiency (%)</th>
<th>Swelling Index (%)</th>
<th>Drug Content (%)</th>
<th>Drug Release at 12th hour(%)</th>
<th>Mucoadhesion at 8th hour (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>95.33</td>
<td>540</td>
<td>77.58</td>
<td>84.42</td>
<td>75.14</td>
<td>43.909</td>
<td>64.24</td>
</tr>
<tr>
<td>F2</td>
<td>93.0</td>
<td>530</td>
<td>79.88</td>
<td>86.26</td>
<td>80.92</td>
<td>44.45</td>
<td>70.98</td>
</tr>
<tr>
<td>F3</td>
<td>98.40</td>
<td>520</td>
<td>80.67</td>
<td>87.01</td>
<td>86.70</td>
<td>45.54</td>
<td>78.5</td>
</tr>
<tr>
<td>F4</td>
<td>90.66</td>
<td>610</td>
<td>69.81</td>
<td>78.07</td>
<td>60.69</td>
<td>41.72</td>
<td>45.44</td>
</tr>
<tr>
<td>F5</td>
<td>92.0</td>
<td>600</td>
<td>73.64</td>
<td>80.31</td>
<td>63.58</td>
<td>42.81</td>
<td>52.39</td>
</tr>
<tr>
<td>F6</td>
<td>95.60</td>
<td>570</td>
<td>77.44</td>
<td>81.27</td>
<td>69.36</td>
<td>43.090</td>
<td>58.10</td>
</tr>
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</table>

**Table 8. in vitro dissolution study for osmotic tablet**

<table>
<thead>
<tr>
<th>Time (Hour)</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug release(%)</td>
<td>0.79</td>
<td>3.22</td>
<td>7.91</td>
<td>10.92</td>
<td>13.52</td>
<td>16.38</td>
<td>19.24</td>
<td>23.41</td>
<td>25.23</td>
<td>27.05</td>
<td>31.73</td>
<td>38.83</td>
<td>42.13</td>
</tr>
</tbody>
</table>
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Fig 1. FTIR Spectra of pure Esomeprazole drug

Fig 2. FTIR study of Mixture 3: (Esomeprazole + Pectin + Sodium alginate+gelatin)

Fig 3. Zero order plot for F3 batch

Zero order plot

\[ y = 3.6346x + 2.7154 \]
\[ R^2 = 0.998 \]

Fig 4. Higuchi plot for F3 batch

Higuchi plot

\[ y = 16.294x - 13.148 \]
\[ R^2 = 0.9949 \]

Fig 5. Korsemeyer peppa's plot for F3 batch

Korsemeyer peppa's plot

\[ y = 1.501x + 0.8355 \]
\[ R^2 = 0.9958 \]

Fig 6. First order plot for F3 batch

First order plot

\[ y = -0.0209x + 1.9963 \]
\[ R^2 = 0.9969 \]

Fig 7. In-vitro dissolution study for osmotic tablet
CONCLUSION
It can be concluded from the study that Esomeprazole microspheres embedded in an oral osmotic tablet system will progressively deliver a measurable, reproducible amount of drug over a prolonged period could exhibit improved therapeutic effect, quality character of formulation and patient compliance.

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CONFLICT OF INTEREST
No conflict of interest.

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