Preparation and evaluation of a sustained-release suspension containing theophylline microcapsules

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A great effort has been devoted to the preparation of sustained-release formulations of theophylline to prevent large fluctuations of serum concentration and increasing the therapeutic efficacy followed by patient compliance. In the present study, microcapsules of theophylline with ethyl cellulose (EC) were prepared by emulsion-solvent evaporation method in different polymer to drug ratios. Size, morphology, drug loading and release behavior of microcapsules were also studied. Microcapsules were then formulated into suspensions to provide an oral liquid dosage form for drug and resulting suspensions were examined for stability and release characteristics in various storage times. Results showed that microcapsules prepared in drug to polymer ratio 1:1.4 by emulsifying polymer solution in liquid paraffin presented the sustained-release properties which met the United States Pharmacopeia (USP) (2007) requirements (t₅₀% and t₈₀% of these microparticles were 150 and 360 min, respectively). The suspensions prepared by these microcapsules were also stable in the study period and their release profiles were consistent to the original microcapsules. The results allow for the conclusion that the formulated suspension can be used as a sustained-release formulation for theophylline in treatment of obstructive pulmonary disorders.

Key words: Theophylline, microencapsulation, suspension, sustained-release, ethyl cellulose.

INTRODUCTION

Theophylline is a methylxanthine alkaloid which is used as bronchodilator in treatment of chronic obstructive pulmonary disorders especially asthma. Although, it is used for about 70 years, the complications associated with its use are still unsolved (Obeidat et al., 2009; Soni et al., 2010). Theophylline is a narrow therapeutic index drug with a short half-life. Conventional dosage forms of theophylline should be administered 3 to 4 times a day to provide effective concentration and to avoid large fluctuations in blood concentration. This leads to poor patient compliance and enhanced risk of gastrointestinal (GI) and cardiovascular adverse effects. Sustained-release formulations would provide steady blood concentrations with minimum fluctuation and results in higher therapeutic efficacy and lower risk of toxicity (Roy et al., 2007; Zhang et al., 2008).

Among sustained-release drug delivery systems, microcapsules have received much attention because of uniform distribution in GI tract which leads to uniform absorption and decreasing risk of local effects on GI tract. Another advantage of microparticulate systems is their feasibility to be incorporated into liquid dosage forms such as suspensions. In addition to sustain the drug release, microencapsulation of theophylline can decrease its irritating effect on GI mucosa and mask drug taste (Lavasanifar et al., 1997). Due to ease of swallowing and flexibility in dosage adjustment, liquid dosage forms are preferred especially in pediatric and geriatric patients (Bodmeier et al., 1991; Cuña et al., 2000). Different techniques of microencapsulation have been developed for controlled delivery of different drugs including

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emulsion-solvent evaporation for terbutaline (Cuña et al., 2000), in-situ gelation for theophylline (Miyazaki et al., 2000), emulsion-solvent diffusion for ibuprofen (Kawashima et al., 1991) and spray drying for paclitaxel (Mu et al., 2005). Choosing a suitable microencapsulation method is highly dependent on the drug characteristics, type of polymer used and economic considerations. Emulsion-solvent evaporation technique is one of early methods of microencapsulation which has been widely studied for preparation of polymeric microcapsules. In this technique, a polymer solution which drug substance is dissolved or dispersed in is emulsified in the external phase. By evaporation of the solvent, polymeric capsules are formed around the drug particles. The size and state of the particle in the internal phase play an important role in the final status of the microparticles. The choice of the internal and the external phase of the emulsion, type of emulsifier and method of homogenizing two phases will effectively determine the characteristics of the final microparticles (Matsumoto et al., 2008). Therefore, the method is very flexible for different types of polymers and hydrophilic and lipophilic drugs, and by selecting suitable solvent and emulsifier; various combinations of drug substances and polymers could be applied. We selected ethyl cellulose (EC) as the sustaining polymer since it is a water-insoluble polymer with good film forming ability, durability and low cost and extended drug release properties (Shi et al., 2008; 2009). EC is a non-biodegradable and biocompatible and gastro-resistant polymer which has been extensively used as drug release retardant which easily forms microcapsules with a one-step encapsulation method (Das and Rao, 2006; Sudhamani et al., 2010).

Taking all these into consideration, we aimed at preparing sustained release microcapsules of theophylline by emulsion-solvent evaporation technique using EC. Although theophylline encapsulation in EC microspheres for sustained delivery have been reported in several studies (Pachuau et al., 2008; Thakare et al., 2011), incorporating the microcapsules into the suspension base was not reported elsewhere. The novelty of our work was to provide a microparticle containing oral liquid sustained release dosage form for easy use in pediatric and geriatric patients.

MATERIALS AND METHODS

The following materials were obtained from commercial sources: EC (ethoxy content 46%, Aldrich, USA), acetone, dichloromethane, liquid paraffin, acacia, ammonium hydroxide 25%, methyl paraben, propyl paraben, sodium lauryl sulfate (SLS), theophylline and sucrose (Merck, Germany), sorbitol syrup 70% and tragacanth (Modarres, Iran). All other chemicals and solvents were of analytical grade.

Preparation of microcapsules

Microcapsules were prepared by emulsion-solvent evaporation technique with two strategies. First strategy was based on an oil-in-water (o/w) emulsion which prepared after examining large number of variables. For preparing the oil phase, required amount of EC (in three ratios to drug; 1, 2 and 3) was completely dissolved in dichloromethane and 800 mg theophylline was thoroughly dispersed in the mixture by stirring. The oil phase was emulsified into the aqueous phase (1.5% SLS solution in water) under stirring at 300 rpm. The resulting emulsion was stirred for 45 min at room temperature to remove dichloromethane completely. The formed microcapsules were filtered, washed and dried at room temperature.

Second strategy was based on emulsifying the drug-containing EC solution in an oil phase. The optimum condition was selected after performing a set of experiments and evaluating the size and drug loading percentage of the particles. The internal phase of the emulsion contained required amount of theophylline dispersed in the EC solution in acetone. The internal phase was then incorporated into the external phase contained 1.3% Tween 80 in 100 ml liquid paraffin. The mixture was stirred at room temperature for 5 h to remove acetone and the resulting microcapsules were then filtered and washed with n-hexane and dried at room temperature. Eight formulations (f1 to f8) were prepared by this strategy in the drug to polymer ratios of 1:1, 1:1.2, 1:1.3, 1:1.4, 1:1.5 and 1:2.

Morphological studies of microcapsules

In order to demonstrate the formation of microcapsules and preliminary studies of their shape, resulting microcapsules were studied using a simple optical microscope (HM-LUX3, Leitz, Germany). Samples of microcapsules were selected randomly. Size of microcapsules was also determined using hemocytometer.

Determination of drug loading of microcapsules

The drug content of microcapsules was determined according to USP 30 method for testing content uniformity of sustained-release capsules of theophylline (USP, 2007). Briefly, a sample of microcapsules containing 100 mg of drug was triturated with 20 ml of water, transferred to a 100 ml volumetric flask, 25 ml of 6 N ammonium hydroxide added, sonicated for about 45 min, and cooled to room temperature. The mixture was diluted to volume and mixed. The mixture was then filtered and diluted with water and the absorbance of this solution and a standard solution of theophylline, similarly prepared was read at 270 nm with ultraviolet (UV)-visible spectrophotometer (550SE, Perkin-Elmer, USA). The concentration of drug in the sample was then determined according to the standard solution of theophylline.

Preparation of suspensions

Microcapsules with the optimum range of dissolution (dissolution test will be discussed in following sections) and shape were selected to be formulated in suspensions. Two suspension formulations were prepared as the medium of suspensions (Table 1), either contains 100 mg theophylline / 5 ml (Kawashima et al., 1991).

Characterization of suspensions

Rheology

The rheology of the suspensions was determined using a Brookfield rotational viscometer (Metler RM180) with measuring bob No.2 and
measuring tube No.2.

**Sedimentation volume**

The sedimentation volume (F) was obtained based on the following equation:

\[ F = \frac{V_1}{V_0} \]

\( V_1 \) is the equilibrium volume of sediment and \( V_0 \) is the total volume of suspension before sedimentation. Equilibrium volume of sediment is the volume which remains unchanged for 3 weeks (Gennaro, 2000; Sinko, 2006).

**Degree of flocculation**

Degree of flocculation (\( \beta \)) was estimated using this equation:

\[ \beta = \frac{F}{F_e} \]

\( F \) is the sedimentation volume of the flocculated suspension, and \( F_e \) is the sedimentation volume of the suspension when deflocculated (Gennaro, 2000; Sinko, 2006).

**Ease of redispersibility:** The number of shears required to redisperse a sedimented suspension in a cylindrical glass graduate is an indicator of ease of redispersibility (N) (Jones et al., 1970).

**Freeze/Thaw cycles**

Physical and microscopic changes of suspensions under sudden thermal changes were investigated. Suspensions were kept in a 40°C oven for 24 h and then transferred to a 0°C freezer for 24 h (Lieberman, 1990).

**Normal temperature fluctuation**

Inspection of physical and microscopic changes of the suspension during a gradual decrease in temperature from 40 to -5°C was also performed. For this purpose, suspensions were kept for 24 h in each temperature (Sinko, 2006).

**pH of suspensions:** pH of suspensions was determined using a Rotring pH meter (Dalal and Narurkar, 1991).

### Drug release studies

The USP paddle method was used for testing the release of theophylline from microcapsules and suspensions. Experiments were performed according to dissolution test No. II for sustained-release theophylline preparation using a USP dissolution apparatus (Pharma test, PTZWS3, Germany).

The dissolution medium was consisted of 900 ml phosphate buffer (pH 4.5) maintained at 37°C stirred at rate of 75 rpm. An amount of microcapsule or suspension containing 100 mg theophylline was used for each dissolution experiment. At appropriate time intervals, 20, 40, 60, 90, 120, 180, 240, 300, 360, 420 and 480 min, a 3 ml sample of dissolution medium was withdrawn and replaced by an equal volume of medium to maintain the volume constant. Samples were filtered, diluted, and analyzed for theophylline concentration at 270 nm to characterize the dissolution profiles. For reading the absorbance of samples obtained from the dissolution of suspensions, dissolution media containing drug free suspension was used as the blank. Dissolution efficiency percentage after 8 h (DE\%) was considered as a basis for comparing the dissolution profiles. DE\% was calculated based on the following equation:

\[ DE\% = \frac{\int_0^t y \, dt}{ty_{100}} \times 100 \]

DE is the ratio of area under the dissolution curve at a given time to the total area at the same time once the entire content is released (Khan, 1975).

### Kinetic models analysis

The release data were fitted to different kinetic models in Microsoft Excel 2007 software as follows to determine the model which better described the kinetics of the release behavior. First-order kinetic

\[ \ln W = \ln W_0 - k_t \]

Hixson-Crowell’s cube root of time

\[ W^{1/3} = W_0^{1/3} - k_t \]

and square-root of time

\[ W = W_0 - k_t^{1/2} \]

where \( W \) is the amount of drug remaining to be released and \( W_0 \) is the initial amount of drug (Sprockel and Price, 1989).

### Statistical analysis

SPSS software version 12 was used for all statistical analysis. Student t-test and one-way analysis of variance (ANOVA) followed by a Duncan post hoc test, was used for comparison between DE%
Table 2. Drug loading percentage of the microcapsules prepared by two strategies (n = 6).

<table>
<thead>
<tr>
<th>Preparation strategy</th>
<th>Polymer to drug ratio</th>
<th>Type of stirrer</th>
<th>Loading percentage (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aqueous</td>
<td>1</td>
<td>Propeller stirrer</td>
<td>89.9 ± 0.9</td>
</tr>
<tr>
<td>Aqueous</td>
<td>2</td>
<td>Propeller stirrer</td>
<td>85.6 ± 0.4</td>
</tr>
<tr>
<td>Aqueous</td>
<td>3</td>
<td>Propeller stirrer</td>
<td>80.1 ± 0.7</td>
</tr>
<tr>
<td>Oil</td>
<td>1</td>
<td>Magnet stirrer</td>
<td>72.0 ± 0.7</td>
</tr>
<tr>
<td>Oil</td>
<td>1.2</td>
<td>Magnet stirrer</td>
<td>70.1 ± 0.6</td>
</tr>
<tr>
<td>Oil</td>
<td>1.3</td>
<td>Magnet stirrer</td>
<td>69.2 ± 0.7</td>
</tr>
<tr>
<td>Oil</td>
<td>1.4</td>
<td>Magnet stirrer</td>
<td>68.8 ± 0.9</td>
</tr>
<tr>
<td>Oil</td>
<td>1.5</td>
<td>Magnet stirrer</td>
<td>66.9 ± 0.7</td>
</tr>
<tr>
<td>Oil</td>
<td>2</td>
<td>Magnet stirrer</td>
<td>62.0 ± 0.9</td>
</tr>
</tbody>
</table>

Table 2. Drug loading percentage of the microcapsules prepared by two strategies (n = 6).

Figure 1. Release profile of microcapsules prepared in aqueous phase (n = 6).

Figure 2. Release profiles of microcapsules prepared in oil phase with different polymer to drug ratios (n = 6).

and other parameters between two or more than two formulations, respectively. P-value less than 0.05 was considered significant.

RESULTS

Microscopic studies of microcapsules

Inspection of microcapsules by optical microscopy showed that microcapsules prepared by first strategy in aqueous phase were smaller with a rough surface, while microcapsules prepared in oil phase were spherical with a smooth uniform surface and acceptable degree of homogeneity. Size of microcapsules prepared in aqueous phase was in the range 200 to 230 µm which was increased by increasing polymer to drug ratio. The size of microcapsules prepared in oil phase were in the range of 480 to 530 µm for drug to polymer ratios 1:1, 1:1.2 and 1:1.3 while it suddenly decreased to 240-265 µm for ratios of 1:1.4, 1:1.5 and 1:2.

Drug loading and release studies

Results of loading percentage of microcapsules prepared by two strategies are shown in Table 2. Loading was higher in microcapsules prepared in aqueous phase (80 to 90%) compared to ones prepared in oil phase (62 to 72%). It was decreased as the polymer to drug ratio increased and this trend was observed for microcapsules prepared by both strategies. Figure 1 shows the release profiles of microcapsules prepared in aqueous phase. Results of DE% of these microcapsules are not presented, because the release profile was not controlled and the formulation did not satisfy the goal of preparation of sustained release formulation of theophylline.

Release profiles of microcapsules prepared by second strategies are shown in Figure 2. By increasing polymer
Release profiles of mi


crocapsules prepared in oil phase with polymer to drug ratio 1.4 formulated in (a) Suspension I and (b) Suspension II after various storage times (n = 6).

Figure 3. Release profiles of microcapsules prepared in oil phase with polymer to drug ratio 1.4 formulated in (a) Suspension I and (b) Suspension II after various storage times (n = 6).

was slower compared with the microcapsules prepared by the first strategy.

Release behavior of both suspensions met the requirements presented in USP and no significant difference (P > 0.05) was observed in release profiles and DE% for both suspensions on first day and after 12 weeks which indicates the stability of suspensions. Figure 3 shows the release profiles of suspensions in different storage times. Results of DE% are also listed in Table 3. Fitting the release data to the different kinetic models showed that the release kinetics of microcapsules with different polymer to drug ratios were significantly different (P < 0.05) and by increasing the ratio of polymer to drug, kinetic was changed from Higuchi to Hixson-Crowell. In contrast, the values of kinetic constant, K, and correlation coefficient, R, calculated for both suspensions were not significantly different between kinetic models (P > 0.05). Values of correlation coefficients and kinetic constants (K) obtained by fitting data to different kinetic models are shown in Table 4.

Characterization of suspensions

As shown in Figure 4, both suspensions showed a thixotropic rheogram with shear thinning behavior. Suspension I presented higher thixotropy and lower viscosity than suspension II. pH values for suspension I and II were 5.98 ± 0.04 and 7.16 ± 0.05, respectively, which is suitable for an oral suspension of theophylline according to the pKₐ of the drug.

Results of physical tests performed on suspensions are shown in Table 5 which indicates the suitability of the suspension properties. Sedimentation volume of suspensions was less than 0.9 and the suspensions were easily redispersed by 2 or 3 revolutions.

No changes were observed in flocculation and crystallization of both suspensions during freeze / thaw cycles and normal temperature fluctuation tests.

DISCUSSION

Emulsion-solvent evaporation technique in aqueous systems for preparation of microcapsules is preferred over non-aqueous systems because of economic considerations and easier final clean-up of the system (Torres et al., 1998). Preparation of EC microcapsules by this method was not provided a continuous polymeric wall around the drug particles. This is mostly due to the limitation in selecting a solvent for dispersing polymer which is immiscible with the aqueous external phase of the emulsion. The preparation method in the oil phase was more reproducible and flexible and acetone was used instead of dichloromethane which is less toxic. The resulting microcapsules of this method were free flowing. The difference in shape of microcapsules prepared by these methods might be a consequence of difference in
Table 3. DE₈% obtained for various microcapsules prepared in oil phase and resulting suspensions (n = 6).

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microcapsules with polymer to drug ratio 1</td>
<td>89.22</td>
<td>0.10</td>
</tr>
<tr>
<td>Microcapsules with polymer to drug ratio 1.2</td>
<td>68.49</td>
<td>0.26</td>
</tr>
<tr>
<td>Microcapsules with polymer to drug ratio 1.3</td>
<td>62.73</td>
<td>0.19</td>
</tr>
<tr>
<td>Microcapsules with polymer to drug ratio 1.4</td>
<td>58.27</td>
<td>0.43</td>
</tr>
<tr>
<td>Microcapsules with polymer to drug ratio 1.5</td>
<td>51.27</td>
<td>0.29</td>
</tr>
<tr>
<td>Microcapsules with polymer to drug ratio 2</td>
<td>44.78</td>
<td>0.30</td>
</tr>
<tr>
<td>Suspension I, after 24 h</td>
<td>58.27</td>
<td>0.86</td>
</tr>
<tr>
<td>Suspension I, after 1 week</td>
<td>58.42</td>
<td>0.78</td>
</tr>
<tr>
<td>Suspension I, after 3 weeks</td>
<td>58.56</td>
<td>0.82</td>
</tr>
<tr>
<td>Suspension I, after 6 weeks</td>
<td>58.72</td>
<td>0.45</td>
</tr>
<tr>
<td>Suspension I, after 9 weeks</td>
<td>58.94</td>
<td>0.68</td>
</tr>
<tr>
<td>Suspension I, after 12 weeks</td>
<td>59.11</td>
<td>0.48</td>
</tr>
<tr>
<td>Suspension II, after 24 h</td>
<td>59.19</td>
<td>0.22</td>
</tr>
<tr>
<td>Suspension II, after 1 week</td>
<td>59.23</td>
<td>0.35</td>
</tr>
<tr>
<td>Suspension II, after 3 weeks</td>
<td>58.75</td>
<td>0.72</td>
</tr>
<tr>
<td>Suspension II, after 6 weeks</td>
<td>58.66</td>
<td>0.23</td>
</tr>
<tr>
<td>Suspension II, after 9 weeks</td>
<td>58.33</td>
<td>0.37</td>
</tr>
<tr>
<td>Suspension II, after 12 weeks</td>
<td>58.22</td>
<td>0.29</td>
</tr>
</tbody>
</table>

% DE₈, Dissolution efficiency percentage after 8 h.

Table 4. Values of correlation coefficients (R) and kinetic constants (K) obtained by fitting data to different kinetic models.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>First order</th>
<th>Higuchi</th>
<th>Hixson-Crowell</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>K/2.303</td>
<td>R</td>
<td>K (min⁻¹/²)</td>
</tr>
<tr>
<td>Microcapsules with polymer to drug ratio 1</td>
<td>0.0041 ± 0.0001</td>
<td>0.9572 ± 0.0019</td>
<td>2.7572 ± 0.0219</td>
</tr>
<tr>
<td>Microcapsules with polymer to drug ratio 1.2</td>
<td>0.0034 ± 0.0001</td>
<td>0.9495 ± 0.0022</td>
<td>5.0032 ± 0.0166</td>
</tr>
<tr>
<td>Microcapsules with polymer to drug ratio 1.3</td>
<td>0.0028 ± 0.0001</td>
<td>0.9707 ± 0.0014</td>
<td>5.0353 ± 0.0325</td>
</tr>
<tr>
<td>Microcapsules with polymer to drug ratio 1.4</td>
<td>0.0022 ± 0.0001</td>
<td>0.9911 ± 0.0037</td>
<td>4.9300 ± 0.0270</td>
</tr>
<tr>
<td>Microcapsules with polymer to drug ratio 1.5</td>
<td>0.0016 ± 0.0000</td>
<td>0.9954 ± 0.0024</td>
<td>4.5201 ± 0.0193</td>
</tr>
<tr>
<td>Microcapsules with polymer to drug ratio 2</td>
<td>0.0011 ± 0.0001</td>
<td>0.9947 ± 0.0016</td>
<td>3.7472 ± 0.0349</td>
</tr>
<tr>
<td>Suspension I, after 24 h</td>
<td>0.0022 ± 0.0001</td>
<td>0.9892 ± 0.0030</td>
<td>4.8541 ± 0.0930</td>
</tr>
<tr>
<td>Suspension II, after 24 h</td>
<td>0.0022 ± 0.0001</td>
<td>0.9874 ± 0.0077</td>
<td>4.8710 ± 0.0674</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD (n = 6).
Figure 4. Rheograms of (a) Suspension I and (b) Suspension II prepared from microcapsules of oil phase with polymer to drug ratio 1.4. Rheology of the suspensions was characterized using a Brookfield viscometer (Metler RM180) with measuring bob No.2 and measuring tube No.2.

Figure 4. Rheograms of (a) Suspension I and (b) Suspension II prepared from microcapsules of oil phase with polymer to drug ratio 1.4. Rheology of the suspensions was characterized using a Brookfield viscometer (Metler RM180) with measuring bob No.2 and measuring tube No.2.

Increasing the size of the particles with increasing polymer to drug ratio may be due to the higher concentration of the polymer in the dispersed phase which results in increased viscosity of the solution and therefore enhanced volume occupied by the polymer. Microcapsules with sizes around 200 µm are easily dispersed in a liquid suspension without a gritty sensation (Cuñá et al., 2000).

Two strategies were used for microencapsulation to examine the effect of hydrophilicity of the internal and external phase on drug loading. Since theophylline is a hydrophilic drug; there may be some partitioning of drug out to the aqueous phase and lower loading in this strategy as reported for zidovudine encapsulated EC microspheres (Das and Rao, 2006). Using oil phase would increase the loading; however, this was not observed in our results and the drug loading was higher by the first strategy in aqueous phase.

As reported elsewhere, entrapment of drug in the microcapsules is dependent on the continuity and integrity of the particle wall which is controlled by polymer to drug ratio (Halder and Sa, 2006). As shown in Figure 1, while increasing polymer to drug ratio, decreased the dissolution rate, the three sets of microcapsules did not provide the sustained release and 90% of drug was released in 20 min. The difference between three formulations was not significant. The release profile of these microcapsules was not controlled and the formulation did not satisfy the goal of preparation of sustained release formulation of theophylline. Higher release rate of microcapsules prepared by this strategy may be due to the smaller size and therefore larger surface area of the particles (Guyot and Fawaz, 1998).

Dependency of release to polymer to drug ratio, has also been reported for furosemide-loaded (Akbuga, 1991) and tramadol-loaded (Akbuga, 1991) EC microspheres (Naeem Aamir et al., 2011), which is due to the increased hydrophobic thickness of the polymeric wall followed by the longer passage way of the drug through the encapsulating wall (Naeem Aamir et al., 2011). Although drug loading was lower for microcapsules prepared by this method, the slower rate of release of theophylline from these microcapsules is related to the larger size of particles and more uniform structure of the polymeric wall. This observation has also been reported before that release from EC microcapsules was dependent on size and loading of particles (Bodmeier et al., 1994).

According to USP (2007), sustained-release formulations of theophylline should release 10 to 30% of their drug content in the first hour and a minimum of 80% after 8 h. Therefore, the microcapsules prepared in drug to polymer ratio 1:1.4 in oil phase were used to formulate suspensions. The release profile was better fitted to Higuchi model which means that the release is mostly controlled by diffusion. Release of EC microspheres loaded with furosemide, tramadol and zidovudine was also reported to be proportional to the square root of time (Akbuga, 1991; Das and Rao, 2006; Naeem Aamir et al., 2011).

the evaporation rate of the solvent. Similar results were obtained in microencapsulation of terbutaline-loaded ion exchange resins (Cuñá et al., 2000). Rapid evaporation of the solvent results in microcapsules with a rough surface (Radwan et al., 1995). Surface of microcapsules with lower drug loading was smoother because of lower amount of drug crystals on the surface. Increasing the
References

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Table 5. Results of physical parameters evaluated for characterization of suspensions.

<table>
<thead>
<tr>
<th>Suspension number</th>
<th>β</th>
<th>F</th>
<th>N</th>
<th>State of flocculation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspension I</td>
<td>3.97 ± 0.04</td>
<td>0.79 ± 0.01</td>
<td>2</td>
<td>Flocculated</td>
</tr>
<tr>
<td>Suspension II</td>
<td>3.80 ± 0.04</td>
<td>0.84 ± 0.01</td>
<td>3</td>
<td>Flocculated</td>
</tr>
</tbody>
</table>

β, Degree of flocculation; F, sedimentation volume; N, ease of redisperisibility.

Acknowledgement

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References


Dev. Ind. Pharm. 21:1453-1462.