DESIGN AND OPTIMIZATION OF RANITIDINE HYDROCHLORIDE FLOATING MICROSPHERES

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ABSTRACT

Objective: The aim of this study was to develop a gastroretentive microspheres system of an anti-ulcer drug Ranitidine hydrochloride (RH), floating on simulated gastric fluid for more than 12 hours was formulated by solvent evaporation technique. Eudragit E-100 (EE100) and Ethyl cellulose (EC), biocompatible polymers were used to form microspheres of RH by response surface methodology.

Methodology: The formulated microspheres were characterized for their micromeric properties, optical microscopy, in-vitro buoyancy studies, percentage drug entrapment efficiency (EE %) and in-vitro drug release studies. Optimization studies were carried out by taking RPM (stirring speed), polymer ratio and type of polymer as independent variables and percentage drug entrapment and in vitro release after 2.6 and 12 hours as responses using 3-level factorial design.

Results and Discussion: The formulated microspheres were free floating and optical microscopy studies indicated that the microspheres were almost spherical in shape. The prepared microsphere formulations having EE% of 47.5%-79.3% %, and buoyancy of 72-92% with floating time up to 12 hours. In-vitro drug release studies of RH microspheres showed a controlled release of 12 hours.

Conclusion: The data obtained in this study thus suggest that floating microspheres of an anti-ulcer drug can be successfully designed to give controlled drug delivery and improved oral bioavailability.

Keywords: Gastroretentive, Microspheres, Optimization, Ranitidine hydrochloride.

INTRODUCTION

Drug absorption from oral controlled release (CR) dosage forms is often limited by the short gastrointestinal retention time, available for absorption. Floating drug delivery systems are among the several approaches that have been developed in order to increase the gastric residence time of the dosage forms[1]. The synthetic polymer has been used to prepare floating microspheres. The present study was based on floating microspheres of both hydrophilic and acrylic polymers using (RH) as a model drug. It is an anti-ulcer drug that has been widely used in treating gastric and duodenal ulceration and also in Zollinger Ellison syndrome. It is poorly absorbed from the lower GIT and has a short elimination half-life of 2-3 hours and bioavailability of 50% [2].

MATERIALS AND METHODS

Materials

RH, kindly donated by Medical Union Pharmaceuticals, Abu-Sultan, Ismailia, Egypt), EC (BIO BASIC INC, Mississauga, Ontario-3R1G6, Canada); E100 (Rohm Pharma GMBH 50277 1-243 Germany), N-Hexane, Acetone, Heavy liquid Paraffin, Hydrochloric acid (pure lab. Chemicals, USA, El-Nasr chemical company, Cairo, Egypt); Sorbitan Monooleate (Span 80), Guangdonglanghua Chemical Co., India. All other chemicals were analytical reagent grades.

Methods

Preparation of Microspheres

RH microspheres were prepared by the emulsion-solvent evaporation technique. The external phase was prepared by addition of 1% Span 80 in heavy liquid paraffin. The polymers used (EC or E100) were dissolved in acetone until clear solution was obtained. The required amount of the drug was then added to obtain the internal phase. The external phase was mixed with the internal phase to carry out the emulsification process. Acetone was allowed to evaporate by continuous stirring at different speeds and then a room temperature using magnetic stirrer. Stirring was continued at room temperature until complete evaporation of the solvent (about 5 hours). Liquid paraffin was decanted and the microspheres produced were filtered off, washed three times with n-hexane (3x 50 ml) to remove the remaining oily phase and then dried over night at room temperature (25°C).

Table 1: Suggested formulae of RH microspheres

<table>
<thead>
<tr>
<th>Formula No.</th>
<th>RH (mg)</th>
<th>EC (mg)</th>
<th>E100 (mg)</th>
<th>Span 80 (mg)</th>
<th>D/P R</th>
<th>Speed (rpm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>500</td>
<td>1250</td>
<td>---</td>
<td>1%</td>
<td>1.25</td>
<td>300</td>
</tr>
<tr>
<td>F2</td>
<td>500</td>
<td>625</td>
<td>625</td>
<td>1%</td>
<td>1.25</td>
<td>400</td>
</tr>
<tr>
<td>F3</td>
<td>500</td>
<td>625</td>
<td>625</td>
<td>1%</td>
<td>1.25</td>
<td>400</td>
</tr>
<tr>
<td>F4</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>1%</td>
<td>1.1</td>
<td>400</td>
</tr>
<tr>
<td>F5</td>
<td>500</td>
<td>---</td>
<td>1250</td>
<td>1%</td>
<td>1.25</td>
<td>500</td>
</tr>
<tr>
<td>F6</td>
<td>500</td>
<td>1000</td>
<td>1000</td>
<td>1%</td>
<td>1.4</td>
<td>500</td>
</tr>
<tr>
<td>F7</td>
<td>500</td>
<td>250</td>
<td>250</td>
<td>1%</td>
<td>1.1</td>
<td>300</td>
</tr>
<tr>
<td>F8</td>
<td>500</td>
<td>---</td>
<td>2000</td>
<td>1%</td>
<td>1.4</td>
<td>400</td>
</tr>
<tr>
<td>F9</td>
<td>500</td>
<td>---</td>
<td>1250</td>
<td>1%</td>
<td>1.25</td>
<td>300</td>
</tr>
<tr>
<td>F10</td>
<td>500</td>
<td>---</td>
<td>250</td>
<td>1%</td>
<td>1.1</td>
<td>300</td>
</tr>
<tr>
<td>F11</td>
<td>500</td>
<td>1000</td>
<td>1000</td>
<td>1%</td>
<td>1.4</td>
<td>300</td>
</tr>
<tr>
<td>F12</td>
<td>500</td>
<td>2000</td>
<td>---</td>
<td>1%</td>
<td>1.4</td>
<td>400</td>
</tr>
<tr>
<td>F13</td>
<td>500</td>
<td>625</td>
<td>625</td>
<td>1%</td>
<td>1.25</td>
<td>400</td>
</tr>
<tr>
<td>F14</td>
<td>500</td>
<td>1250</td>
<td>---</td>
<td>1%</td>
<td>1.25</td>
<td>500</td>
</tr>
<tr>
<td>F15</td>
<td>500</td>
<td>625</td>
<td>625</td>
<td>1%</td>
<td>1.25</td>
<td>400</td>
</tr>
</tbody>
</table>
Optimization of microspheres formulation using factorial design (Box-Behnken design)

Optimization was carried out by the 3 level factorial design to produce the desirable effective percent drug entrapment and a sustained drug release pattern over 12 hours. The optimization of the floating microspheres was carried out by taking into consideration the type of polymer used, the amount of polymer and the stirring rate (RPM) as formulation variables and the percentage drug entrapment and the in vitro drug release at different times (2hr-6hr-12hr) as responses. The relationship between the process variables and the responses were evaluated by the 3 level full factorial design and response surface methodology [3,4].

The suggested formulae of RH microspheres were tabulated in tables (1,2).

Determination of the entrapment efficiency in the prepared microspheres:

The EE% of RH microspheres was determined in 0.1 N HCl by the following Method [5]

A weighed quantity of microspheres equivalent to 100mg of the pure drug was taken in 100ml volumetric flask and dissolved in 0.1 N HCl using sonication for 5min and the volume was made up to 100ml with 0.1 N HCl. The solution was then filtered through (0.45 µm membrane filter). The absorbance was measured spectrophotometrically at 312.6 nm after suitable dilutions. The absorbance was then measured at 312.6 nm after suitable dilutions and 0.1 N HCl using sonication for 5min and the volume was made up to 100ml with 0.1 N HCl. All analyses were carried out in triplicates.

Micromeritic properties of the prepared RH microspheres

The prepared microspheres were evaluated through determination of the following parameters:

a- Densities of microspheres

Both loose bulk density (Db) and tapped bulk density (Dt) were determined. A quantity of 10g microspheres from each batch was introduced into a 10 ml measuring cylinder. The initial volume was observed, and then the cylinder was allowed to stroke. The tapping was continued until no further change in volume was noted. LBD and TBD were calculated using the following formula [6]

\[ D_b = \frac{W_t}{\text{bulk volume}} = \frac{W_t}{V_b} \]

\[ D_t = \frac{W_t}{\text{tapped volume}} = \frac{W_t}{V_t} \]

b- Hausner Ratio

It is the ratio between bulk density and tapped density. It gives an idea about the flow characters of powder particles. [7]

Hausner ratio = \( D_t / D_b \)

c- Compressibility percent (Car’s Index)

Compressibility is indirectly related to the relative flow rate, cohesiveness, and particle size of a powder. The compressibility percent of a material can be estimated as: [8]

\[ \text{Compressibility \%} = \left( D_t - D_b / D_t \right) \times 100 \]

d- Angle of Repose

It was measured by passing the microspheres through a funnel which was maintained at a fixed height in all experiments. The height (h) and radius (r) of the cone were determined. The angle of repose is calculated from the equation: [9]

\[ \tan \theta = \frac{h}{r} \]

In-vitro buoyancy of RH microspheres

The floating microspheres (100 mg) were spread over the surface of the dissolution medium (simulated gastric fluid, SGF, pH (1.2) that was agitated by a paddle rotated at 100 rpm. After agitation for a predetermined time interval, the microspheres that floated over the surface of the medium and those settled at the bottom of the flask were recovered separately. After drying, each fraction of the microspheres was weighed and their buoyancy was calculated by the following equation: [10]

Buoyancy \%(\%) = \frac{Q_f}{(Q_f + Q_s)}

Where Qf and Qs are the weight of the floating and the settled microspheres respectively

In-vitro Release Study

The in-vitro release of RH from the prepared microspheres in hard gelatin capsules filled with known amount of microspheres (equivalent to 100 mg of RH) was carried out at 37 ± 0.5 °C for 12 hours, using apparatus II [11]. The baskets were rotated at 100 rpm. The dissolution medium was 900 ml 0.1 N HCl pH 1.2. Samples of 5 ml were withdrawn and replaced with fresh medium at appropriate time intervals. The drug content in the filtered samples was measured spectrophotometrically at 312.6 nm after suitable dilutions. The release experiments were repeated in triplicates.

RESULTS AND DISCUSSION

Entrapment efficiency (EE%) of RH microspheres

The range of the EE% of the prepared microspheres was found to be between 47.5% for formula F3 and 93.9% for formula F13 as shown in table (5).

Figures (1-2) showed the effect of the different independent variables on EE% of RH microspheres. As the polymer ratio increased (X1), the EE% (Y1) decreased (1,0,1, 1,2and 1,3). Increasing the speed of rotation (X2), EE% was decreased. Polymer type (X3) affected the EE% of RH microspheres as EE% increase in case of RH/EC microspheres as compared with RH/E100 microspheres.
From the figures, there is a direct proportionality between $X_2$ and $(Y_1)$. While, there is an inverse proportionality between $X_1$ and $(Y_1)$.

**Micromeritic properties of RH microspheres**

The prepared RH microspheres were studied for their micromeritic properties, which include the angle of repose, bulk and tapped densities, Hausner ratio, and compressibility index.

**a- Angle of repose ($\Theta$)**

The values of angle of repose of prepared RH formulae ranged from $19.8^\circ$ to $29.14^\circ$ which may give indication that microspheres had good flowability. Concerning the data obtained for the angle of repose for the prepared RH microspheres, See table (3). It was found that F9 showed the best value ($19.8^\circ$) with excellent flowability while formula F11 showed the worst value ($29.14^\circ$) with good flowability.

**b- The bulk and tap densities**

The flow properties of the microspheres were investigated by measuring the bulk density, tapped density and Carr’s index[14,15]. Both the bulk and tap densities were determined with equations described above.

**c- The Hausner ratio**

The value of the Hausner ratio was found to give indication about the flow properties of microspheres. The values less than 1.25 indicate better flowability than values greater than 1.25 [16]. According to the data obtained for Hausner ratio for the prepared RH microspheres, it was found that F13 showed the best value (1.11) which indicated good flowability while formula F11 showed the worst value (1.22) which indicated poor flowability.

**d- Compressibility % (Carr’s index)**

The maximum compressibility percent for the tested RH formulae was 18.5% for formula F11 which indicated fair passable flowability and the minimum one was 10% for formula F13 which indicated excellent flowability.

### Table 3: Micromeritics parameters, EE% and Percentage of buoyant RH microspheres

<table>
<thead>
<tr>
<th>F. No.</th>
<th>Angle of repose (AR) (°)</th>
<th>Bulk density (gm/cm$^3$)</th>
<th>Tapped density (gm/cm$^3$)</th>
<th>Hausner ratio (HR)</th>
<th>Carrs index (CI)</th>
<th>EE%</th>
<th>% of buoyant microspheres</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>23.14</td>
<td>0.525±0.002</td>
<td>0.610±0.002</td>
<td>1.161</td>
<td></td>
<td>62±1.0</td>
<td>79+2.2</td>
</tr>
<tr>
<td>F2</td>
<td>24.05</td>
<td>0.489±0.002</td>
<td>0.579±0.001</td>
<td>1.184</td>
<td></td>
<td>59±1.5</td>
<td>83+2.5</td>
</tr>
<tr>
<td>F3</td>
<td>24.05</td>
<td>0.489±0.002</td>
<td>0.579±0.001</td>
<td>1.184</td>
<td></td>
<td>59±1.4</td>
<td>83+3.3</td>
</tr>
<tr>
<td>F4</td>
<td>28</td>
<td>0.450±0.001</td>
<td>0.535±0.001</td>
<td>1.190</td>
<td></td>
<td>53±1.3</td>
<td>90+4.4</td>
</tr>
<tr>
<td>F5</td>
<td>22</td>
<td>0.325±0.003</td>
<td>0.395±0.002</td>
<td>1.217</td>
<td></td>
<td>47±1.4</td>
<td>92±4.4</td>
</tr>
<tr>
<td>F6</td>
<td>20.85</td>
<td>0.462±0.004</td>
<td>0.555±0.002</td>
<td>1.2</td>
<td></td>
<td>55±1.1</td>
<td>86+3.9</td>
</tr>
<tr>
<td>F7</td>
<td>23.7</td>
<td>0.557±0.003</td>
<td>0.644±0.001</td>
<td>1.155</td>
<td></td>
<td>66±1.23</td>
<td>78+2.1</td>
</tr>
<tr>
<td>F8</td>
<td>27.47</td>
<td>0.398±0.003</td>
<td>0.472±0.002</td>
<td>1.185</td>
<td></td>
<td>50±1.6</td>
<td>88+2.3</td>
</tr>
<tr>
<td>F9</td>
<td>19.8</td>
<td>0.531±0.004</td>
<td>0.616±0.001</td>
<td>1.16</td>
<td></td>
<td>63±1.5</td>
<td>75+2.2</td>
</tr>
<tr>
<td>F10</td>
<td>20.3</td>
<td>0.494±0.003</td>
<td>0.564±0.001</td>
<td>1.16</td>
<td></td>
<td>56±1.4</td>
<td>80+3.1</td>
</tr>
<tr>
<td>F11</td>
<td>29.14</td>
<td>0.363±0.001</td>
<td>0.446±0.003</td>
<td>1.22</td>
<td></td>
<td>49±0.46</td>
<td>91±2.7</td>
</tr>
<tr>
<td>F12</td>
<td>21.04</td>
<td>0.599±0.006</td>
<td>0.674±0.002</td>
<td>1.125</td>
<td></td>
<td>74±3.07</td>
<td>72+1.9</td>
</tr>
<tr>
<td>F13</td>
<td>20.3</td>
<td>0.627±0.005</td>
<td>0.696±0.001</td>
<td>1.11</td>
<td></td>
<td>79±3.13</td>
<td>73+2.8</td>
</tr>
<tr>
<td>F14</td>
<td>24.05</td>
<td>0.489±0.004</td>
<td>0.579±0.002</td>
<td>1.184</td>
<td></td>
<td>59±1.09</td>
<td>83+1.7</td>
</tr>
<tr>
<td>F15</td>
<td>24.9</td>
<td>0.505±0.005</td>
<td>0.594±0.002</td>
<td>1.176</td>
<td></td>
<td>61±0.3</td>
<td>84+3.4</td>
</tr>
</tbody>
</table>
In-vitro buoyancy of RH microspheres

Microspheres still continued to float without any apparent gelation, thus indicating that microspheres can exhibit excellent buoyancies. The relative density of the microspheres is higher at higher polymer concentrations. So, the microspheres having higher polymer concentrations were less buoyant than those with lower polymer concentrations[1, 2]. The formula F5 showed highest buoyancy of 92±4.4% while the formula F12 showed the lowest buoyancy of 72±1.9% as showed in table (3).

In-vitro release of RH microspheres

In vitro drug release showed a biphasic release pattern for all formulae with an initial burst effect as showed in figures (9-11). The cumulative percentage of drug release after 12 hr ranged from 53.1% to 99.9% for the formulae F13, F5 respectively. Figures (3-8) showed the main effect plot and interaction effects of X1, X2, and X3 on Y2, Y3, and Y4 (release of RH after 2, 6, and 12 hr). Increasing speed of rotation (X1); in-vitro release of RH was increased. It was also observed that as polymer ratio (X2) increased, the drug release was decreased as the increased density of the polymer matrix at higher polymer concentration resulted in an increased diffusional path length. Furthermore, smaller microspheres were formed at lower polymer ratio and had a larger surface area exposed to dissolution medium, resulted in faster drug release[17, 18, 19]. The polymer type (X3) either EC or E 100 or combination of both polymers was affected the release of RH as the release of drug from RH/E100 microspheres was higher than RH/EC microspheres.
Fig. 6: Main effect plot for in vitro 6hr

Fig. 7: Standardized pareto chart for in vitro 12hr

Fig. 8: Main effect plot for in vitro 12hr

Fig. 9: In-vitro release of drug from RH-EC microspheres
These variables were optimized with a fifteenth run Box-Behnken design as shown in table (1), when using E E100 as a polymer of ratio 1.8 and rotation of speed 450 rpm, optimum response for the entrapment efficiency (51.5%), for the in-vitro release after two hour (60.3), for the in-vitro release after six hours (83.6%), and for the in-vitro release after twelve hours (95.5%) and the resulted microspheres had spherical shape as shown in figure (20).

CONCLUSION

The present study has been a satisfactory attempt to formulate floating microspheres of an anti-ulcer drug, Ranitidine hydrochloride ethyl cellulose floating microparticles, J. of Microencap.,25(5):305-314 (2008).


