A significant proportion of the populations have difficulty in swallowing solid oral dosage forms (1). This problem becomes more acute for the administration of sustained action dosage forms due to the increase in volume of the delivery system. An oral pharmaceutical suspension presents a novel means of circumventing the potential problems associated with the administration of such systems.

Microencapsulation of a drug has been suggested to control drug release and to reduce or eliminate gastrointestinal tract irritation (2, 3). The incorporation of microspheres as a dispersed phase in a suspension has been proposed earlier since these systems may spread out more uniformly in the gastrointestinal tract, thereby causing a reduction in local irritation when compared to a single-unit dosage form (4–7). The formulation of controlled release suspensions, however, presents a significant challenge to pharmaceutical scientists due to the risk of drug leaching to the suspending medium during storage. Some of the strategies that have been employed to overcome these drawbacks included the use of ion-exchange resins, saturated drug solution as a suspending medium and preparation of dry suspensions for reconstitution before use (8). A reconstitutable suspension can offer several advantages such as maintenance of the chemical stability of the active compounds until reconstitution at the start of treatment. The same suspension can be easily administered to children of different ages by adapting the volume to swallow.

Ibuprofen, is a non-steroidal anti-inflammatory, antipyretic and analgesic drug (9). The short half-life (about 2 h) and the low single administration dose make ibuprofen a very good candidate for the formulation of controlled release multiple-unit dosage forms. At the same time, great attention has been devoted on the possibility to prepare ibuprofen microspheres in order to formulate oral controlled release systems, to protect the gastric mucous membrane from drug irritation or to mask its unpleasant taste (10–13).

Formulation and Evaluation of Reconstitutable Suspensions Containing Ibuprofen-Loaded Eudragit Microspheres

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Abstract: The objective of this work was to develop and evaluate reconstitutable suspensions of ibuprofen-loaded microspheres prepared with an acrylic polymer (Eudragit RS-PM®). The microspheres were prepared by the quasi-emulsion solvent diffusion technique. To prepare reconstitutable suspension formulation, the microspheres used had a mean particle size of 316.6 µm and 99.8% loading efficiency. Xanthan gum was chosen as the suspending agent for the suspension formulations. D-sorbitol was used to impart palatability of suspensions. The amount of D-sorbitol affected sedimentation volume and redispersibility properties of suspensions. The highest improving effect was shown with 20.0% and 25.0% of D-sorbitol concentrations. It was observed that dispersion media of suspensions showed non-Newtonian flow characteristics. To ensure minimum drug leakage from the microspheres into the suspension, the pH was buffered at 3.60 using citrate buffer. The ibuprofen content calculated from the suspended microspheres was consistent with that from microspheres alone. This result indicated that no leakage of drug occurred from the microspheres in the suspension on storage. Moreover, the same release rate of ibuprofen from the microspheres suspension and microspheres alone indicated that the suspension medium studied did not affect the property of drug release. This study suggested that stable suspensions of ibuprofen-loaded microspheres could be formulated with 0.6% w/v xanthan gum by the addition of 20% w/v D-sorbitol.

Keywords: ibuprofen, microspheres, reconstitutable suspension, D-sorbitol

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In this study, the preparation of a reconstitutable suspension of ibuprofen was developed by using ibuprofen microspheres prepared with an acrylic polymer (Eudragit® RS PM™). The microspheres were prepared by the quasi-emulsion solvent diffusion technique. Microspheres were distributed in dry mixture and reconstituted with required volume of water to form oral liquid suspensions. The repose angle, sedimentation volume and redispersibility, rheological properties, pH values, leakage of drug from suspended microspheres and drug release properties of suspension during storage were investigated.

EXPERIMENTAL

Reagents and equipment

Ibuprofen (Eczacıbaşı, Turkey), Eudragit RS PM™ (Röhm-Pharma, Germany), xanthan gum (Aldrich, Germany), D-sorbitol (Sigma, Germany), polyvinyl alcohol (m.w. = 72 000), sodium lauryl sulfate, citric acid and sodium citrate (Merck, Germany). All other chemicals were of analytical grade and distilled water was used for all experiments.

Scanning electronic microscopy (SEM) (Jeol Model JSM-6400, Tokyo, Japan), optical microscope (Nikon AFM, USA), Brookfield viscometer (Model DV II, Brookfield Engineering Laboratories Inc., Stoughton, USA), pH meter (Meter Lab PHM 201, France), UV spectrometer (Shimadzu UV-1202, Japan), dissolution tester (Aymes, Turkey).

Preparation of microspheres

In order to prepare the microspheres, modified quasi-emulsion solvent diffusion method was used as described in previous studies (14–19). Briefly, weighed amount of ibuprofen and acrylic polymer were dissolved in ethanol at 45°C. The formed ethanolic solution was poured into water containing polyvinyl alcohol and was stirring continuously with a propeller type agitator (RZR-2000, Heidolph Electro, Germany). The system was thermally controlled at 20°C. After 30 min of stirring, the microspheres were separated by filtration, washed twice with 50 mL of water and then dried in oven at 37°C for 24 h. Dried microspheres were stored in a desiccator containing CaCl₂.

From the different microsphere formulation variables used, a formulation with desired characteristics was chosen to prepare suspension formulations. The chosen microsphere formulation was prepared using 2 g of ibuprofen, 1 g of Eudragit RS PM, 5 mL of ethanol and 200 mL of polyvinyl alcohol solution (0.05% w/v).

Preparation of the dry mixtures for reconstitutable suspensions

In the suspension formulations, xanthan gum was used as suspending agent. To impart palatability, D-sorbitol was used as a polyol. Citric acid and sodium citrate were used as pH modifiers. To produce dry mixture for reconstitution, all the powder components were reduced to more or less the same particle size. Ingredients present in small quantities (buffer components, sodium benzoate and sodium lauryl sulfate) were mixed homogeneously. The same procedure was followed for xanthan gum and ibuprofen-loaded microspheres (equivalent to 200 mg of ibuprofen/dose). Such ingredients were mixed with a portion of D-sorbitol according to the principle of the geometric dilution. The representative formulations for the preparation of dry mixtures are tabulated in Table 1.

To prepare the reconstituted suspension, 10 mL of water was added to the dry suspension powder in two steps and stirred with spoon until a homogenous product was obtained.

SEM analysis

The shape and surface morphology of microspheres were investigated by scanning electron microscopy (SEM). For the sample preparation, a

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Xanthan gum (%)</th>
<th>D-sorbitol (%)</th>
<th>Citric acid (%)</th>
<th>Sodium citrate (%)</th>
<th>Sodium benzoate (%)</th>
<th>Sodium lauryl sulfate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>0.6</td>
<td>5</td>
<td>1.44</td>
<td>0.72</td>
<td>0.2</td>
<td>0.05</td>
</tr>
<tr>
<td>S2</td>
<td>0.6</td>
<td>10</td>
<td>1.44</td>
<td>0.72</td>
<td>0.2</td>
<td>0.05</td>
</tr>
<tr>
<td>S3</td>
<td>0.6</td>
<td>15</td>
<td>1.44</td>
<td>0.72</td>
<td>0.2</td>
<td>0.05</td>
</tr>
<tr>
<td>S4</td>
<td>0.6</td>
<td>20</td>
<td>1.44</td>
<td>0.72</td>
<td>0.2</td>
<td>0.05</td>
</tr>
<tr>
<td>S5</td>
<td>0.6</td>
<td>25</td>
<td>1.44</td>
<td>0.72</td>
<td>0.2</td>
<td>0.05</td>
</tr>
</tbody>
</table>
Figure 1. Scanning electron micrographs of microspheres

Figure 2. Dependence of sedimentation volume of suspensions on the concentration of D-sorbitol

Figure 3. Rheological properties of suspension formulations containing different amounts of D-sorbitol
small aliquot of the microparticles were mounted onto metal stubs using double-sided adhesive tape. Excess microparticles were removed by tapping the stub sharply. After being vacuum-coated with a thin layer (100–150 Å) of gold at 25 mA current and 10⁻⁵ Torr pressure for 200 s, the microparticles were examined by SEM operated at 15 kV accelerating voltage.

**Microscopy studies**

The microscopic observation of suspended microspheres was determined using an optical microscope.

**Repose angle**

For measurement a repose angle of suspension powder, it was passed through a conical flask which had a 0.9 cm diameter and was laced 10 cm above the horizontal surface. The height (h) of the heap formed was measured with a cathetometer and the radius (r) of the cone base was also determined. Repose angle (Φ) was calculated from following equation (19):

\[ \Phi = \tan^{-1}\left(\frac{h}{r}\right) \]  

**Determination of the sedimentation volume**

To study the sedimentation in reconstituted suspension, the sedimentation volume was measured at selected time intervals during storage without agitation for a period of 10 days and was recorded in terms of the ratio of the ultimate settled height (Hu) to the original height (Ho), as expressed in the following equation (20):

\[ F = \frac{H_u}{H_o} \]  

**Determination of the redispersibility**

The redispersibility of a suspension was evaluated qualitatively. The test consisted of manually shaking the cylinder after the sedimentation experiments were completed. Based on the time and the effort required to convert the sediment to homogeneous suspension, the formulations were evaluated. One inversion was considered as 100% easy to be redispersed. Every additional inversion decreased the percent ease of redispersibility by 5% (21).

**Rheological studies**

The rheological profile of each formulation after constitution, in terms of viscosity, was determined by using the Brookfield viscometer. All measurements were performed at a controlled temperature of 25 ± 1°C using spindle LV 4. The flow curve was plotted between shear rate and shear stress.

**pH values**

The pH of suspensions was measured with the aid of a pH meter.

**Determination of the leakage of drug from suspended microspheres**

An aliquot of 0.5 mL was withdrawn from the suspensions for determination of leakage of drug from suspended microspheres during storage. The aliquot was filtered and the microspheres washed with water to remove the suspending vehicle and
then dried in oven at 37°C for 24 h. Dried microspheres were dissolved with ethanol. The dissolved drug amount was measured spectrophotometrically at 264 nm.

**In vitro release study**

Drug release tests on the suspension with microspheres and the original microspheres were carried out by using the paddle method specified in USP XXVII (22). A suspension sample was quantitatively transferred to the vessel bottom using a syringe. Paddle speed and bath temperature were set at 50 rpm and 37 ± 0.5°C, respectively. The samples per batch were tested in 900 mL of pH 6.8 phosphate buffer. An aliquot of the release medium was withdrawn at predetermined time intervals and equivalent amount of fresh medium was added to the release medium. The absorption of the samples was recorded at a wavelength of 264 nm spectrophotometrically. Sink conditions were maintained during all measurements. The means of six aliquots are given.

**RESULTS AND DISCUSSION**

Ibuprofen microspheres were prepared for reducing the side effects, masking the characteristic irritative taste of ibuprofen and improving the bioavailability in previous studies. In our previous studies, ibuprofen microspheres were prepared using quasi-emulsion solvent diffusion method (18, 19). The reasons to choose this method as the microsphere production method were its simplicity, low cost, success with poor aqueous solubility drugs and the production of microspheres of relatively high drug loading. In this study, microspheres prepared with 2:1 drug to polymer ratio were selected for suspension formulations since they have higher loading efficiency and suitable micromeritical properties to disperse in aqueous medium. According to the encapsulation efficiency results obtained in our previous study, the drug content of the microspheres showed good correlation with the theoretical drug loadings (19). The high content of ibuprofen in microspheres was believed to be due to the poor solubility of drug in poor solvent. The chosen microsphere formulation had 99.8% loading efficiency. SEM image of microspheres (Figure 1) showed that the microspheres were spherical with a smooth surface. The microspheres used had a mean size of 316.6 µm. As indicated in our previous study that repose angle value of chosen microsphere formulation was under 30° (18.06°). This result demonstrated that chosen microsphere formulation has suitable flow properties.

<table>
<thead>
<tr>
<th>Storage period (days)</th>
<th>% Ibuprofen content ± SD*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>66.53 ± 0.28</td>
</tr>
<tr>
<td>1</td>
<td>65.87 ± 0.07</td>
</tr>
<tr>
<td>2</td>
<td>65.94 ± 0.13</td>
</tr>
<tr>
<td>3</td>
<td>67.31 ± 0.07</td>
</tr>
<tr>
<td>4</td>
<td>67.76 ± 0.08</td>
</tr>
<tr>
<td>5</td>
<td>67.68 ± 0.24</td>
</tr>
<tr>
<td>6</td>
<td>65.63 ± 0.35</td>
</tr>
<tr>
<td>7</td>
<td>64.38 ± 0.12</td>
</tr>
<tr>
<td>8</td>
<td>64.07 ± 0.21</td>
</tr>
<tr>
<td>9</td>
<td>65.59 ± 0.19</td>
</tr>
<tr>
<td>10</td>
<td>64.94 ± 0.07</td>
</tr>
</tbody>
</table>

*Values represent the mean ± SD of three experiments.

Table 2. Physical properties of suspension powder.

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Angle of repose (°) ± SD*</th>
<th>% Ease of redisperibility</th>
<th>pH (after reconstitution)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>26.85 ± 0.15</td>
<td>70</td>
<td>3.58</td>
</tr>
<tr>
<td>S2</td>
<td>27.08 ± 0.01</td>
<td>70</td>
<td>3.58</td>
</tr>
<tr>
<td>S3</td>
<td>27.14 ± 0.08</td>
<td>80</td>
<td>3.59</td>
</tr>
<tr>
<td>S4</td>
<td>27.30 ± 0.15</td>
<td>90</td>
<td>3.60</td>
</tr>
<tr>
<td>S5</td>
<td>27.30 ± 0.57</td>
<td>90</td>
<td>3.59</td>
</tr>
</tbody>
</table>

*Values represent the mean ± SD of three experiments.
um due to its acceptable toxicological and safety properties for food and pharmaceutical applications. It is soluble in water and imparts its high viscosity at low concentration with thixotropic flow characteristics, which increase with increasing concentration (23, 24). Viscosity of xanthan solutions is unaffected by pH changes between pH 1 and 13. Moreover, the three-dimensional network formed by the associated chains makes xanthan gum an efficient stabilizer for suspensions and emulsions (25). Based on results of our preliminary data, 0.6% w/v xanthan gum was used as the suspending agent for the microsphered suspensions.

D-sorbitol used to impart palatability, gave a well-structured vehicle in which the microspheres remained suspended for an extended period. At a xanthan gum concentration of 0.6%, there was a increase in sedimentation volume with increasing D-sorbitol concentration up to 20.0%. Above this concentration, the suspension was found to be stable even after standing for 10 days, i.e., the sedimentation volume was 1.0, as shown in Figure 2. The studies concerning the sedimentation volume of suspensions clearly indicated that the coexistence of D-sorbitol with xanthan gum at the optimum concentration in the dispersion medium are prerequisites for making coarse microspheres stable in suspension.

Repose angle results showed that all suspension powder had suitable flow properties as shown in Table 2. All repose angles were under 30°.

On the case of redispersibility of the suspension, D-sorbitol amount had an effect, as shown in Table 2. The highest improving effect was shown with 20.0% and 25.0% D-sorbitol concentrations.

Buffer components (citric acid and sodium citrate) were used to adjust the pH of the constituted suspension to pH 3.60, where ibuprofen is considered to be almost insoluble. pH values of formulations after constitution varied as 3.58ñ3.60 (Table 2).

The rheological properties of suspensions were investigated in order to clarify the relationship between the viscosity and suspendability by using a rotation viscometer. As shown in Figure 3, dispersion media of suspensions were non-Newtonian fluids. Moreover, sedimentation volume and redispersibility results showed that viscosity values of 8 formulation containing 20.0% D-sorbitol to be adequate for microsphere dispersibility.

Ibuprofen content determination studies demonstrated that no leakage of drug occurred from the microspheres in the suspension on storage (Table 3). The acidity of the suspension medium was attributed as the cause of drug leakage being prevented from microspheres. Because of the low solubility of ibuprofen (pKa 5.2) in the acidic medium, it was unable to diffuse out from the microspheres to the medium.

The drug release rate of the suspended microspheres and dry microspheres were investigated in pH 6.8 phosphate buffer, as shown in Figure 4. The ibuprofen release rate from the suspended microspheres was consistent with that from dry microspheres. This result indicated that the suspension medium studied did not affect the property of drug release.

CONCLUSION

We can conclude that a liquid pharmaceutical preparation for oral administration capable of providing a sustained release of ibuprofen was successfully obtained. Stable suspensions of ibuprofen-loaded microspheres could be formulated at pH 3.60 with 0.6% w/v xanthan gum by the addition of 20% w/v D-sorbitol as a coexisting polyol. Leakage of drug from the microspheres in the reconstituted suspensions was not found to occur on storage for 10 days. Finally, the release studies carried out on the suspension formulation did not show any statistically significant differences from the profiles of microspheres alone.

REFERENCES


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