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A comparison of microencapsulation by various emulsion techniques

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Summary

This report presents a comparison between microencapsulation by emulsion-solvent evaporation (ESE), modified emulsion-solvent evaporation (MESE) and emulsion non-solvent addition (ENSA). Paracetamol was microencapsulated with cellulose acetate butyrate using each method, and the microsphere characteristics were compared. The arithmetic mean of the microspheres ranged from 659 ± 131 μm to 783 ± 73 μm. Drug release from microspheres prepared by ESE was significantly slower ($33 \pm 5.6\%$ in 8 h) compared to MESE microspheres ($40 \pm 1.9\%$) or ENSA microspheres ($51 \pm 4.1\%$). The rate of non-solvent addition (1–2 ml/min) did not significantly affect the release profile. The drug content of microspheres prepared by ESE was significantly lower ($77 \pm 1.3\%$) compared to MESE ($83 \pm 1.8\%$) or ENSA ($86 \pm 2.9\%$).

Introduction

The literature contains numerous reports detailing techniques for microencapsulating drug particles with polymers. Several parameters should be considered when comparing the various processes, including microsphere performance, simplicity, and duration of manufacture.

Several recent papers have reported on the emulsion-solvent evaporation (ESE) method of microencapsulation (Mortada, 1982; Pongpaibul et al., 1984; Suzuki and Price, 1985; Chang and Price, 1986). This technique is simple and the factors affecting microcapsule size distribution and drug release are easily modified. In the emulsion-solvent evaporation (ESE) process, a polymer solution containing drug is emulsified in an immiscible polymer non-solvent and polymer deposition around the drug particles occurs as a result of partitioning of the polymer solvent from the dispersed phase to the continuous phase, followed by removal through evaporation (Sprockel and Price, in press; Prapaitrakul and Whitworth, in press). This solvent removal can be a time-consuming process, requiring up to 12 h or more for complete evaporation depending on the batch size and temperature (Pongpaibul and Whitworth, 1986a).

If the rate of solvent extraction from the emulsified polymer solution can be enhanced, the

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ESE process may become more appealing. Sayed and Price (1986) modified the emulsion-solvent evaporation (MESE) process for microencapsulation by adding a fixed volume of a miscible non-solvent to the polymer solution prior to emulsification. A polymer non-solvent is a liquid which does not dissolve the polymer, and which can be miscible or immiscible with the solvent. Incorporation of the non-solvent in the polymer solution resulted in a faster deposition of the polymer.

Alternatively, a non-solvent, which is miscible with both the external phase and the solvent, could be added to the external phase at a constant rate following emulsification of the polymer solution containing drug (Kaeser-Laird et al., 1984; Pongpaibul and Whitworth, 1986b). In this emulsion non-solvent addition (ENSA) technique both the volume of non-solvent and the rate of addition are controlled.

Presumably, one of the major advantages of the MESE and the ENSA methods of microencapsulation over the ESE method is the reduced time required for manufacture. However, a comparison of the MESE and the ENSA methods with the ESE method has not been reported. The purpose of this investigation was to compare the ESE technique with the MESE and the ENSA techniques for microencapsulation of paracetamol particles, using as parameters microsphere size distribution, microsphere drug content, and drug release.

Materials and Methods

Materials

The following materials were used as received from the supplier: *N*-acetyl-*p*-aminophenol (Sigma); cellulose acetate butyrate (17% butyryl, 29% acetyl, and 1.5% hydroxyl content; Eastman Chemical Products, Inc.); acetone, liquid paraffin, hexane, and ethyl acetate (Fisher Scientific); and polyoxyethylene sorbitan monooleate and sorbitan monooleate (ICI Americas, Inc.).

Emulsion-solvent evaporation (ESE)

Cellulose acetate butyrate was dissolved in acetone (solvent) to form a 6% solution. The paracetamol particles were dispersed in the polymer solution at a drug : polymer (D : P) ratio of 3 : 1 (internal phase). The external phase consisted of liquid paraffin at 25 °C containing 1% sorbitan monooleate. The drug dispersion was emulsified in the liquid paraffin solution at 1400 rpm and agitation was continued at 25 °C until all the polymer solvent (acetone) had evaporated under normal atmospheric pressure (approximately 12 h). The same manufacturing conditions of temperature, pressure and rate of agitation (rpm) were duplicated for the MESE and ENSA methods (see below). The microspheres were collected, washed twice with 100 ml of hexane to remove any remaining oily phase, and dried under reduced pressure for at least 24 h. The characteristics of the ESE microspheres were used as a basis for comparison with microspheres prepared by the MESE and the ENSA method.

Modified emulsion-solvent evaporation (MESE)

The procedure for MESE was similar to the ESE process, except that hexane (non-solvent) was added dropwise to a 6% CAB in acetone (solvent) solution containing dispersed paracetamol (D : P, 3 : 1) over a 15 min period, with gentle agitation by a magnetic stirrer. The acetone to hexane ratio was 4 : 1. Following emulsification of the drug dispersion in the liquid paraffin/sorbitan monooleate solution, the acetone and hexane were evaporated under conditions similar (25 °C, 1400 rpm) to ESE for approx. 8 h. Microsphere collection, washing and drying was as described for ESE.

Emulsion non-solvent addition (ENSA)

Paracetamol was dispersed in a 6% CAB in acetone (solvent) solution as described for ESE. The drug dispersion was emulsified in a liquid paraffin/sorbitan monooleate solution under similar conditions (25 °C, 1400 rpm). After 5 min, 60 ml of hexane (non-solvent) were added to the emulsion under constant agitation at a rate of 1 ml/min (ENSA-1) or 2 ml/min (ENSA-2). Following complete addition of the hexane (0.5–1 h), the microspheres were collected, washed and dried as described for ESE.

Process reproducibility

To establish process reproducibility, duplicate batches of microspheres were prepared by each of the three methods. Variation in the percent drug release, drug content and particle size was used as a parameter to evaluate reproducibility.

Microsphere characterization

The microspheres were placed on a standard nest of sieves and vibrated for 5 min; the arithmetic mean diameters were calculated.

For each batch of microspheres triplicate samples of microspheres with a mean diameter of 512 μm (425–600 μm) were subjected to drug release studies using an aqueous solution of polyoxyethylene sorbitan monooleate (0.02%) at 37 ± 0.5 °C with an agitation rate of 100 ± 1 rpm. Periodic samples were assayed spectrophotometrically at 260 nm for their drug content.

To determine the drug content 4 samples of microspheres (425–600 μm) from the same batch were placed in 250-ml separatory funnels. Ethyl acetate (20 ml) was added and gentle agitation was used to dissolve the CAB polymer. HCl (0.1 N, 100 ml) was then added and the drug was allowed to partition with intermittent agitation for 24 h. The drug contents of the aqueous layers were determined by spectrophotometry at 260 nm.

Paracetamol stability

Since paracetamol was in contact with several organic solvents during the microencapsulation process, degradation of the drug in the presence of these solvents was a possibility. For this reason the stability of paracetamol in these solvents was investigated. Triplicate samples of paracetamol (20 mg) were dissolved/suspended in 30 ml of acetone, hexane, or ethyl acetate in 100-ml volumetric flasks and allowed to stand for 24 h at 25 °C. HCl (0.1 N, 50 ml) was added and the organic solvents were evaporated under reduced pressure at 25 °C; the volume was made up to 100 ml with 0.1 N HCl. In addition, aqueous solutions of paracetamol in distilled water and 0.1 N HCl were stored at 25 °C for 24 h. The ultraviolet spectra of these stored solutions were similar to the corresponding spectra of freshly prepared aqueous solutions of paracetamol.

Statistical analysis of the data

The drug contents of and percentages of drug released from microspheres prepared by the different methods were analyzed by a one-way analysis of variance with a protected least significant difference test ($P = 0.05$). The characteristics from duplicate microsphere batches were compared using a studentized t-test ($P = 0.05$).

Results and Discussion

Microsphere formation

The three methods of microencapsulation (ESE, MESE, and ENSA) have in common the emulsification of the polymer solution containing dispersed drug in an immiscible external phase (in this case the liquid paraffin solution). The microsphere size distribution depended on the droplet size of the emulsion and on the extent of aggregation between forming microspheres. Polymer deposition within the droplets occurred through the removal of the polymer solvent. Upon complete removal of the solvent, solid microspheres of CAB containing paracetamol resulted. The method of solvent removal differed between the three methods.

In the ESE method solvent removal was accomplished by evaporation at room temperature and pressure. The polymer solvent, acetone, was soluble in liquid paraffin to a limited extent. Upon emulsification of the polymer solution 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. The rate of acetone partitioning depended on the size of the emulsion droplets, since partitioning is a surface area phenomenon. The partitioned acetone in the external phase evaporated from the surface and was replaced by a further partitioning of acetone. Therefore, the rate of solvent removal was dependent upon the rate of solvent partitioning and evaporation.

The hexane added to the polymer solution in the MESE method was miscible with both the acetone and the liquid paraffin. After emulsification the hexane probably partitioned into the liquid paraffin, thereby increasing the affinity of the

external phase for acetone. The initial rate and the extent of acetone partitioning into the external phase may have been increased by the hexane. An increased partitioning of acetone into the liquid paraffin would have increased the rate of solvent removal. Once the hexane evaporated the partitioning of acetone became similar to that for the ESE method. The added hexane reduced the preparation time from 12 to 8 h. In this method the rate of solvent removal depended ultimately on acetone evaporation, but the initial affinity of the external phase was temporarily increased.

In contrast, solvent removal in the ENSA method does not depend on acetone evaporation, but rather on the non-solvent present in the external phase. The rate of non-solvent addition far exceeds that of solvent evaporation; therefore, the rate of solvent extraction from the droplets was controlled by the rate of non-solvent addition. Upon complete addition of the non-solvent, solid microspheres were collected even though the external phase contained acetone. The time required for microsphere preparation by the emulsion technique was drastically reduced by the addition of the non-solvent.

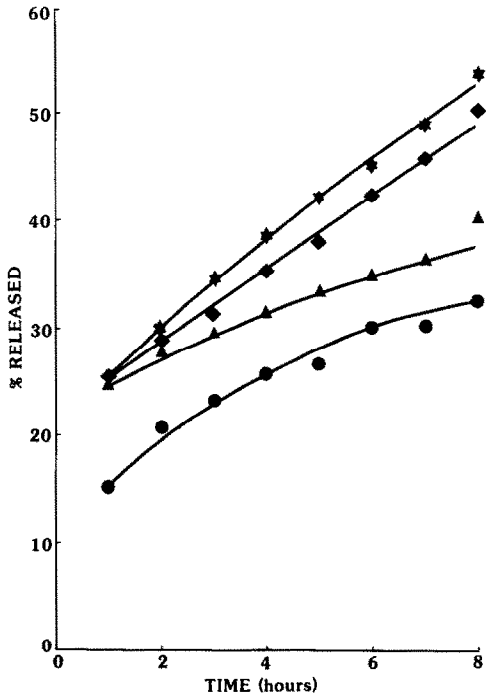

Fig. 1. Effect of method of microencapsulation on drug release from microspheres. Key: (●) ESE; (▲) MESE; (◆) ENSA-1; (★) ENSA-2.

Microsphere size distribution

The arithmetic mean size of microspheres produced by the ESE or the ENSA methods was comparable, whereas the arithmetic mean size of microspheres obtained by the MESE method was smaller (see Table 1). With the ESE and ENSA methods the internal polymer phase was identical with similar viscosities. The addition of hexane to the polymer solution in the MESE method lowered the viscosity of the internal phase. This difference in viscosities may be responsible for the disparity in mean sizes of microspheres, by influencing the size distribution of droplets formed upon emulsification of the polymer solution into the external phase. Interestingly, microspheres prepared by ENSA with non-solvent addition rates of 1 or 2 ml/min had very similar mean sizes, indicating that the addition rates studied had little influence on size distribution (see Table 1).

TABLE 1

Effect of microencapsulation method on particle size (μm), percent drug released in 8 h (R_8) and percent drug content (DC) of the microspheres (mean ± SD)

Method	Size	R_8	DC
ESE	769	33 ± 5.6	77 ± 1.3
MESE	659	40 ± 1.9	83 ± 1.8
ENSA-1	783	51 ± 4.1	86 ± 2.9
ENSA-2	781	53 ± 1.7	84 ± 5.1
LSD *		6.0	4.8

* Least significant difference at $P = 0.05$ calculated from the ANOVA.

Microsphere drug content

The drug contents of microspheres (425–600 μm) prepared by the different methods is listed in Table 1. No significant difference was seen between drug contents of microspheres prepared with the MESE or ENSA method. The drug contents of microspheres resulting from the ESE method was significantly lower. The ESE microspheres had a drug content close to the theoretical value (75%), indicating that some polymer loss occurred with

the MESE or ENSA method. The polymer loss may be due to the excess acetone (solvent) maintained in the external phase by the hexane (non-solvent).

Microsphere drug release

In comparing the drug release from microspheres prepared by the different methods it is apparent that ESE produced slower releasing microspheres than either MESE or ENSA (see Fig. 1). However, no significant difference existed between the percentages of drug released at 8 h (R_8) from microspheres prepared with ENSA at different addition rates. The differences in R_8 between methods were significant.

The faster drug release with MESE or ENSA microspheres compared to ESE microspheres may be due to the higher drug content of the MESE and ENSA microspheres. This explanation will not, however, account for the significant difference in drug release between MESE and ENSA microspheres, since there is no significant difference between their drug contents (see Table 1). It can be argued that the more rapid solidification of the polymer during microencapsulation with the ENSA method may result in a more permeable polymer matrix, which may cause a faster drug release. Specific permeability studies are, however, necessary to confirm or reject this hypothesis.

Process reproducibility

To ensure that the observed differences in drug release between the microspheres were real differences, attributable to the methods used, and were not due to batch-to-batch variation, duplicate batches were made with each method. In comparing the percentages of drug released at each time point, drug content and arithmetic mean diameter, no significant differences were detected between the duplicate batches.

Conclusion

The incorporation of the polymer non-solvent in the emulsion-solvent evaporation technique (ESE) for microencapsulating small particles did significantly reduce the preparation time required. Significant increases were detected in the drug contents of and drug release from microspheres prepared by the MESE or ENSA methods. These differences were not sufficiently large, however, to invalidate the MESE and ENSA methods, and with careful optimization microspheres with the desired characteristics can be prepared in a relatively short time.

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