Factors Influencing Microencapsulation of a Waxy Solid by Complex Coacervation

P. L. MADAN, L. A. LUZZI, and J. C. PRICE▲

Abstract □ Microencapsulation of stearyl alcohol particles by complex coacervation in a gelatin–acacia system was studied. Spherical particles of solid stearyl alcohol were prepared by vibrating reed and vibrating capillary methods. Encapsulation was attempted on several size fractions of these particles by conventional procedures, but only particles below 250 μ in diameter were encapsulated. A modified procedure was developed to encapsulate particles larger than 250 μ. Microscopic observations indicated that the coacervate droplets had little affinity for the stearyl alcohol particles and that encapsulation of smaller particles was apparently accomplished by aggregation and coalescence of several droplets around the particles. Encapsulation of particles larger than 250 μ by the modified procedure was possibly the result of the direct interaction of gelatin with acacia on the surface of the particles.

Keyphrases □ Microencapsulation of waxy solid (stearyl alcohol) by complex coacervation—effect of colloid concentration and particle size □ Waxy solids, encapsulation by complex coacervation—stearyl alcohol in gelatin-acacia system, effect of colloid concentration and particle size □ Coacervation, complex—microencapsulation of stearyl alcohol in gelatin-acacia system

Microencapsulation is finding increased use in pharmaceuticals from the clinical as well as therapeutic aspects. Among the various methods used for microencapsulation, complex coacervation is one of the oldest methods known and has been used for a wide variety of applications (1).

The literature concerning microencapsulation is not extensive, and most of it comes from company brochures or U. S. patents. Apparently there are no reported attempts to study the problems encountered in encapsulating waxy solids. Therefore, this investigation was undertaken to: prepare spherical particles of a solid waxy material; encapsulate the particles by the process of complex coacervation; collect the encapsulated particles in the form of free-flowing, discrete particles; and study selected factors relating to the formation of microcapsules.

EXPERIMENTAL

Materials—The materials used were: acacia USP, pigskin gelatin[1] with an isoelectric point at pH 8.0, stearyl alcohol USP, polysorbate 20[2], and a polyelectrolyte dispersing agent[3].

Preparation of Particles to Be Encapsulated—Of the several methods examined for the production of spherical monodispersed particles, two were adopted for the production of stearyl alcohol particles. A method similar to that described by Wolf (2), using a vibrating reed dipped into liquefied material, was used to make particles up to 200 μ in diameter. The apparatus used is illustrated schematically in Fig. 1. Particles larger than 200 μ in diameter were prepared using a vibrating capillary apparatus similar to that described by Mason *et al.* (3). The apparatus used for this vibrating capillary method is illustrated schematically in Fig. 2.

A nest of sieves was employed for the separation of particles in various size ranges. Particles passing through one sieve and retained on the next finer sieve were assigned the arithmetic mean size of the two screen openings. Sieve numbers 200, 170, 100, 80, 60, and 40 were used to obtain particles having average diameters of 81, 163, 213, and 335 μ. The particles thus obtained were spherical in shape and had a predictably narrow size distribution.

Microencapsulation Procedure—The initial procedure used for microencapsulation reported in this study was essentially based on the one used by Luzzi and Gerraughty (4) and can be summarized as taking place in four steps: (*a*) establishment of a system with the liquid vehicle containing the coating materials as a continuous phase and the material to be encapsulated as a dispersed phase, (*b*) changing the dispersion characteristics of the colloids to cause phase separation of the wall material, (*c*) deposition of the liquid colloidal wall material as a continuous coating about the dispersed material to be coated, and (*d*) hardening of the deposited coating material.

All experiments were conducted under experimentally identical conditions. The gelatin and acacia solutions were prepared by dissolving, separately, equal quantities of gelatin and acacia in 20 ml. of distilled water. These solutions were allowed to hydrate for at least 12 hr. before being used. Coacervation was carried out at 40° using a water bath maintained at 40 ± 1°.

A known weight of the solid stearyl alcohol particles was dispersed in acacia solution by gentle stirring. Gelatin solution was added to this dispersion, and the encapsulation procedure described by Luzzi and Gerraughty (4) was followed, except that after denaturation of the coagulated gelatin–acacia complex with formaldehyde, the mixtures were diluted with distilled water so that the combined colloid strength was not more than 1%. The chilled solids were then recovered from the coacervation mixture by suspending the filtered mass in 70% isopropanol. The mixture was filtered again through a coarse filter paper and air dried at room temperature to yield free-flowing, discrete particles.

The entire process was observed microscopically to determine if encapsulation was taking place. In the case of 335-μ particles where

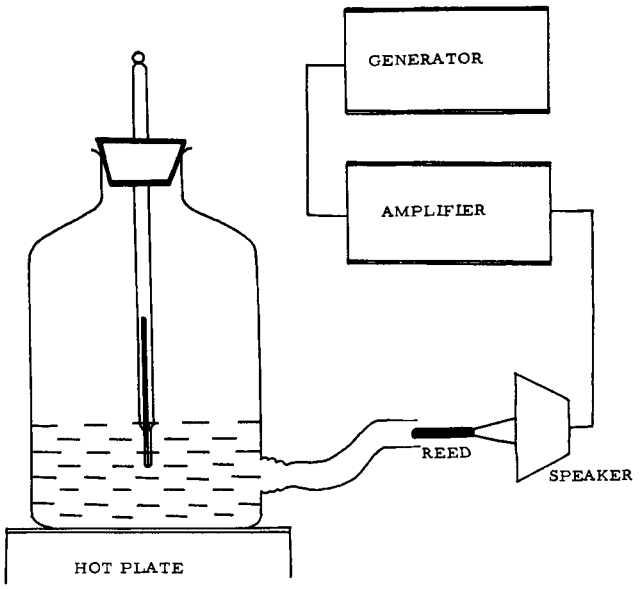

Figure 1—*Schematic diagram of vibrating reed apparatus for making spherical particles.*

[1] The American Agricultural Co., Detroit, Mich.
[2] Tween 20, Atlas Powder Co., Wilmington, Del.
[3] Darvan #7, R. T. Vanderbilt Co., New York, N. Y.

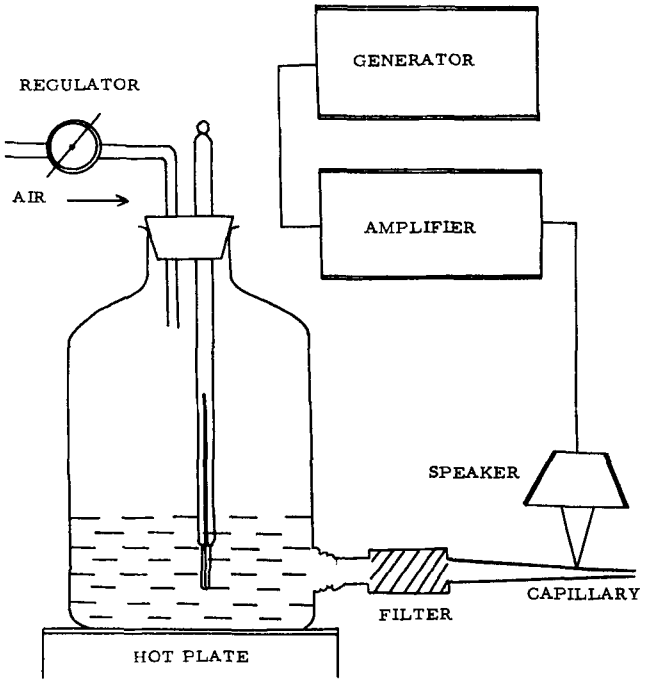

Figure 2—*Schematic diagram of vibrating capillary apparatus for making spherical particles.*

encapsulation did not take place, the experiments were repeated with modified procedures as follows:

1. Addition of formaldehyde solution and cooling of the system to 10° were reversed.
2. Polysorbate 20 in concentrations of 0.125, 0.250, 0.375, 0.500, 1.25, and 2.50% was incorporated in the coacervation mixture.
3. A polyelectrolyte dispersing agent[3] in concentrations of 0.125, 0.250, 0.375, 0.500, 1.25, and 2.50% was incorporated in the coacervation mixture.
4. Acacia-coated particles were prepared by melting and then congealing the stearyl alcohol particles in acacia solution. A known weight of stearyl alcohol particles was dispersed in acacia solution with gentle stirring, and the dispersion was heated to 60°. At this temperature, stearyl alcohol particles melted and apparently became coated with acacia. The dispersion was then cooled quickly to congeal the particles and encapsulation followed as previously described.

Colloid Concentration and Particle-Size Studies—A series of coacervation mixtures were prepared by dissolving separately 200, 400, 600, 800, and 1000 mg. each of gelatin and acacia in 20 ml. of distilled water. Encapsulation was attempted using particles having average diameters of 81, 163, 213, and 335 μ (maximum diameters 88, 177, 250, and 420 μ, respectively). In all experiments the total surface area of stearyl alcohol particles was kept constant; 0.1 g. of 81-μ, 0.2 g. of 163-μ, 0.3 g. of 213-μ, and 0.4 g. of 335-μ diameter particles were used. The entire procedure in all systems studied was followed microscopically to determine if encapsulation was taking place.

RESULTS AND DISCUSSION

Particle Preparation—To attain reproducibility of studies to evaluate the factors relating to the formation of microcapsules, it was desirable to achieve some degree of uniformity of the material to be encapsulated. Ideally, both particle shape and particle size should be uniform and of known characteristics, preferably spherical in shape and monodisperse.

It was found that the apparatus based on those described in the literature were inadequate to maintain monodispersity of particles over a period of time long enough to yield quantities sufficient for this study. The inability to maintain a single size of particles over a long period of time is attributed primarily to insufficient temperature control. Of the two methods used, a modification of the vibrating reed method described by Wolf (2) was more suitable for preparation of small particles, up to 200 μ in diameter, whereas the vibrating capillary method described by Mason *et al.* (3) was more suitable for the preparation of particles larger than 200 μ. Sphericity of the particles by either method was good.

Table I—Effect of Colloid Concentration and Particle Diameter on Encapsulation

Total Concentration of Acacia and Gelatin, %	Particle Diameter, μ	Microscopic Examination of Encapsulation: Untreated Particles[a]	Microscopic Examination of Encapsulation: Particles Melted and then Congealed in Acacia Solution
1	81	Encapsulation	Encapsulation
1	163	No encapsulation	Encapsulation
1	213	No encapsulation	Encapsulation
1	335	No encapsulation	Encapsulation
2	163	Encapsulation	Encapsulation
2	213	Encapsulation	Encapsulation
2	335	No encapsulation	Encapsulation
3	335	No encapsulation	Encapsulation
4	335	No encapsulation	Encapsulation
5	335	No encapsulation	Encapsulation

[a] Includes particles subjected to modified Procedures 1, 2, and 3.

Encapsulation—Encapsulation of stearyl alcohol particles by the method described by Luzzi and Gerraughty (4) was found to be satisfactory for particles up to 250 μ in diameter, except that there was a large amount of unused gelatin and acacia in the dispersed form as well as in the coagulated complex form which prevented the separation of individual microcapsules from the coacervate mixture. This difficulty could be overcome by dilution of the mixture after coacervation and denaturation with formaldehyde so that the total colloid concentration at the time of filtration was not more than 1%.

The capsules thus prepared tended to form agglomerates and yielded a cake-like mass on drying. For the purposes of this investigation and in order to evaluate factors relating to the formation of the capsule wall, it was essential to obtain the capsules in the form of free-flowing particles. Various techniques were tried, but the most satisfactory method was to suspend the capsules in 70% isopropanol before they were dried. The isopropanol treatment produced a suspension which dried to free-flowing discrete particles (Fig. 3).

Effect of Colloid Concentration and Particle Size on Encapsulation—Microscopic examination during the encapsulation procedure using different sizes of stearyl alcohol particles revealed (Table I) that an unmodified method of encapsulation could be successfully employed for encapsulation of particles up to 250 μ in diameter. Particles averaging 81 μ in diameter were successfully encapsulated in a system containing 1% of total colloids, whereas the concentration of colloids needed for encapsulation of 163- and 213-μ diameter particles was twice that amount. However, 335-μ average diameter particles were not encapsulated with this system, even when the

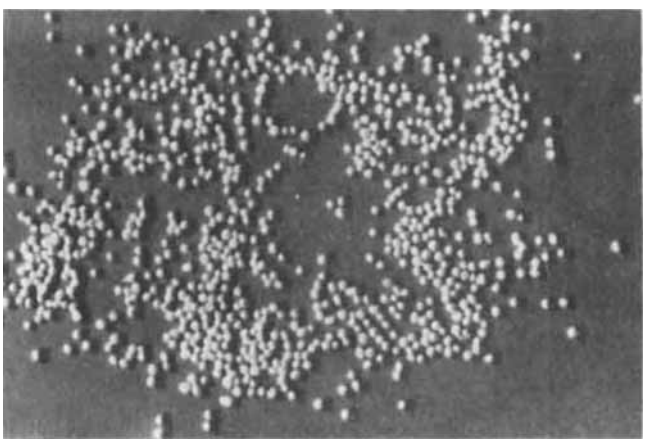

Figure 3—*Photograph of discrete microcapsules produced by treatment with isopropanol.*

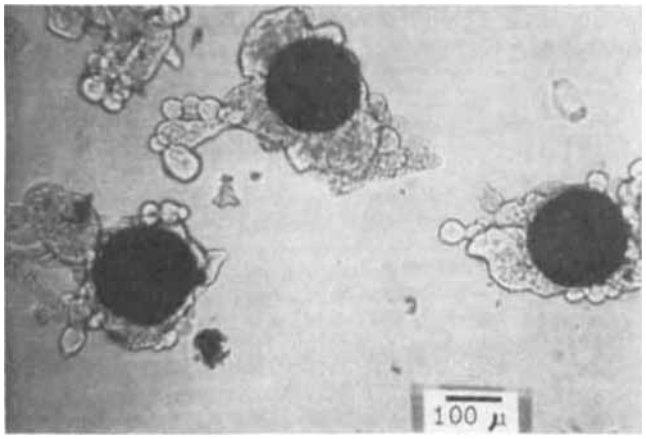

Figure 4—*Photomicrograph of 163-μ stearyl alcohol particles showing encapsulation (2% colloid concentration).*

concentration of the coacervation mixture was increased to five times the concentration used for encapsulating 81-μ diameter particles. Incorporation of the polyelectrolyte dispersing agent and/or the surfactant polysorbate 20 did not yield capsules of 335-μ diameter particles, nor did reversing of procedure so that cooling preceded the formaldehyde addition. However, when the modified technique of first melting and then congealing the stearyl alcohol particles in acacia solution was employed, particles larger than 213 μ in diameter could be successfully encapsulated with total colloid concentrations as low as 1%.

Two mechanisms have been suggested for encapsulation (1): (*a*) a single coacervate droplet may encompass one or a group of immiscible nuclei; and (*b*) individual coacervate droplets may be adsorbed to, or coalesce about, the particles. Figure 4, showing encapsulation of 163-μ particles, supports the point of view of encapsulation by aggregation and coalescence of several droplets to envelop the smaller particles. Microscopic examination during the encapsulation process indicated that the majority of the particles were encapsulated by the aggregation and partial coalescence of coacervate droplets around the stearyl alcohol particles (in sizes ranging from 81- to 213-μ average diameter). Although microphotographs of large stearyl alcohol particles showed some coacervate droplets lodged against them, coverage was incomplete, with large sections of the larger particles (335 μ and above) showing no coverage at all (Fig. 5). For all practical purposes, the particles above 335 μ in diameter were not encapsulated.

Most of the coacervate droplets in the system had diameters under 40 μ; therefore, encapsulation of particles by a single coacervate droplet seems to be infrequent for the sizes of particles used here.

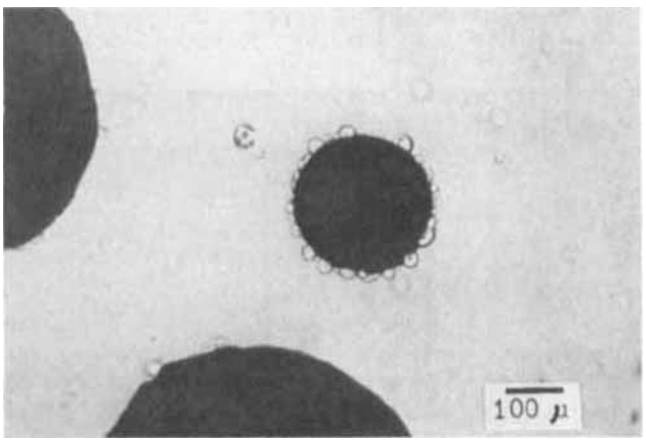

Figure 5—*Photomicrograph of different sizes of stearyl alcohol particles showing incomplete coverage of the larger particles.*

Several factors may contribute to the failure of encapsulation of particles greater than 335 μ:

1. The affinity of the coacervate droplets for the stearyl alcohol surface is not great; therefore, the velocity *difference* between the droplets and the particles as the mixture is stirred tends to prevent the aggregation of droplets around the particles. There is some evidence to support this in that higher stirring speeds hinder encapsulation of small particles (below 213-μ average diameter).
2. The probability that sufficient numbers of droplets will aggregate and coalesce to encompass a particle decreases as the particle size increases. Table I shows, for example, that particles having average sizes of 163–213 μ were not encapsulated at 1% colloid concentration but were encapsulated at 2% colloid concentration.
3. Since the stearyl alcohol particles have a lower density than the suspending medium, they have a tendency to rise to the top of the mixture when the mixture is allowed to come to rest. The coacervate droplets are somewhat more dense than the medium and tend to settle to the bottom of the mixture. A small particle may not have a sufficient rising force to overcome the yield value of the coacervate droplet matrix and, hence, become trapped and encapsulated. The larger particles may possess sufficient rising force to overcome the yield value of the matrix and rise out of the droplet mass.
4. The small particles may be more easily "wetted" by the coacervate droplets.

When the modified method of melting and then congealing stearyl alcohol particles in acacia solution before encapsulation was used, particles larger than 213 μ in diameter were encapsulated in all colloid concentrations examined. Apparently, acacia is adsorbed more strongly by liquid than by solid stearyl alcohol and is retained after solidification. The acacia adsorbed to the particles then reacts directly with gelatin in the coacervation process to form the microcapsules. This mechanism of encapsulation has not previously been reported but could help to explain the encapsulation of a number of substances, especially oily liquids. Further experiments are in progress to test the validity of this hypothesis.

SUMMARY AND CONCLUSIONS

This investigation was undertaken to prepare spherical particles of solid stearyl alcohol in various size ranges, to encapsulate these particles by the process of complex coacervation, and to study the factors relating to the formation of microcapsules. It was found that the conventional method of encapsulation with the gelatin–acacia system could be used for particles up to 213-μ average diameter but that larger particles (above 335-μ average diameter) were not encapsulated by this procedure. In the case of the smaller particles, encapsulation appeared to occur by aggregation and coalescence of coacervate droplets around the particles. Failure to encapsulate the larger particles was shown microscopically to be due to incomplete coverage of the particles by the coacervate droplets.

Encapsulation of the larger particles was accomplished by first melting and then congealing the stearyl alcohol particles in acacia solution prior to encapsulation. Liquefaction of the stearyl alcohol possibly allowed adsorption of acacia which was then retained after solidification. The adsorbed acacia then probably reacted directly with gelatin during the coacervation process.

REFERENCES

(1) L. A. Luzzi, *J. Pharm. Sci.*, **59**, 1367(1970).

(2) W. R. Wolf, *Rev. Sci. Instrum.*, **32**, 1124(1961).

(3) B. J. Mason, O. W. Jayarante, and J. D. Wood, *ibid.*, **40**, 247(1963).

(4) L. A. Luzzi and R. J. Gerraughty, *J. Pharm. Sci.*, **56**, 634 (1967).

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