Microencapsulation of Paracetamol by Various Emulsion Techniques Using Cellulose Acetate Phthalate

Ali Nokhodchi* and Djavad Farid

Microencapsulation is defined as the application of a thin coating to individual core materials that have an arbitrary particle-size range from 5 to 5000 μm (1,2). This coating can retard the release of a drug (3); modify the availability of the core; change a core's chemical properties such as solubility and reactivity and physical properties such as color and particle shape (4); and alter the heat sensitivity and photosensitivity of the core (5). Microencapsulation may improve the absorption of a drug and reduce side effects such as irritation of the gastrointestinal mucosa (6).

Cellulose acetate phthalate (CAP) is used widely as an enteric coating for tablets and capsules. Several researchers have investigated the use of CAP as a polymer with either aqueous (7) or nonaqueous (8–10) manufacturing vehicles to microencapsulate a drug by a coacervation phase-separation procedure. Nokhodchi and Farid microencapsulated acetylsalicylic acid using CAP and a nonsolvent to obtain spherical microcapsules (11). The factors affecting the microencapsulation of aspirin using CAP (11) and the effect of compression force (9) and type of excipient (12) on drug release from microcapsules also have been investigated.

The nonsolvent addition method has been reported by many authors (13–16); however, very few studies have compared the various methods of CAP microencapsulation. Sprockel and Prapaitrakul compared microencapsulation of paracetamol by various emulsion techniques using cellulose acetate butyrate as a polymer (17). The aim of the present study was to compare the emulsion solvent evaporation (ESE) technique, the emulsion nonsolvent addition (ENSA) method, and the modified emulsion solvent evaporation (MESE) method for microencapsulation of paracetamol using CAP as the coating agent.

The ESE method is simple, and the factors affecting microcapsule size distribution and drug release in this method can be modified easily. In the ESE procedure, a polymer solution containing a drug is emulsified in an immiscible polymer nonsolvent. Polymer deposition around the drug particles occurs as a result of partitioning the polymer solvent from the dispersed phase to the continuous phase and removing the solvent by evaporation. The removal process can be time consuming depend-
ing on the batch size and temperature (16). If the rate of solvent extraction from the emulsified polymer could be enhanced, then ESE would become a more commonly used method.

Sayed and Price modified the MESE method for microencapsulation by adding a fixed volume of a miscible non solvent to the polymer solution before emulsification (18). A polymer non solvent is a liquid that does not dissolve the polymer and can be miscible or immiscible with the solvent. Incorporation of the non solvent into the polymer solution resulted in a faster deposition of the polymer. In the ENSA method, a non solvent that is miscible with both the external phase and the solvent is added to the external phase at a constant rate following emulsification of the polymer solution containing the drug. Sprockel and Prapaitrakul showed that the release rate from paracetamol microcapsules prepared by ESE was significantly lower compared with those of MESE microcapsules and ENSA microcapsules, and the drug content of microspheres prepared with ESE was significantly lower compared with those of MESE and ENSA microspheres (17). In this study the same drug was chosen, but the polymer was changed from cellulose acetate butyrate to CAP to examine whether previous findings could be applied to another polymer.

**Materials and methods**

**Materials.** N-acetyl-p-aminophenol (paracetamol, Sigma, St. Louis, MO), acetone (Merck, Whitehouse Station, NJ), chloroform (Merck), hexane (Merck), liquid paraffin (Merck), Tween 80 (Merck), CAP (Röhm Pharma, Piscataway, NJ), and simethicon (Sigma) were used.

**Methods. Preparation of microcapsules.** The authors prepared paracetamol microcapsules using three methods: ESE, MESE, and ENSA. In each of these techniques, paracetamol microcapsules were prepared with CAP as the coating agent, acetone as the polymer solvent, chloroform and hexane as the non solvent, and liquid paraffin as the encapsulation vehicle. Three batches of paracetamol microcapsules were produced with each method.

**ESE method.** CAP was dissolved in acetone. By stirring the mixture at 600 rpm, the authors dispersed paracetamol particles (the ratio of drug to polymer was 4:1) in liquid paraffin that contained 1% w/w polysorbate 80 (i.e., Tween 80) and two drops of simethicon as an antifoaming agent. The polymer solution was added slowly to the drug dispersion by means of a burette. The resultant mixture was agitated at room temperature (25 ± 2 °C) until the acetone (i.e., polymer solvent) evaporated. The liquid paraffin was decanted, and the microcapsules were collected, washed twice with 50 mL of chloroform to remove any remaining oily phase, and dried under reduced pressure for at least 12 h. The rate of stirring and the ratio of drug to polymer were kept constant for the three methods studied.

**MESE method.** This procedure was similar to the ESE method described previously except that during a period of 10–15 min hexane (a non solvent) was added to the liquid paraffin that contained dispersed paracetamol and polymer solution. The ratio of acetone to hexane was 3:2. Following emulsification of the drug dispersion in liquid paraffin containing 1% w/w Tween 80, the acetone and hexane were evaporated in conditions similar to those of the ESE method. The microcapsules were collected in the same way as described for ESE.

**ENSA method.** The procedure was the same as the ESE method described previously except that 5 min after the polymer solution was added to the liquid paraffin that contained dispersed paracetamol particles, 50 mL of chloroform (a non solvent) also was added during a period of 15 min. Agitation of liquid paraffin containing paracetamol, polymer solution, and chloroform then was performed for 20 min. The microcapsule collection procedure was the same as described for ESE.

**Assay of paracetamol.** To determine the total drug content of the microcapsules, 100 mg of microcapsules was ground to a fine powder and dissolved in 1000 mL of 1 N HCl by stirring for 15 min. In these conditions the quantity of paracetamol was determined spectrophotometrically at 245 nm. Three determinations of the microcapsule content from the same batch for each method were performed.

**In vitro dissolution.** The USP basket method was used for all the in vitro dissolution studies. Distilled water containing 0.02% w/w Tween 80, which simulated gastric fluid (pH 1.2) without enzyme, was used as a dissolution medium. The rate of stirring was 100 ± 4 rpm.

A quantity of 100 mg of microcapsules with a mean particle size of 710–1000 μm obtained from each method was placed in 900 mL of dissolution fluid and maintained at 37 ± 1 °C. At appropriate intervals, 5 mL of the sample was extracted and filtered through a 0.45-μm filter (Millipore, Bedford, MA). The dissolution media then were replaced by 5 mL of fresh dissolution fluid to maintain a constant volume in the dissolution flask. The samples were analyzed at 245 nm using a UV spectrophotometer.

**Particle-size determination.** The microcapsules were placed on a nest of sieves and vibrated for 10 min. The arithmetic mean diameters then were calculated.

**Results and discussion**

The ESE process of microencapsulation by means of emulsion techniques involves dispersing or dissolving a core substance (i.e., a drug) in a film-forming polymer solution and dispersing this mixture in a vehicle that is both poorly miscible with the solvent of the polymer solution and does not dissolve the polymer or core substance. A non solvent for the polymer or core substance that is miscible with the polymer solvent and poorly miscible with the encapsulation vehicle then is added to the system using either the ENSA or MESE method, thereby precipitating the polymer film around the core material and forming isolated microcapsules.

To identify the region of microencapsulation, three-phase diagrams (i.e., liquid paraffin, CAP, and acetone) were used for each method of microencapsulation. Typical phase diagrams were based on the percent weight per weight concentration of the components, and various phases were obtained during microencapsulation. The gel-phase region yielded a gel, the microcapsule region yielded clearly defined microcapsules, and the liquid region yielded an emulsion. Table I lists the optimum conditions for the preparation of microcapsules for ESE, MESE, and ENSA. The gel phase occurs almost immediately when a high
concentration of CAP exists. Light mineral oil can dissolve as much as 10% acetone, thus removing it from the CAP solution and creating a gel that is too viscous to be properly dispersed in the vehicle. The liquid-polymer region contains the highest concentration of solvent, and the viscosity and cohesion are low so that the coacervate is unable to form microcapsules. Table I also shows that the region of microcapsule of paracetamol in the ESE method is more extensive than that of the other methods. In other words, in the ENSA method, the region of microcapsule is small.

In the ESE technique, acetone (a polymer solvent) was soluble in liquid paraffin to a limited extent. When acetone was added to liquid paraffin, some of the acetone partitioned into the liquid-paraffin external phase. The extent of acetone partitioning depended on the affinity between liquid paraffin and acetone, and the rate of partitioning depended on the size of the emulsion droplets. The partitioned acetone in the external phase evaporated from the surface and was replaced by further partitioning of acetone.

In the MESE method, hexane was added to liquid paraffin. Because hexane is miscible with both acetone and liquid paraffin, some hexane probably partitioned into the liquid paraffin, increasing the affinity of the external phase for acetone. An increased partitioning of acetone into liquid paraffin would have resulted in an increased rate of solvent removal.

In the ENSA method, acetone was not removed. A nonsolvent for the polymer and the core substance that is miscible with the polymer solvent and poorly miscible with the encapsulation vehicle was added to the system, thereby precipitating the polymer film around the core material and forming isolated microcapsules. All three methods produced spherical microcapsules. Figure 1 shows the scanning electron micrograph of the microcapsules produced by the ENSA method.

The ENSA technique was the most rapid of the three methods. With this technique, the time necessary for microcapsule formation was consistently <40 min, whereas the ESE and MESE techniques required at least 2–3 and 5–7 h, respectively.

The drug content of microcapsules (710–1000 μm) obtained by the three methods is shown in Table II. One-way analysis of variance showed that significant differences (p < 0.05) existed among the amounts of drug content of microcapsules obtained by the use of the three methods. The drug content of microcapsules resulting from the MESE method was significantly lower, whereas the drug content of microcapsules obtained from the ENSA method was significantly higher (p < 0.05). However, these small differences would not be important in practice.

Table I: The optimum conditions for the preparation of paracetamol microcapsules for three methods of microencapsulation.

<table>
<thead>
<tr>
<th>Method</th>
<th>Liquid Paraffin (%)</th>
<th>Acetone (%)</th>
<th>CAP (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESE</td>
<td>8–96</td>
<td>3–80</td>
<td>1–5</td>
</tr>
<tr>
<td>MESE</td>
<td>19–96</td>
<td>3–78</td>
<td>1–5</td>
</tr>
<tr>
<td>ENSA</td>
<td>75–96</td>
<td>3–30</td>
<td>1–5</td>
</tr>
</tbody>
</table>

Table II: Effect of microencapsulation method on particle size, percent drug content of the microcapsules, and T_{90%}.

<table>
<thead>
<tr>
<th>Method</th>
<th>Particle Size (μm)</th>
<th>Drug Content (%)</th>
<th>T_{90%} (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESE</td>
<td>1094</td>
<td>67.1 ± 0.6</td>
<td>105 ± 2</td>
</tr>
<tr>
<td>MESE</td>
<td>1045</td>
<td>65.3 ± 0.3</td>
<td>68 ± 8</td>
</tr>
<tr>
<td>ENSA</td>
<td>897</td>
<td>69.9 ± 0.5</td>
<td>99 ± 4</td>
</tr>
</tbody>
</table>

Figure 1: Scanning electron micrograph of paracetamol microcapsules produced by the ENSA method (×50 magnification).

Figure 2: The effect of method of microencapsulation on drug release from microcapsules.
Table II lists the mean sizes of microcapsules produced by the three methods. The ESE method produced significantly larger microcapsules than the other methods as a result of the aggregation of paracetamol particles or the aggregation of small microcapsules.

Figure 2 shows the release of paracetamol from microcapsules obtained by the use of the three methods. Analysis of variance showed that the release of paracetamol from microcapsules was affected by changing the method of microencapsulation \((p < 0.05)\). Figure 2 shows that the drug release from microcapsules prepared by the ESE method produced slower-releasing microcapsules than did the other methods. The time required for 90\% drug release \(T_{90\%}\) calculated for microcapsules prepared by ESE, MESE, and ENSA methods was 105 ± 2, 68 ± 8, and 99 ± 4 min, respectively.

Sprokel and Prapaitrakul also compared the drug release from microcapsules prepared by the use of the three methods (17). They showed that ESE produced slower-releasing microcapsules than did either MESE or ENSA. In their study, the faster drug release with MESE or ENSA microcapsules compared with ESE microcapsules may be a result of the higher drug content of the MESE and ENSA microcapsules. This explanation does not account for the significant differences in drug release between ESE or ENSA and MESE microcapsules in the present study because the microcapsules prepared by MESE had slightly lower drug content than did ENSA and ESE microcapsules, whereas the \(T_{90\%}\) for MESE microcapsules was less than that of the other microcapsules. One could argue that the more rapid solidification of the polymer during microencapsulation with the MESE method results in a more permeable polymer matrix, an outcome that may cause a faster drug release. However, specific permeability studies are necessary to confirm or reject this hypothesis.

To assess process reproducibility, three batches were made with each method. Analysis of variance showed that no significant differences \(p > 0.05\) existed among three batches of microcapsules obtained with each method in terms of microcapsule size, drug content, and \(T_{90\%}\). One could conclude that the differences observed in drug content, microcapsule size, and drug release among the microcapsules are the result of the method used and are not the result of batch-to-batch variation.

**References**


**FYI**

**Call for presentations**

The International Pharmaceutical Industry Congress has announced a call for presentations for inclusion in the education programs at IPIC 2003, also known as Interphex, scheduled for 31 March–2 April 2003 in New York, New York. Topics include but are not limited to automation, bioinformatics, biotechnology, compliance and regulatory issues, and contract services. Abstracts must be 100–200 words and contain original, unpublished noncommercial material that discusses work, case studies, research, or discoveries. The submission deadline is 2 August 2002.

For more information or to submit an abstract, contact Stacie Fuchs, International Pharmaceutical Industry Congress, 383 Main Ave., Norwalk, CT 06851, tel. 203.840.5537, fax 203.840.9537, sfuchs@reedexpo.com, http://pharmacongress.net.