PREPARATION OF EUDRAGIT E100 MICROSPHERES BY MODIFIED SOLVENT EVAPORATION METHOD

VANDANA SINGH 1* and AMRENDRA KUMAR CHAUDHARY2

1 Translam Institute of Pharm Education and Research, Meerut, UP-250001, India
2 School of Pharmaceutical Sciences, Shobhit University, Meerut, UP-250110, India

Abstract: The objective of this investigation was to develop the hollow microspheres as a new dosage form of floating drug delivery system with prolonged stomach retention time. Hollow microspheres containing ranitidine hydrochloride were prepared by solvent evaporation method using Eudragit RLPO dissolved in a mixture of dichloromethane and ethanol. The maximum yield and drug loading amount of hollow microspheres were 88.45% and 80 ± 4.0%, respectively. The in vitro release profiles showed that the drug release rate decreased with increasing viscosity of Eudragit RLPO, while diameter of hollow microspheres increased with the increase of drug polymer weight ratio. Hollow microspheres could prolong drug release time (approximately 24 h) and float over stimulate gastric fluid for more than 12 h. These results demonstrated that ranitidine HCl hollow microspheres were capable of sustained delivery of the drug for longer period with increased bioavailability.

Keywords: floating microspheres, ranitidine hydrochloride, buoyancy, in vitro release

Floating Drug Delivery Systems (FDDS) or Hydrodynamically Balanced Systems (HBS) are among the several approaches that have been developed in order to increase the gastric residence time (GRT) of dosage forms (1–3). Floating microspheres are gastro-retentive drug delivery systems based on non-effervescent approach. The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion, flotation, sedimentation, expansion, modified shape systems, or by the simultaneous administration of pharmacological agents that delay gastric emptying (4). Hollow microspheres are in strict sense, spherical empty particles without core. These microspheres are characteristically free flowing powders consisting of synthetic polymers. Solid biodegradable microspheres incorporating a drug dispersed or dissolved throughout particle matrix have the potential for controlled release of drugs. Floating microspheres have emerged as an efficient means of enhancing the bioavailability and controlled delivery of many drugs. The increasing sophistication of delivery technology will ensure the development of increasing number of gastro-retentive drug delivery systems to optimize the delivery of molecules that exhibit absorption window, low bioavailability, and extensive first pass metabolism (5, 6). Ranitidine was used as 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 gastrointestinal tract and has a short elimination half-life 2–3 h (7, 8). The objective of the present study was to develop floating microspheres of ranitidine in order to achieve an extended retention in the upper GIT, which may result in enhanced absorption and thereby improved bioavailability. The prepared microspheres were evaluated for size, entrapment efficiency, buoyancy and in vitro release. The effect of various formulation variables on the size and drug release was investigated.

MATERIALS AND METHODS

Materials

Ranitidine hydrochloride, obtained as a gift sample from Cipla Research and Development division (Mumbai), was employed as a model drug. The polymer Eudragit RLPO was procured from Colorcon Asia, Goa. Organic solvents dichloromethane and ethanol were purchased from SD Fine Chemicals, Mumbai. Heavy liquid paraffin was used as dispersion medium along with Tween 80 as an emulsifying agent. All the other chemicals used were of analytical grade.

* Corresponding author: e-mail: vandankhushi@gmail.com; mobile: 09450146777
Rationale for selection of ingredients and processes in formulation

Ranitidine hydrochloride, an H₂ receptor antagonist, with short half-life and a low oral bioavailability of 50%, was selected as a model drug to formulate a controlled release formulation with improved oral bioavailability, by prolonging the gastric residence time. Eudragit RLPO is a hydrophobic polymer which prolongs the release of water-soluble and water insoluble drugs from its matrices. The organic solvents chosen, dichloromethane and ethanol (95%), have lower toxicity potential compared to many other solvents and do not have any hazardous effect on the body because they evaporate during the process. Dichloromethane is partly extracted by the liquid paraffin, while the remaining evaporates. Ethanol is a good solvent for the drug. The polymer precipitates as the solvents evaporate during the formulation process to form porous microspheres. The method used is more correctly referred to as ‘oil-in-oil’ dispersion method or ‘dry-in-oil’ method (9) instead of w/o (water in oil) emulsification method, since a polymeric solution in organic solution is considered oil-in-micro encapsulation technology (10). The major problem of the o/w emulsification technique is the low encapsulation efficiency of moderately water soluble drugs (ranitidine hydrochloride is water soluble) due to diffusion of drug from the organic dispersed phase into the aqueous continuous phase, which results in poor entrapment. Therefore, liquid paraffin was used as the dispersion media or external phase along with Tween 80, which is a non-ionic surfactant. Tween 80 acts as a droplet stabilizer and prevents coalescence of the droplets by localizing at the interface between the dispersed phase and dispersion medium.

Formulation of the floating microspheres (11)

Three batches of microspheres were prepared by taking drug : polymer ratio as 1:1, 1:2 and 1:3 with same drug and polymer. The formulation batches were designed as A1, A2, and A3 (1:1, 1:2, 1:3, respectively). Drug and polymer in different proportions were weighed and co-dissolved at room temperature to a mixture of ethanol and dichloromethane (1% v/v) with vigorous agitation to form uniform drug polymer dispersion. This was slowly poured into the dispersion media or external phase along with Tween 80, which is a non-ionic surfactant. Tween 80 acts as a droplet stabilizer and prevents coalescence of the droplets by localizing at the interface between the dispersed phase and dispersion medium.

Percentage yield

The percentage yield value of microspheres was determined from the ratio of amounts of solidified total microsphere to total solid material used in the inner phase, multiplied by 100.

\[ \% \text{ Yield} = \frac{\text{Weight of microspheres}}{\text{Weight of solid starting material}} \times 100 \]

Size analysis (12)

The size was measured using an optical microscope (Olympus NWF 10x, Educational Scientific Stores, India) fitted with an ocular micrometer and stage micrometer. The mean particle size was calculated by measuring 200 to 300 particles with the help of a calibrated ocular micrometer.

Scanning electron microscopy

Scanning electron microscopy (SEM) was performed to characterize the surface of formed microspheres. Microspheres were mounted directly onto the sample stub and coated with gold film under reduced pressure. This film acts as a conducting medium on which a stream of electron was allowed to flow and then photograph was taken with SEM.

Micromeritic properties (13)

Microspheres were characterized for micromeritic properties, such as particle size, true density, tapped density, compressibility index, and flow properties. The bulk density and tapped density were measured and the compressibility index was calculated using the formula:

\[ \text{Compressibility index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100 \]

Determination of entrapment efficiency (14, 15)

To determine the incorporation efficiency, 40 mg of microspheres were taken, thoroughly triturated and suspended in a minimal amount of dichloromethane. The suspension was filtered to separate shell fragments. Drug contents were analyzed spectrophotometrically at 315 nm (7, 8).

\[ \text{Drug entrapment efficiency} = \frac{\text{Experimental drug content}}{\text{Theoretical drug content}} \times 100 \]

Buoyancy percentage (16, 17)

An in vitro buoyancy study was carried out using an USP XXIV dissolution apparatus (type II)
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(DA-6DR USP standards; Veego-Scientific, Mumbai, India) filled with 900 mL 0.1 M acidic solution (HCl) containing 0.02% v/v Tween 80 as a dispersing medium. The medium was agitated with a paddle rotating at a speed of 100 rpm for 12 h. After each time interval, two fractions of the microspheres were observed, one was floating on the surface of the medium and the other was the settled portion. The settled portion of the microspheres was collected and recovered separately at a predetermined time interval, dried in vacuum and weighed. The buoyancy percentage was calculated by the following formula:

\[
\text{% Buoyancy of microspheres} = \frac{\text{Weight of floating microspheres}}{\text{Initial weight of floating microspheres}} \times 100
\]

**In vitro release studies** (16, 17)

The release rate of ranitidine from floating microspheres was determined in a United States Pharmacopeia (USP) XXIV basket type dissolution apparatus. Drug loaded microspheres (weight equivalent to 50 mg of drug) were introduced into the 900 mL of 0.1 M HCl containing Tween 80 (0.5% v/v). The dissolution fluid was maintained at 37 ± 2°C at a rotation speed of 100 rpm. Perfect sink conditions prevailed during the drug release study. Five milliliters samples were withdrawn at regular intervals for 12 h and analyzed spectrophotometrically at 315 nm. The initial volume of dissolution fluid was maintained by adding 5 mL of fresh dissolution fluid after each withdrawal. All experiments were run in triplicate.

**RESULTS AND DISCUSSION**

**Percentage recovery yield**

The percentage practical yields slightly decreased as the polymer ratio increased. The maximum yield was found to be 88.45% in A-1 with heavy liquid paraffin (Tab. 1). Discrete free-flowing microspheres were produced at 700 rpm. The type of mechanical device used for stirring also influenced the size of particles formed. The magnetic stirrer often gave larger particles and at times sticky masses, due to its comparatively lower stirring speed when compared to the propeller agitator, which has a higher stirring speed. Thus, discrete, free-flowing particles were formed with the propeller agitator.

**Size analysis**

Microspheres were prepared using a gradually increasing eudragit concentration in combination with a fixed concentration of drug to assess the effect of polymer concentration on the size of microspheres. The mean particle size of the microspheres significantly increased with increasing eudragit concentration and was in the range 247 ± 13 µm to 286 ± 16 µm (Tab. 2). The viscosity of the medium increases at a higher polymer concentration resulting in enhanced interfacial tension. Shearing efficiency is also diminished at higher viscosities (18, 19). This results in the formation of larger particles.

**Table 1. Characterization of ranitidine floating microspheres.**

<table>
<thead>
<tr>
<th>Batch code</th>
<th>Yield (%)</th>
<th>Angle of repose (θ°)</th>
<th>Compressibility index (Ci)</th>
<th>Hausner’s ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>88.45</td>
<td>24.34 ± 2.5</td>
<td>9.5 ± 1.2</td>
<td>1.1 ± 0.061</td>
</tr>
<tr>
<td>A2</td>
<td>86.00</td>
<td>28.46 ± 2.4</td>
<td>8.2 ± 1.3</td>
<td>1.0 ± 0.045</td>
</tr>
<tr>
<td>A3</td>
<td>82.88</td>
<td>31.49 ± 3.7</td>
<td>10.3 ± 1.9</td>
<td>1.1 ± 0.032</td>
</tr>
</tbody>
</table>

**Table 2. Various formulation parameters for floating microspheres.**

<table>
<thead>
<tr>
<th>Batch code</th>
<th>Mean particle size (µm)</th>
<th>Incorporation efficiency (%)</th>
<th>Buoyancy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>247 ± 13</td>
<td>71.0 ± 2</td>
<td>82 ± 2</td>
</tr>
<tr>
<td>A2</td>
<td>272 ± 11</td>
<td>74.8 ± 4</td>
<td>70 ± 3</td>
</tr>
<tr>
<td>A3</td>
<td>286 ± 16</td>
<td>80.0 ± 4</td>
<td>69 ± 5</td>
</tr>
</tbody>
</table>
Flow properties
The flow properties of all the formulations were found out by measuring the angle of repose and compressibility index, results are shown in Table 1. The values of angle of repose were of the range 24–31°, which are within the normal acceptable range of 20–40°. The porous microspheres thus showed reasonably good flow potential. This is further substantiated by the values of compressibility index (Ci) which was in the range 8.2–10.3, indicating good flow characteristics of the microspheres.

Scanning electron microscopy
Surface topography revealed that the mean particle size of various batches of microspheres were within the range of 247 ± 13 to 286 ± 16 μm (Fig. 1). An increase in polymer ratio is found to have an increase in particle size due to coating of microspheres (Tab. 2). Ranitidine microspheres were found to have rough and hollow surface and are slightly spherical. The hallow nature was responsible for the microspheres floatability.

Estimation of drug incorporation efficiency
The values of total % drug incorporation efficiency are shown in Table 2. High incorporation efficiency was seen with higher concentrations of polymer with the drug.

In vitro buoyancy studies
In vitro buoyancy studies reveal that, in spite of stirring the dissolution medium for more than 12 h, 69–82% of A-3 to A-1 still continued to float without any apparent gelation, thus indicating that microspheres exhibit excellent buoyancies, which can be attributed to the pores and cavities present in them. Figure 2 shows the buoyant microsphere formulations. The relative buoyancies are also shown in Table 2. The relative density of the microspheres is higher at higher polymer concentrations and the porosity is less. So the microspheres having higher polymer concentrations were less buoyant than those with lower polymer concentrations. The formulation A1 showed the highest buoyancy (82 ± 2.0%). The particle size also has an influence on buoyancy, smaller particles exhibited higher buoyancies in comparison to larger microspheres as seen in Table 2. Thus, the sizes of particles also play an important role in buoyancy.

In vitro release studies
In vitro release studies were performed in 0.1 M HCl for 12 h. The release of ranitidine signifi-
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cantly decreased with increasing eudragit concentration (Fig. 3). The cumulative percentage of drug release after 12 h was found to be 98.23%, 90.11% and 75.25% for the formulations A1–A3, respectively. It was found that the drug release was prolonged up to 12 h. Ranitidine hydrochloride is water soluble and the release of the drug was retarded due to the hydrophobic and insoluble nature of the polymer used. It was also observed that as the polymer ratio increased the drug release was decreased. The increased density of the polymer matrix at higher concentrations results in an increased diffusional path length. This may decrease the overall drug release from the polymer matrix. Furthermore, smaller microspheres are formed at a lower polymer concentration and have a larger surface area exposed to dissolution medium, giving rise to faster drug release. Ranitidine release was higher in the case of microspheres prepared at a higher agitation speed but the difference in drug release was not statistically significant. In vitro drug release studies also showed a biphasic release pattern for all formulations with an initial ‘burst effect’, which may be attributed to the drug present on the surface. Formulation A3 showed a better controlled release while A1 showed the maximum cumulative drug release. After the first hour, the drug release in the formulations followed a steady pattern approximating zero order release. An ideal controlled release formulation of ranitidine hydrochloride should release ~28% of the drug in the first hour, whereas the conventional tablets 6.16% per hour up to 12 h. These values were obtained by calculating a theoretical drug release profile for 12 h.

CONCLUSION

In vitro data obtained for floating microspheres of ranitidine hydrochloride showed excellent floatability and prolonged drug release. Microspheres of different size and drug content could be obtained by varying the formulation variables. Thus, the prepared floating microspheres may prove to be potential candidates for delivery devices adaptable to any intra-gastric condition.

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REFERENCES


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