Development and Optimization of pH-Independent Extended Release Matrix Tablet of Propranolol Hydrochloride Using Eudragit RSPO by Hot Melt Granulation

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Citation

Abstract
Extended release tablets offer many advantages in oral administration of medications. This study reports the development and evaluation of controlled release propranolol hydrochloride matrix tablets. Matrix tablets weighing 600 mg containing 80 mg propranolol hydrochloride were fabricated by hot melt granulation method and direct compression of the granules. They contain polyethylene glycol 4000, polyvinyl acetate and eudragit RSPO in different ratios. Tablets were evaluated for their physical characteristics and drug release as well as swelling behavior. Results showed that the rate of release of propranolol hydrochloride was dependent on concentrations of polyvinyl acetate and eudragit RSPO in the formulation. Also in-vitro swelling study indicates that the tested formula has considerable swelling that follows almost zero-order pattern. Analysis of release mechanism using various available models showed that release of propranolol hydrochloride from matrix tablets fitted to Korsmeyers – Peppas equation indicated an anomalous non-fickian transport suggesting that the drug release is mainly a diffusion-erosion controlled mechanism. In conclusion, propranolol hydrochloride can be prepared as extended-release pH independent matrix tablet using eudragit RSPO, polyvinyl acetate and polyethylene glycol 4000 by hot melt granulation technique. Sustained release of drug was achieved up to 12 hours and the release pattern follows Peppas model.

1. Introduction

Oral administration is the most common and preferable route for drug delivery. This is attributed to patients’ acceptance, ease of administration, accurate dose, cost-effectiveness of preparation and longtime stability. Extended release dosage forms which release the drug over extended periods of time are developed in order to improve the pharmacotherapy [1]. The advantages of extended release dosage forms include maintenance of a steady drug plasma level over prolonged time thus reducing the fluctuation of drug plasma level, maintenance of the therapeutic drug level hence stabilizing the medical treatment and reducing the side effect of drug, reduction in the frequency of drug administration which improves patient’s compliance and consequence
therapeutic efficacy [2, 3]. Various physical and chemical approaches have been successfully applied to produce the controlled delivery systems that extend drug release into the gastrointestinal tract with the desired release profile. Today, most proprietary and nonproprietary extended-release technologies are based on polymeric systems [4].

Drug release from these extended release systems is generally based on one or a combination of drug diffusion through pores of a barrier, tortuous channels, or a viscous gel layer between polymer chains [5, 6], system swelling followed by diffusion and/or erosion and dissolution [7], or osmotic pressure induced release drug solution, suspension or wet mass forced out of the system [8, 9]. Modified release tablet could be manufactured by direct compression [10], dry granulation by compaction [11] wet granulation [12], and hot melt extrusion and granulation [13, 14].

Polymethacrylates are synthetic cationic and anionic polymers of diethylaminoethylmethacrylates, methacrylic acid and methacrylic acid esters in varying ratios. Eudragit polymers are copolymers of acrylic and methacrylic acid or their esters. Different substitutions produce different properties [15]. Eudragit is insoluble in water but it swells, which enables the incorporated drugs to be released from the formulation by means of diffusion through the swollen matrix [16]. The Eudragit polymers are listed in the FDA inactive ingredients guide. They are generally regarded as non-toxic and non-irritant materials.

Eudragit® RSPO is a copolymer of ethyl acrylate, methyl methacrylate and a low content of methacrylic acid ester with quaternary ammonium groups. The ammonium groups are present as salts and make the polymers permeable [17]. It has a pH-independant swelling capacity with low permeability which makes it suitable for extended release dosage forms [18].

Propranolol hydrochloride, is a β-adrenergic blocking agent, a competitive inhibitor of the effects of catecholamines at β-adrenergic receptor sites [19]. It is widely used in therapy for its antihypertensive, antiangorous and antiarrhythmic properties. Furthermore, it has a short elimination half-life of 3 hours, which makes it a suitable candidate to be delivered at a controlled rate [20]. It is a weak basic drug of pKa 9.5, soluble in water and ethanol and slightly soluble in chloroform [21].

The purpose of this work is to prepare a matrix tablet of propranolol hydrochloride, utilizing hot melt granulation and direct compression of the tablets, by using different concentration of eudragit RSPO incorporated in bases of various polyethylene glycol/Polyvinyl acetate ratio as extended release pH-independent oral tablet dosage form.

2. Materials and Methods

2.1. Materials

Propranolol hydrochloride was kindly given from the Arab Pharmaceutical Manufacturing Co.LTD. Jordan. Batch No: 1004377, eudragit RSPO (Evonik Rohm, Pharma polymers. Germany, batch No: G120638508), polyethylene glycol 4000 & 6000 (Xilong Chemical Industry Incorporate Col. China, batch No: 110828), polyvinyl acetate 45000 MW (Wacker Chemie AG Burghausen / Germany, batch No: 1308219), magnesium stearate (Riedel-De-Haen AG seelie, Germany).

2.2. Methods

2.2.1. Preparation of Calibration Curve

Calibration curve of propranolol hydrochloride was prepared in 0.1N HCl pH 1.2, phosphate buffer pH 6.8 and distilled water (pH ≈ 7.2-7.4) using UV visible spectrophotometer (UV 1601- Shimadzu, Japan) as follows: working standard of 100 μg/ml was prepared, aliquots of 0.2 ml to 1.0 ml from the stock solution representing 2-10 μg/ml of drug were transferred to 10 ml volumetric flask and the volume was adjusted to 10 ml with the solvent. Absorbance of the above solution were taken at 290 nm against the blank solution prepared in the same manner without adding the drug. A graph of absorbance vs. concentration was plotted.

2.2.2. Compatibility Study of API with Excipients

i. Differential Scanning Calorimetry

The differential scanning calorimetry measurements were performed on DSC-823e (Canada). The samples equivalent to 5 mg of propranolol hydrochloride alone and other excipients (alone and in F 15 "table 1") were sealed in aluminum pans with inert atmosphere, by purging nitrogen at a flow of 20 ml/min, with scanning rate of 10°C min-1 over 25°C to 200°C.

ii. Fourier Transform Infrared Spectroscopy (FT-IR Study)

FTIR spectra were obtained by using FTIR spectrometer (FTIR 8400S Japan).Samples of 2 mg were ground and mixed thoroughly with 198 mg potassium bromide. The IR spectra of drug alone and with excipients were taken (Polyvinyl acetate, polyethylene glycol, eudragit RSPO and F15 (table 1)). The pellets of potassium bromide were prepared by direct compression (Hydraulic unit model 3912). Forty scans were obtained at a resolution of 4cm⁻¹, from 4000 to 400 cm⁻¹.

2.2.3. Preparation of Tablets

Tablets of matrix type were prepared by hot melt-granulation method and direct compression of granules by accurately weighing the ingredients of the matrix, polyethylene glycol, polyvinyl acetate, eudragit RSPO, and magnesium stearate. Polyethylene glycol was melted in a porcelain dish avoiding overheating that might cause some polyethylene glycol to volatize or turn yellow. Polyvinyl acetate was stirred into the molten polyethylene glycol until it dissolved completely (the bases were melted by order of melting point). During this step the temperature was not allowed to rise above 130 °C otherwise the system developed a yellow color (Propranolol hydrochloride has a thermal
stability up to 162 °C and a melting point ranges from 163-165°C.

Propranolol hydrochloride; previously sieved through a 250 μm mash screen, was mixed gradually into molten mass until a homogeneous dispersion was obtained. The blend was allowed to cool and solidify at room temperature and stored overnight in screw-capped gars before being granulated. The granulation process of the mass was done using mortar and pestle; the granules were sieved through 30 # mesh and retained on 30 # mesh to obtain uniform size granules. The granules were assessed for bulk density, tapped density, compressibility index (Carr’s consolidation index), angle of repose and Hausner's ratio according to the requirements of USP34, 2011. The granules were then compressed by 8-stations rotary tablet press (Kambert Machinery, India). The hardness of the tablets was adjusted to be in the range of 8-12 KP and the weight of each tablets 600 mg ± 5%, (i.e. using conduction of compression to target of tablets). Table 1 shows composition of different prepared formulas. Table 1. Composition of different prepared formulas.

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Propranolol hydrochloride (mg)</th>
<th>Polyethylene glycol (4000)</th>
<th>Polyvinyl acetate %w/w</th>
<th>Eudragit RSPO %w/w</th>
<th>Magnesium stearate (mg)</th>
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<tr>
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<td>445</td>
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</tr>
<tr>
<td>F15</td>
<td>80</td>
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<td>50</td>
<td>3</td>
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<td>80</td>
<td>157</td>
<td>10</td>
<td>50</td>
<td>3</td>
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</tbody>
</table>

2.2.4. Evaluation of Tablets

i. Dimension

Thickness and diameter were measured using a calibrated barmier caliper. Five tablets of each formulation were picked randomly and dimensions determined (USP 34).

ii. Hardness and Friability

Hardness and Friability were tested according to the requirements of (USP 34). The hardness of the tablets was determined using Monsanto hardness tester expressed in kg/cm². Friability was measured by (Erwka, 100500 Germany).

iii. Weight Variation

The reproducibility of the tablet weight and propranolol hydrochloride contents were considered to be satisfactory for the purposes of the present investigation. Twenty tablets of each formula were weighed individually and all together, an average weight of tablet was calculated and results were evaluated according to USP29.

iv. Drug Content Variation

The drug content of the matrix tablets was determined according to USP 29 which requires that the amount of the active ingredient in each of the 10 tested tablets lies within the range of 85% to 115% of the standard amount. Ten tablets were weighed then taken into a mortar and crushed into fine powder. An accurately weighed portion of the powder equivalent to about 80 mg of propranolol hydrochloride matrix tablet was transferred to a conical flask containing 100ml of 0.1N HCl and pH 6.8. It was shaken by mechanical means for 30 minutes, and then sonicated for 5 minutes. Then 5 ml was filtered through 0.45 μm filter and appropriate dilutions were made and the absorbance of which was measured at 290 nm by UV-1601 (Shimadzu, Japan) spectrophotometer. The allowable limits of weight of active ingredient were taken ±15% (85-115%).

v. In- Vitro Drug Release Study

The release rate of propranolol hydrochloride matrix tablet was determined using USP 34 (2011) dissolution testing apparatus II (paddle), (Hanson, USA).

The pH of the dissolution medium was monitored throughout the course of each dissolution study. In all courses, pH remained constant at the desired value of (pH 1.2, pH 6.8, and D.W (pH = 7.2 – 7.4.).

vi. Determination of Swelling Behavior of Tablets

Swelling and erosion studies were performed using the method described by Reynold et al.[22]. Weights of tablets (w1) were taken on previously weighed watch glass and placed in a flat bottom dissolution vessel, containing different pHs (1.2, 6.8 & DW) at 37°C. At one hour time intervals (1- 7 hours), the tablets were withdrawn and excess amount of water was removed from the tablet by using blotting paper; and weighed (w3) on a single pan balance. The wet tablets were dried in an oven at 40 °C for 24 hours then placed in desiccators and finally weighed as dry weight (w2). The experiment was repeated three times for each individual time interval. The swelling and erosion studies were carried out with a stirring speed of 100 rpm (paddle type II). The calculated results were given as % swelling.
Percent Swelling = \left( \frac{(w3 - w1)}{w1} \right) \times 100 \quad (1)

Percent Erosion = \left( \frac{(w1 - w2)}{w1} \right) \times 100 \quad (2)

Where \( w1 \) = original weight of tablet, \( w2 \) = weight of dried tablets, \( w3 \) = weight of tablet after removing excess water.

### 2.2.5. Statistical Analysis

The results of the experiments are given as a mean samples ± standard deviation (SD) and were analyzed one sample T-test and variance using SPSS 18.

### 3. Results and Discussion

#### 3.1. Analysis of Propranolol Hydrochloride

The absorbance of propranolol hydrochloride showed linearity with the prepared concentrations (4-140 mcg/ml) obeying Beer's law with correlation of 0.99989 in 0.1N HCl as shown in Fig. 1. The same linearity was obtained in pH 6.8 and distilled water with correlation of 0.9994 and 0.9995 respectively.

#### 3.2. Compatibility Study

The differential scanning calorimetry patterns of eudragit RSPO shows fused melting point peak at 60°C (Fig. 2). The optimized formulations (F15) also shows same endothermic peak similar to that of pure drug (Fig. 2. C). However, the polyethylene glycol shows broad endothermic fusion peak at 70 °C (Fig. 2. D). The differential scanning calorimetry curve of pure propranolol hydrochloride exhibits a single sharp endothermic peak at 160 °C corresponding to the melting point of drug (Fig. 2. E) and the polyvinyl acetate shows broad endothermic fusion peak at 46°C (Fig. 2. F), whereas these observations of differential scanning calorimetry study indicate absence of significant interaction between drug and polymer in tablet formulations. Also, from the differential scanning calorimetry, the area of the melting endotherm is significantly reduced in the physical mixture (Fig.2. B) but is still detected; however, it is greatly diminished in the optimized formula. This could suggest the presence of the drug in a molecular dispersion in the optimized formula where the drug was co-melted with the excipients.

Drug polymer interaction was also checked by comparing the IR spectra of the physical mixture of drug with the excipients used with the IR spectrum of pure drug. As shown in Fig. 3 (A), propranolol hydrochloride gives the peaks in IR spectrum at 2965 cm\(^{-1}\) due to the presence of amine group, 3283 cm\(^{-1}\) due to the hydroxyl group, 1267.27 cm\(^{-1}\) due to stretching of the aryl alkyl ether, 798 cm\(^{-1}\) due to a-substituted naphthalene. Figure 3 (E) revealed the presence of peaks at 2964.69 cm\(^{-1}\), 3482.95 cm\(^{-1}\), 1650 cm\(^{-1}\), 1100 cm\(^{-1}\). Frequencies of functional groups of pure drug remained intact in physical mixture containing different polymers; hence, there was no major interaction between the drug and excipients used in the study.

#### 3.3. Evaluation of Granules

The granules for matrix tablets were prepared by hot-melt granulation technique and subjected to various pre-compression parameters according to USP 34 regulations and were listed in table 2.

The granules were evaluated for angle of repose, compressibility index and drug content. The results of angle of repose shown in table 2 were between 25 and 30 (< 30) which indicate good flow properties of the granules (USP 34 2011). This was further supported by lower compressibility index values (Carr’s index). Generally compressibility index values up to 15% result in good to excellent flow properties.
(Aulton, 2002; Martindale, 1993), and Hausn'e's ratio range from 1.12 to 1.18, shown in table 2 which indicate good flow properties i.e. in the range given in official standard USP 34. Granules density, porosity and hardness were often interrelated properties.

### 3.4. Evaluation of Tablets

All batches showed uniform thickness (5.40 mm-5.45 mm). In a weight variation test the pharmacopoeia limit for the percentage deviation for tablets weighting more than 324 mg is ± 5% (USP 29).

The average percentage deviation of each tablets’ batch was found to be within the above limit and hence all formulations passed the test of uniformity weight as per official requirements. Good uniformity of drug content was found among different batches of the tablets and the percentage of drug content was within the allowable limit. The hardness of each tablets batch was found to be within the sustained release tablets range of 10.0 - 12.4 kg / cm².

Another measure of tablet strength is friability; Conventional compressed tablets that lose less than 1% of their weight are generally considered acceptable (USP 34). In the present study, the percentage friability of all the batches was below 1%, indicating that the friability is within the USP limit. Also the hardness and thickness were within the acceptable limits. Results are presented in table 3.

#### Table 2. Physical properties of the prepared granules.

<table>
<thead>
<tr>
<th>Formula code</th>
<th>Angle of repose (θ)</th>
<th>Bulk density (g/ml)</th>
<th>Tapped density (g/ml)</th>
<th>Compressibility index %</th>
<th>Hausner Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>25.86</td>
<td>0.4</td>
<td>0.48</td>
<td>16</td>
<td>1.19</td>
</tr>
<tr>
<td>F2</td>
<td>27.55</td>
<td>0.38</td>
<td>0.45</td>
<td>15.6</td>
<td>1.18</td>
</tr>
<tr>
<td>F3</td>
<td>28.97</td>
<td>0.41</td>
<td>0.4</td>
<td>18</td>
<td>1.21</td>
</tr>
<tr>
<td>F4</td>
<td>25.53</td>
<td>0.42</td>
<td>0.47</td>
<td>10.6</td>
<td>1.12</td>
</tr>
<tr>
<td>F5</td>
<td>25.11</td>
<td>0.39</td>
<td>0.45</td>
<td>13.3</td>
<td>1.15</td>
</tr>
<tr>
<td>F6</td>
<td>26.56</td>
<td>0.38</td>
<td>0.44</td>
<td>14.8</td>
<td>1.17</td>
</tr>
<tr>
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<td>0.47</td>
<td>14.9</td>
<td>1.18</td>
</tr>
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<td>F12</td>
<td>26.23</td>
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</tr>
<tr>
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<td>F15</td>
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<td>0.47</td>
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</table>

#### Table 3. Physical characteristics of the prepared tablets.

<table>
<thead>
<tr>
<th>Formula code</th>
<th>Weight Variation (mg)</th>
<th>Drug content (mg)</th>
<th>Friability %</th>
<th>Hardness (kg/cm²)</th>
<th>Thickness (mm)</th>
<th>Diameter (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>599.5 ± 2.08</td>
<td>79.59 ± 0.12</td>
<td>0.24</td>
<td>12.4 ± 0.5</td>
<td>5.44 ± 0.1</td>
<td>15.09 ± 0.01</td>
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<tr>
<td>F2</td>
<td>601 ± 0.57</td>
<td>79.68 ± 0.11</td>
<td>0.22</td>
<td>12.11 ± 1.2</td>
<td>5.42 ± 0.11</td>
<td>15.94 ± 0.1</td>
</tr>
<tr>
<td>F3</td>
<td>603.8 ± 3.4</td>
<td>78.51 ± 0.21</td>
<td>0.26</td>
<td>11.6 ± 0.2</td>
<td>5.44 ± 0.05</td>
<td>15.93 ± 0.01</td>
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<td>79.11 ± 0.09</td>
<td>0.19</td>
<td>10.38 ± 1.2</td>
<td>5.42 ± 0.01</td>
<td>15.91 ± 0.2</td>
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<td>11.1 ± 0.6</td>
<td>5.43 ± 0.11</td>
<td>15.95 ± 0.2</td>
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<td>11.1 ± 2.2</td>
<td>5.44 ± 0.15</td>
<td>15.94 ± 0.05</td>
</tr>
</tbody>
</table>

### 3.5. In-Vitro Drug Release Study

#### 3.5.1. Reproducibility of Results

The spectrophotometrically determined concentration of propranolol HCl in each sample obtained during the drug release studies was, corrected in order to account for the dilution effect caused by replacing 5 ml sample with another 5 ml of fresh dissolution medium using the equation described by Wurster and Taylor[23]:

\[
C_n = C_n(\text{measured}) + \frac{V_s}{V_{tot}} \sum_{n=1}^{t} (C_n \text{ measured})
\]

Where \( C_n \) is the concentration of the nth sampling
expected in the dissolution medium if the previous sample
had not been removed.

\[ C_n \text{(measured)} = \sum_{s=1}^{n-1} (C_n \text{measured}) \]

The amount of propranolol hydrochloride, in milligrams,
released into 900 ml of dissolution medium was calculated
from each of the corrected concentration. The percentage
of dissolved drug was calculated by using the following
formula:

\[ \text{Percent dissolved} = \frac{X \text{ mg}}{900} \times \frac{\text{Assay amount (mg)}}{100}. \quad (4) \]

At least 3 replicates of each release experiment were
carried out and the mean amount of propranolol
hydrochloride released at each time point was used to plot
release rate plots.

Reproducibility of results obtained in this way was assayed
by calculating (a) the coefficient of variation of single results
about their mean value since this allows comparison with the
values obtained by previous works in similar studies and (b)
the limits of error (or confidence limits) of the sample mean
at a probability level of \( P = 0.01 \), since there limits provide a
convenient means of graphically representing the range of
values within which the true mean lies with a probability of
99%, Fig. 4 and 5.

![Fig. 4. Reproducibility of propranolol hydrochloride release data of drug from matrix tablet (F15, dissolution medium 0.1N HCl).](image)

![Fig. 5. Reproducibility of propranolol hydrochloride release data from matrix tablets. (F16, dissolution medium 0.1N HCl).](image)

Although, a time points throughout the release profiles are
somewhat showing variable, the reproducibility of the result
obtained using bases of formulas 15 and 16 are generally
considered to be satisfactory in the light of previously
published data on polymeric matrix tablets (Patel et al. 2006;
Habib et al. 2000).

### 3.5.2. Effect of Polyvinyl Acetate Concentration on Propranolol Hydrochloride Release from Matrix Tablets Containing 50% Eudragit RSPO

Formulas F12-F16; which contained serial increasing
concentration of polyvinyl acetate in a base containing 50%
eudragit RSPO and polyethylene glycol 4000, were used to
investigate the effect of concentration of polyvinyl acetate on
the release of propranolol hydrochloride. Polyvinyl acetate;
being an insoluble rubbery polymer had been used with water
soluble polyethylene glycol 4000 to retard the release of
active pharmaceutical ingredients from matrices. Results
plotted in Fig. 6 and table 4 show that increasing percentage
of polyvinyl acetate resulted in retardation of propranolol
hydrochloride release on 12 hr. taking \( T_{50\%} \) as a point of
comparison, showed a significant reduction in the released
amount of propranolol hydrochloride. The selection of the
proper concentration of polyvinyl acetate should be in
consistence with other investigated factors, most importantly;
the eudragit concentration.

![Fig. 6. Percent release of propranolol hydrochloride from matrix tablets (formulas 12, 13, 14, 15 and 16 in 0.1 N HCl).](image)

<table>
<thead>
<tr>
<th>Polyvinyl acetate concentration (%)</th>
<th>Eudragit RSPO % concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>30</td>
<td>50</td>
</tr>
<tr>
<td>6</td>
<td>44.13 39.47 38.87 36.78</td>
</tr>
<tr>
<td>8</td>
<td>42.62 39.12 36.32 34.76</td>
</tr>
<tr>
<td>10</td>
<td>41.6  38.97 37.64 33.82</td>
</tr>
</tbody>
</table>
3.5.3. Effect of Eudragit RSPO Concentration on Release Rate of Propranolol Hydrochloride from Matrix Tablet Formulations Containing 8% w/w Polyvinyl Acetate

Eudragit RSPO is a pH-independent polymer that is used as a matrix which depends on erosion as a main mechanism of retardation. Formulas F4, F7, F10 and F15; which contain increasing amount of eudragit RSPO of 10%, 20%, 30% and 50% respectively with a constant amount of polyvinyl acetate (8%), were used to investigate the effect of eudragit concentration on Propranolol hydrochloride release. In addition, another formula was prepared without eudragit in which the weight of the tablet was completed by polyethylene glycol 4000. Results in Fig. 7 and table (4) show an increase in retardation effect of eudragit with the increase of its concentration over 10 hours. The low concentration of eudragit corresponds to an increase in the concentration of polyethylene glycol 4000 to complete the weight, and since polyethylene glycol 4000 is water soluble, this will result in more water penetration into the matrix and solubilize the water soluble propranolol hydrochloride resulting in higher release rate. Concentrations higher than 50% might result in severe retardation of drug and failure of the design. Taking T_{50%} as a measurement point, percentage of propranolol hydrochloride release is given in table 4.

![Fig. 7. Effect of eudragit RSPO concentration on propranolol release from matrix tablet. (dissolution medium 0.1 N HCl).](image)

![Fig. 8. Effect of pH of dissolution media on propranolol hydrochloride release from matrix tablets (F15).](image)

All other formulas were studied for drug release following the same protocol (results are not presented). And based on overall results, formulas 15 and 16 were chosen to investigate the erosion behavior and kinetic of drug release.

3.5.4. Effect of pH of Dissolution Medium on Release Rate of Propranolol Hydrochloride from Matrix Tablet Formulations Containing 8% w/w Polyvinyl Acetate with 50% Eudragit RSPO (F15)

The curve in Fig. 8 was plotted from an average values of at least 3 experiments. This curve shows slow release rate with almost (65–70%) of propranolol hydrochloride released in approximately 10 hours at 50% w/w eudragit RSPO concentration level.

The release rate at 50% w/w eudragit RSPO was virtually pH-independent, as confirmed by the almost superimposable release curves in pH 1.2, 6.8 & DW as shown in Fig. 7. This was also proven with every eudragit RSPO level 10, 20, 30. Therefore, it can be said that the release rate of propranolol hydrochloride is pH dependent and this independence becomes more pronounced with increasing pH of the medium.

3.5.5. Swelling and Erosion Behavior of Polyethylene Glycol/Polyvinyl Acetate Matrix Tablet

The matrix system used in this study is mainly composed of polymers of polyethylene glycol, Polyvinyl acetate and Eudragit RSPO. Investigation of matrix hydration and erosion is a valuable exercise in order to better understand the mechanisms of drug release and the relative importance of participating parameters. Consequently, it will be swelling and erosion study on matrices constituted polymers that determine the influence behavior of these polymers on drug release. The swelling behavior is the indication of the rate at which the tablet absorbed water from dissolution media and swelled. This behavior is shown in Fig. 9. The matrix tablet; when exposed to an aqueous medium, did not disintegrate, but immediately after hydration it developed a highly viscous gelatinous surface barrier.

Photographs of F15 matrix tablets taken at various time intervals during dissolution course are shown in Fig.9. These photographs (taken at time intervals of 1, 2, 3, 4, 5 and 24 hrs) show that the size of matrix tablets decreased with time, indicating that the system may be undergoing erosion or dissolution. Photograph number (7) in Figure (9) shows that; after drying, the matrix tablet maintains its shape for longer than 12 hours.

![Fig. 9. Swelling behavior of F15 at different time intervals 1, 2, 3, 4, 5 and 24 hrs.](image)
Swelling and erosion study were carried out on F15 in different pH mediums. The results of these tests are provided as percentage swelling as in Fig. 10 and percentage erosion as in Fig. 11 of initial tablet mass.

These results show that both the erosion and swelling behaviors of the matrix tablet follows zero-order pattern (correlation coefficient = 0.994 for pH 1.2, 0.987 for pH 6.8 and 0.993 for D.W) for linearity between percent weight change and time over a period of 8 hours at three different pH values.

**Fig. 10.** Swelling percentage of F15 matrix tablets at different pHs.

**Fig. 11.** Percent erosion of F15 matrix tablet at different pHs.

### 3.5.6. Kinetic of Drug Release

Results of drug release studies of F15 and F16 were fitted on different models of drug release in vitro. Zero-order, first order, Higuchi model and Peppas model were all tested to investigate the mechanism of drug release from the prepared matrix tablets.

**Table 5.** Fitting of data of drug release from F15 and F16 on different drug release models.

<table>
<thead>
<tr>
<th>Batches</th>
<th>Zero Order</th>
<th>First Order</th>
<th>Higuchi’s Equation</th>
<th>Peppas Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>F15</td>
<td>r 0.9836</td>
<td>a 19.555</td>
<td>0.9934</td>
<td>0.9897</td>
</tr>
<tr>
<td></td>
<td>b 6.1098</td>
<td>1.9143</td>
<td>5.2181</td>
<td>1.6442</td>
</tr>
<tr>
<td>F16</td>
<td>r 0.9833</td>
<td>a 18.875</td>
<td>0.9856</td>
<td>0.9857</td>
</tr>
<tr>
<td></td>
<td>b 6.9474</td>
<td>0.0563</td>
<td>24.041</td>
<td>0.5458</td>
</tr>
</tbody>
</table>

\( r = \text{Correction coefficient} \quad b = \text{Intercept} \quad a = \text{Slope} \)

Good fit of the dissolution data of both matrices is discernible; as \( R^2 \) was higher than 0.96. The mean values of Korsmeyer-Peppas release exponent (n) determined for the drug release from the matrices F15 & F16 ranged from 0.4653 to 0.5458, indicating that the release mechanism was an anomalous non-Fickian transport (0.45 < n < 0.89) (table 5). Based on the \( n \) values, it was observed that the drug release from the matrix occurred by a combination of two mechanisms, diffusion of drug from the tablet matrix and erosion of tablets surfaces as indicated from the photographs in Fig. 9.

### 4. Conclusion

A controlled release matrix tablet for propranolol hydrochloride was successfully formulated using eudragit RSPO 50% by weight and polyvinyl acetate 8% and 10% by weight in polyethylene glycol 4000 using hot-melt granulation and direct compression. Drug release was achieved over a period of 12 hours by pH-independent swelling and erosion of the matrix and diffusion of the drug. The mechanism of drug release was concluded to be by anomalous non-Fickian transport as zero order model.

### References


