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# PHASE DIAGRAM STUDIES OF MICROCAPSULE FORMATION USING HYDROXYPROPYL METHYLCELLULOSE PHTHALATE

Gregorio Garcia Encina†, Suketu P. Sanghvi‡
and J. Graham Nairn*‡
†Universidad de Santiago de Compostela, Laboratorio de Farmacia Galenica, Facultad de Farmacia, Santiago de Compostela, España and
‡Faculty of Pharmacy, University of Toronto, Toronto, Ontario, Canada M5S 2S2.

## ABSTRACT

Microcapsules of hydroxypropyl methylcellulose phthalate were prepared using a non-aqueous emulsion method. The study was designed to determine the region of microcapsule formation in the ternary system of mineral oil, acetone and polymer and to present the data by means of phase diagrams. Increasing amounts of sorbitan monooleate were added to mineral oil to determine the effect of surfactant concentration on the phase diagram. The effect of sorbitan monooleate, sorbitan trioleate and sorbitan monolaurate on the microcapsule region of the phase diagram

* to whom inquires should be addressed

was also investigated. Particle size analysis was carried out to determine if the concentration and type of surfactant used had a significant effect on the size of the microcapsules obtained. Tartrazine was encapsulated as a model drug and its dissolution was studied in acidic and neutral mediums. The results indicate that the addition of sorbitan monooleate increased the microcapsule region of the phase diagram and sorbitan trioleate had a similar effect. However, the microcapsule region in the phase diagram decreased when sorbitan monolaurate was used. The particle size increased with increasing concentration of polymer, irrespective of the type and concentration of surfactant used.



## INTRODUCTION

Hydroxypropyl methylcellulose phthalate (HPMCP) is an enteric polymer with low toxicity[1] and is available in various grades. The grade of HPMCP used in this research was HP–55, which has a phthalyl content of 32.8%, methoxy content of 19.0% and hydroxypropyl content of 5.8%.[2] This polymer has been used in several pharmaceutical formulations to control drug delivery.[3–4] There are numerous reports describing methods for using this polymer for microencapsulation. For example, pan coating has been utilised to microencapsulate pharmaceuticals for X–ray diagnosis of intestinal diseases.[5] The gastric resistance of microgranules prepared by spray drying was found to be a function of polymer concentration and type, and concentration of plasticiser used.[6] Materials that are heat and pH sensitive have been coated with the polymer, by dissolving it in acetone/methanol mixture and forming an emulsion with liquid

paraffin.[7] Enzymes such as Cytochrome C have been dispersed in olive oil and emulsified with the polymer dissolved in dichloroethane/ethanol mixture to prepare sustained release products.[8] Hydroxypropyl methylcellulose phthalate is structurally similar to cellulose acetate phthalate and cellulose acetate trimellitate. Solvent systems which are used with the two preceding polymers can be generally used for HPMCP. However, due to the presence of hydrophobic groups, propyl and methyl, the hydrophobic component of the solvent system eg. dichloroethane, may need to be increased to provide a greater solubility for HPMCP.

This research describes some parameters that affect the microencapsulation procedure using HPMCP using the non-aqueous emulsion technique. Parameters such as appropriate concentration of HPMCP, solvent and dispersion medium were determined from the phase diagram. Also, the effect of the type of surfactant and its concentration were studied. Phase diagrams were prepared to define the region of microcapsule formation and to indicate the effect of the surfactant on the microcapsule region. Microcapsule size and shape analysis were carried out. Tartrazine was encapsulated as a model drug and its dissolution was studied in acidic and neutral solutions.

## MATERIALS AND METHODS

### Materials

Hydroxypropyl methylcellulose phthalate (grade HP-55) was obtained from Biddle Sawyer Corp., New York, N.Y.; sorbitan monooleate, sorbitan monolaurate and sorbitan trioleate (Span 80, Span 20

and Span 85) were obtained from Atkemix Inc., Toronto, Canada; tartrazine and light mineral oil were obtained from British Drug House, Toronto, Canada; petroleum ether (35–60°C) and acetone were obtained from Caledon Chemicals, Georgetown, Canada. The chemicals and solvents were used as received.

Preparation of Phase Diagrams

Varying amounts of the dispersion medium, light mineral oil containing various amounts of sorbitan monooleate (0, 0.5, 1.0 and 3.0% w/w), were added to a round-bottomed reaction kettle. The reaction kettle was equipped with a cover to minimise evaporation and the cover had a port through which the stirrer shaft passed into the dispersion medium. The dispersion medium was stirred at 500 rpm with a stainless steel propeller type blade (5 x 1 cm). Various amounts of HPMCP solution (5, 8, 10, 12 or 15% w/w) in acetone were added by means of an Eppendorf repeator pipette. Following addition of the polymer solution, various quantities of acetone were immediately added to the dispersion medium, as required, to adjust the solvent concentration for the phase diagram studies. The dispersion was stirred for 30 min, following which 100 mL of petroleum ether was rapidly added to the system. Addition of petroleum ether causes hardening of the microcapsules by facilitating the removal of the polymer solvent into the mineral oil phase. The mixture was stirred for an additional 15 min then the liquid was decanted and the product was filtered by suction, washed with two 30 mL portions of petroleum ether and air dried for 12 h. To study the effect of surfactants with different hydrophile:lipophile balance (HLB) on the microcapsule region of the phase diagram, sorbitan monolaurate and sorbitan trioleate were

incorporated at 1% w/w concentration into mineral oil. Phase diagrams were prepared using the same conditions as that for 1% w/w sorbitan monooleate.

Microencapsulation of Tartrazine

Tartrazine (100 mg) was dispersed in 100 mL of mineral oil containing 0, 0.5, 1.0 and 3.0% w/w of sorbitan monooleate. The mixture was stirred at 500 rpm and then 10 mL of 10% w/w HPMCP in acetone was added to the reaction kettle. Immediately following the addition of the polymer solution, 4 mL of acetone were added to the system in every case. The mixture was stirred for 30 min. The rest of the procedure for preparation of the microcapsules was the same as that described above for the phase diagrams.

Particle size analysis

Particle size analysis was carried out on blank microcapsules using an optical microscope. Microscopic examination (Carl Zeiss, Jenaval system) was used to assess the surface texture, pinholes and amount of aggregation. Mean diameters and standard deviations on 50 particles are reported in Table I.

Dissolution of microcapsules

A slightly modified U.S.P. XXII paddle method for Enteric Coated Articles was used to determine the dissolution properties of microencapsulated tartrazine using hydrochloric acid (750 mL of 0.1M) as the initial dissolution medium. The temperature of the solution was maintained at 37°C and it was stirred at 100 rpm throughout the dissolution process. Microcapsules (500 mg) containing tartrazine were added and 10 mL samples of the dissolution medium were withdrawn without replacement. The sampling times were 10, 20, 30, 60 and 120 min

TABLE 1

Mean Diameters and Standard Deviations of Microcapsules

| % Surfactant | A[a] (μm ± SD) | B[a] (μm ± SD) | C[a] (μm ± SD) | D[a] (μm ± SD) |
|---|---|---|---|---|
| 0 | 294.5 ± 112.9 | 584.9 ± 225.5 | 654.0 ± 190.4 | 758.7 ± 158.6 |
| 0.5 | 318.4 ± 139.0 | 385.6 ± 152.1 | 749.4 ± 137.5 | 864.0 ± 141.6 |
| 1.0 | 352.1 ± 98.0 | 410.2 ± 109.4 | 622.7 ± 159.8 | 922.8 ± 132.6 |
| 3.0 | 342.0 ± 66.32 | 428.6 ± 87.7 | 643.8 ± 69.8 | 190.7 ± 79.3 |

[a]Composition : (A) 0.7% HPMCP and 86.7% mineral oil; (B) 1.0% HPMCP and 86.6% mineral oil; (C) 1.3% HPMCP and 86.5% mineral oil; (D) 0.87% HPMCP and 88.04% mineral oil, 100 mg of tartrazine.



after addition of microcapsules. At the end of 120 min, 250 mL of $Na_3PO_4$ (0.2 M) were added to the 700 mL of HCl solution remaining in each flask. The pH was adjusted if necessary, to 6.8 ± 0.05 with 2 M HCl or 2 M NaOH. Samples (10 mL) were withdrawn without replacement at 135, 150 and 210 min from the start of the experiment. The samples were stored in teflon lined screw cap test tubes and analysed immediately after the experiment was completed.

Assay

Tartrazine was assayed at 450 nm spectrophotometrically. A standard curve was prepared for tartrazine in 0.1 M HCl solution, ranging from 1 μg up to 80 μg/mL. The concentrations of tartrazine in acidic solutions from the dissolution experiments, were measured

directly . The neutral solutions were treated with 2 mL of 2 M HCl, vortexed and centrifuged to remove the precipitated HPMCP and the supernatant solution was then analysed.

Scanning Electron Micrographs (SEM)

Microcapsules were fastened by embedding, using silver epoxy glue, to a holder and then gold–sputtered coated for 190 s. All photographs were taken using Ilford FPX 120, 125 ASA film on a Hitachi Scanning Electron Microscope (Model S-250) at 20 kV and x 30 magnification.

## RESULTS AND DISCUSSION

Solubility of HPMCP was examined in acetone, chloroform, methylene chloride and petroleum ether. The polymer has some solubility in chloroform and methylene chloride and therefore these two solvents were not used as a non–solvent (or hardening agent) for HPMCP. Petroleum ether did not dissolve the polymer and was used as the hardening agent. Acetone dissolves HPMCP readily and gave a clear solution of low viscosity and was used as the solvent for HPMCP.

The duration of stirring after the addition of the polymer was set at 30 min as this usually provided sufficient time for formation of microcapsules to be complete.

Phase diagrams

The phase diagrams were based on the percent w/w concentrations of the components. The concentration of mineral oil phase, polymer and solvent for Figures 1A–1E were always the same for a given experimental point. This enables a direct comparison to be made

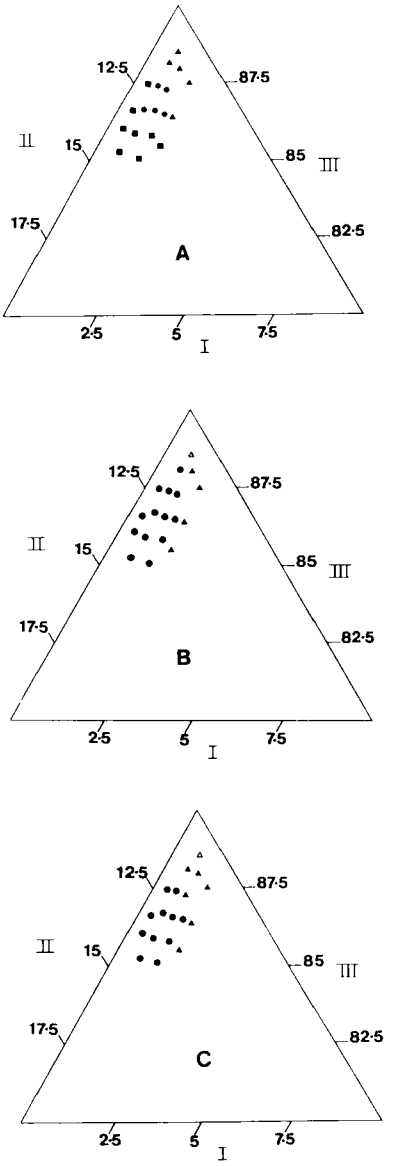



FIGURE 1

Ternary Diagrams of Phase Regions in the HPMCP plus light mineral oil plus acetone system in the presence of 0% (w/w) sorbitan monooleate (A), 1.0% (w/w) sorbitan monooleate (B), 3.0% (w/w) sorbitan monooleate (C), 1.0% (w/w) sorbitan monolaurate (D), and 1.0% (w/w) sorbitan trioleate (E). KEY: (I) HPMCP; (II) acetone; (III) light mineral oil; (■) aggregate region; (▲) gel phase region; (●) microcapsule region and (△) precipitate region.

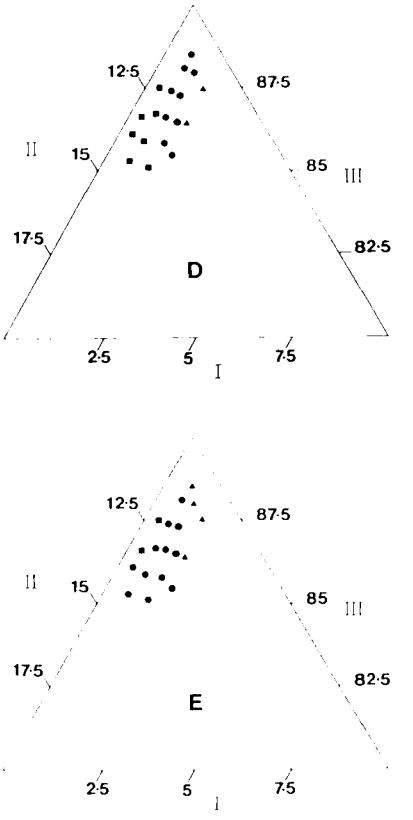



Figure 1 (continued)

of the product obtained with increasing amounts of surfactant and different surfactants used. The experimental points in the phase diagrams were classified on the basis of the product obtained after adding 100 mL of petroleum ether to the system and the products obtained were a) microcapsules b) aggregates of microcapsules c) precipitate and d) gel.

The microcapsule region of the phase diagram in Figure 1A, indicates that microcapsules can be formed when the concentration of

HPMCP is between 0.5 and 1.5% and the range of solvent concentration is between 11.5 and 12.5%. The aggregate region of the phase diagram represents a region of low HPMCP concentration and high acetone concentration. In this region of the phase diagram, small microcapsules could be seen in the mineral oil. However, upon addition of petroleum ether, the small microcapsules joined together to form aggregates. The precipitate region of the phase diagram represents a region of low polymer concentration and high concentration of mineral oil. The acetone present keeps the polymer in solution and the internal phase remains dispersed in mineral oil. Addition of petroleum ether, effects the precipitation of the polymer and the subsequent hardening results in small strands of the polymer as the final product. The gel phase occurs almost immediately after addition of HPMCP solution to mineral oil because there is relatively high concentration of HPMCP and/or mineral oil. The mineral oil can dissolve some acetone, thus removing it from the polymer solution. This creates a very viscous mixture that cannot be dispersed easily in the mineral oil and produces a clumped mass of polymer. Addition of petroleum ether hardens the clumped mass in to the form of a gel.

Figure 1 indicates the region of microcapsule formation in the phase diagrams. As the concentration of sorbitan monooleate is increased from 0 to 3% (Figures 1A–1C), the microencapsulation region is increased in the region of low mineral oil and high HPMCP concentration. The aggregate region (Figure 1A) is not seen in Figures 1B and 1C and has been replaced by the microcapsule region. A possible reason, for the aggregate region changing to microcapsule region upon addition of surfactant, could be that the surfactant is

adsorbed on to the surface of the microcapsules and thus prevents microcapsules from joining together. An observation supporting this hypothesis is the yellow colouration of the microcapsules, indicative of the presence of the surfactant in the microcapsules when 3% sorbitan monooleate is used in mineral oil. Figures 1B and 1C, representing 1 and 3% sorbitan monooleate have similar microcapsule regions in the phase diagrams except in the region of high mineral oil concentration where gel formation has increased slightly with the 3% surfactant.

Additional phase diagrams were drawn from data obtained by using 1% sorbitan monolaurate (Figure 1D) with an HLB value of 8.6 and with 1% sorbitan trioleate (Figure 1E) with an HLB value of of 1.8, in light mineral oil. The phase diagrams illustrating the incorporation of 1% sorbitan monooleate or sorbitan trioleate show somewhat similar regions of microencapsulation. It should be noted that when sorbitan monolaurate, a more hydrophilic agent, was used, the encapsulation region decreased significantly. Furthermore, the aggregate region, that was not seen with 1% sorbitan monooleate, is present when sorbitan monolaurate or sorbitan trioleate is used.

Particle size and microcapsule characterisation

Three specific concentrations (a) 0.7% HPMCP and 86.7% mineral oil; (b) 1.0% HPMCP and 86.6% mineral oil; (c) 1.3% HPMCP and 86.5% mineral oil, were selected to represent different areas within the microencapsulation region of the phase diagram in order to assess particle size and shape. The average particle sizes and standard deviations are given as a function of polymer and surfactant concentration in Table 1. Increasing the concentration of surfactant did not

have an appreciable effect on the particle size. However, when the polymer concentration was increased, at constant surfactant concentration, the particle size of the microcapsules increased significantly. This phenomenon of increased particle size with increasing polymer content was observed at all surfactant concentrations.

The blank microcapsules were examined under microscope for surface texture and shape. The shape of all these microcapsule were spherical regardless of whether they were single or in aggregated form. They had hollow cores, as noted with cellulose acetate phthalate[9] and cellulose acetate trimellitate[10] and had some depressions on the surface. Small microcapsules of ≤ 10 μm size, which were not counted in the particle size analysis, could be seen sticking to the surface of the larger microcapsules. These aggregated microcapsules, were not only smaller in size but also had smoother surface, when compared to large microcapsules.

Particle size analysis of tartrazine containing microcapsules

Particle size analysis of tartrazine containing microcapsules is listed in column D of Table 1. The particle size of the microcapsules increased when the surfactant concentration was increased from 0 to 1%. but decreased considerably from 922 μm to 190 μm when 3% surfactant is used.

The tartrazine containing microcapsules were spherical with hollow cores and depressions on the surface. Unlike the blank microcapsules, the tartrazine microcapsules were not aggregated. The encapsulated tartrazine was dispersed throughout the polymer matrix and occasionally some tartrazine particles could be seen on the surface of the microcapsules.

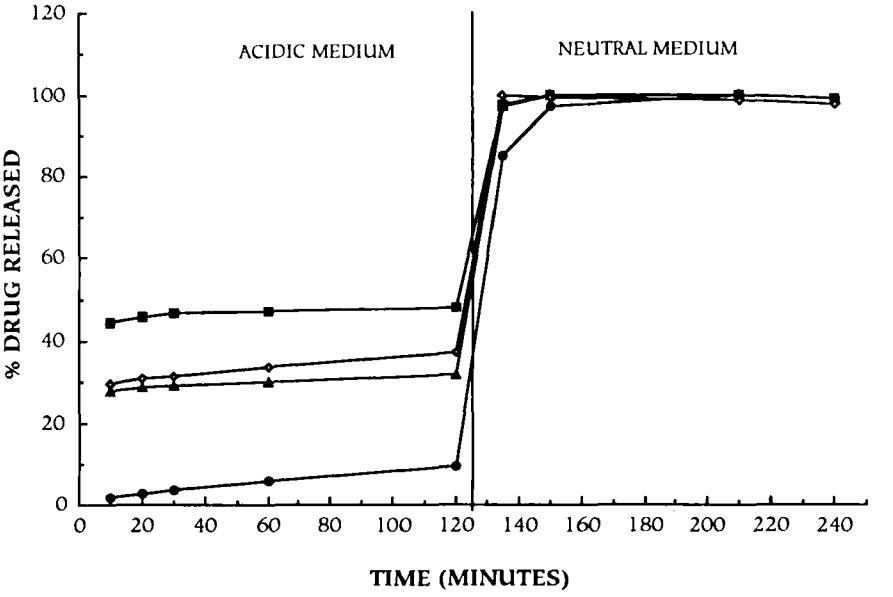



FIGURE 2
Average Percent Drug Release as a function of time for tartrazine-containing microcapsules. KEY: (●) 0% (w/w) sorbitan monooleate; (■) 0.5% (w/w) sorbitan monooleate; (▲) 1.0% (w/w) sorbitan monooleate; and (◇) 3.0% (w/w) sorbitan monooleate.

## Dissolution experiment

Tartrazine was chosen as the model drug since small concentrations can easily be detected using a spectrophotometer. Percent drug released, based on total drug released at 240 min, was plotted against time (Figure 2). HPMCP has been reported to dissolve at a pH of approximately 5.5.[11] In the present study, after the pH of the dissolution medium was rapidly adjusted to a pH of 6.8 from a pH of approximately 1.5, the microcapsules dissolved and released the tartrazine completely by 150 min. The dissolution was continued for an additional 90 min, during which time no further appreciable release of tartrazine was observed.

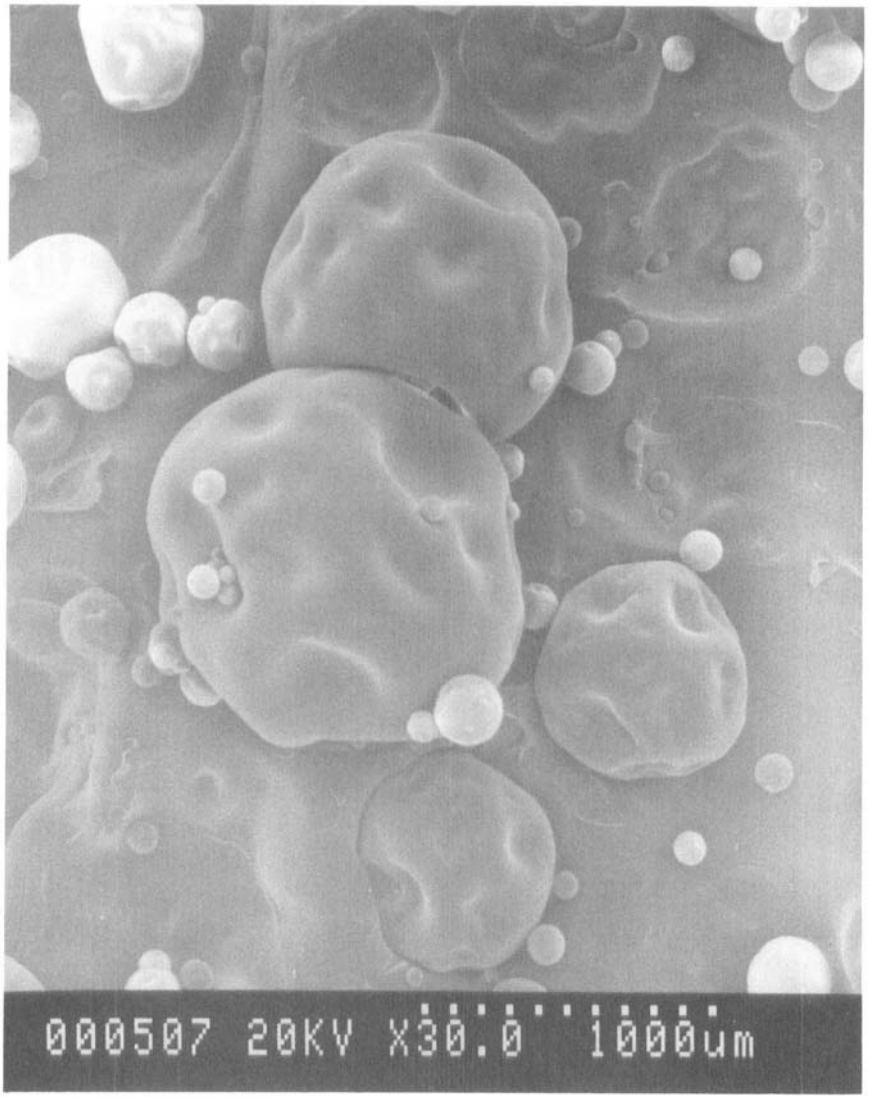
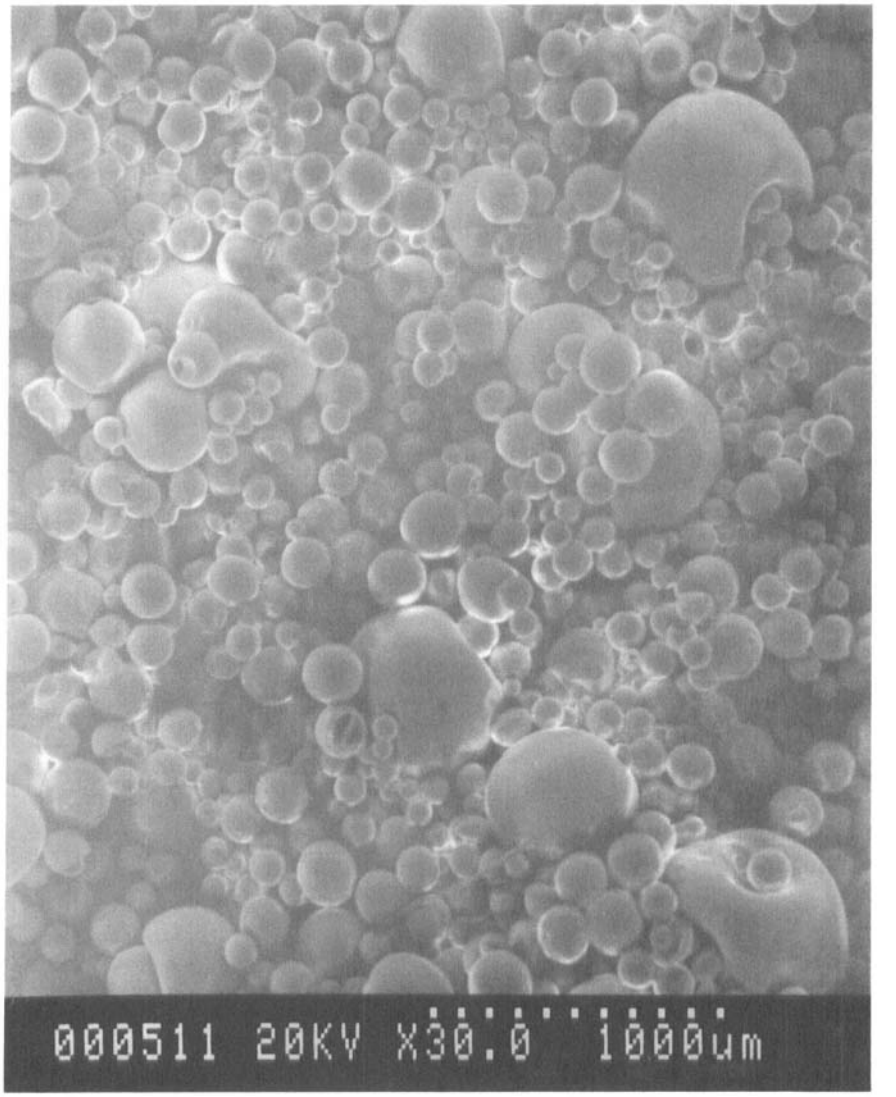


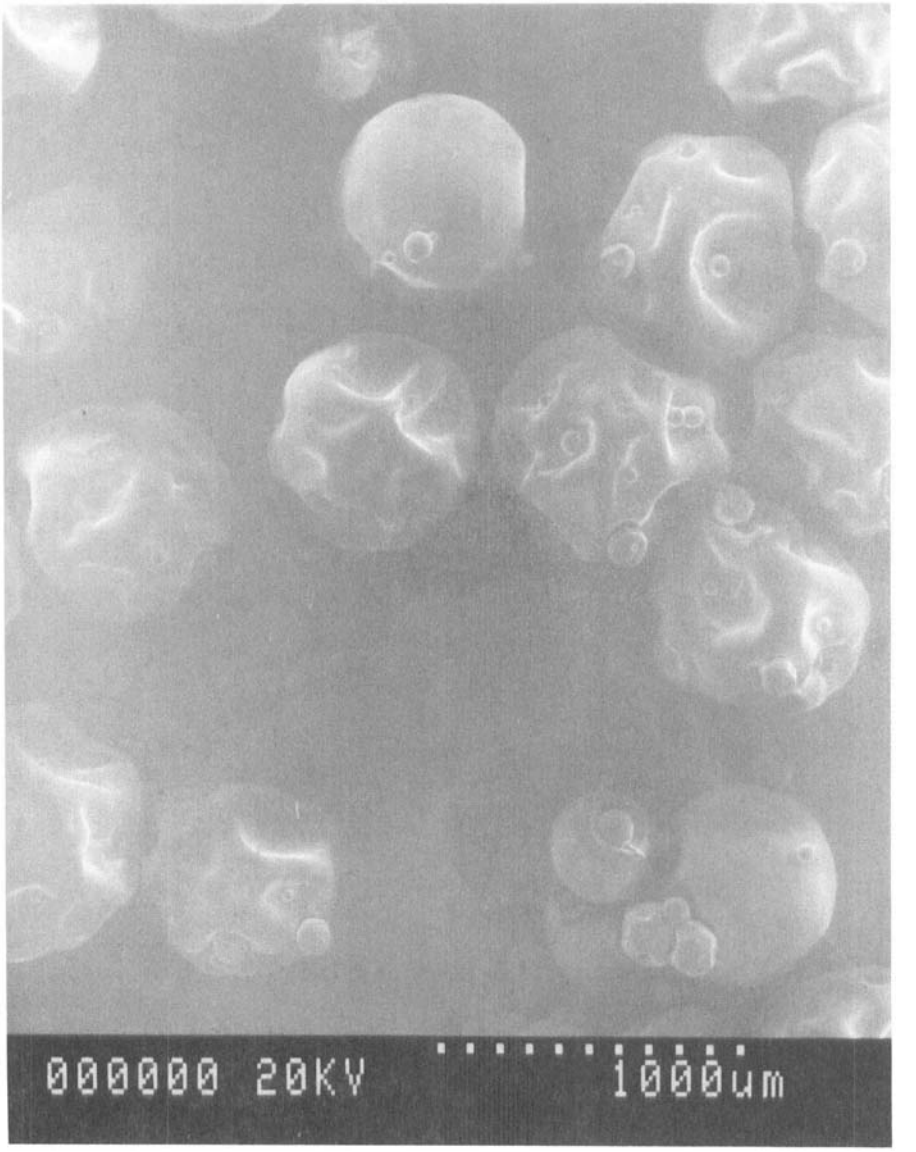

FIGURE 3
Scanning Electron Micrograph of microcapsules. Composition: (A) 100 mL light mineral oil; 6 mL acetone and 10 mL of 15% (w/w) HPMCP in acetone, (B) 100 mL light mineral oil; 6 mL acetone and 10 mL of 8% (w/w) HPMCP in acetone, (C) 100 mL light mineral oil; 4 mL acetone; 10 mL of 10% (w/w) HPMCP in acetone and 100 mg of tartrazine.

Figure 3 (continued)




(continued)

Figure 3 (continued)



The U.S.P. method was modified to allow repeated sampling, to permit investigation of drug diffusion through the polymer in the acidic medium. There was a sudden release of tartrazine ranging from 5% tartrazine with 0% surfactant, up to 45% tartrazine with 0.5% surfactant, probably from the dye embedded in the surface of the microcapsules. This sudden release was followed by slow diffusion of drug from the drug likely embedded just at or under the surface of microcapsules. The drug release in acidic medium was slowest for samples containing 0% surfactant. The extent of drug release in the acidic medium increased when surfactant had been incorporated into the encapsulation medium. The increase of pH of the dissolution medium causes rapid release of the drug, due to dissolution of the microcapsules. The percent dye released then increased sharply and almost total release of the dye was obtained after 15 min of stirring in the neutral medium.

Scanning electron micrograph

The SEM photographs confirm the visual observations made above. The SEM of blank microcapsules shows the depressions on the surface of microcapsule, along with smaller microcapsules (~10 μm) adhering to the surface, as seen in Figure 3A. The smoother surface of the aggregates, as compared to larger microcapsules, can be seen in Figure 3B. The tartrazine containing microcapsules were also spherical and had depressions on the surface, as seen in Figure 3C. The depressions on the surface of the microcapsules could be explained on the basis of rapid hardening of the polymer, due to removal of acetone causing the polymer to shrink, when 100 mL of petroleum ether was added.

## CONCLUSIONS

1. The microcapsule region of the phase diagram indicates that the HPMCP concentration should be between 0.5 and 1.5%, the acetone concentration should be between 11.5 and 12.5%.
2. Addition of sorbitan monooleate increased the microcapsule formation region on the phase diagram.
3. Addition of the hydrophilic surfactant decreased the microcapsule formation region on the phase diagram.
4. Blank microcapsule size increased with increasing concentration of polymer, but was not affected by a change in surfactant concentration.
5. There was a sudden release of tartrazine in acidic pH, followed by a slow diffusion of the drug. Upon increasing the pH of the medium to 6.8, complete dissolution was obtained in 30 min in all cases.



## ACKNOWLEDGEMENTS

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