DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 3(4), 309-314 (1977)

PRODUCTION OF A COACERVATE FILM FOR MICROCAPSULE DIFFUSION STUDIES

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ABSTRACT

Until the last five years, study of microcapsules formed by complex coacervation has been approached almost entirely on an empirical basis. The gelatin-acacia coating formed through complex coacervation is responsible for the sustained release characteristics of the dosage form. Because dissolution of the drug from microcapsules is often limited by the structure and nature of the shell wall, of prime interest would be the construction of an acacia-gelatin film for diffusion studies. Apparent optimal conditions for production of the coacervate film were developed. The conditions were similar to those used to produce microcapsules by various researchers. These conditions produced a coacervate film which could be cut into two square centimeter sections apparently suitable for diffusion studies. Films produced by complex coacervation appeared free from structural defects when observed with a stereo-microscope.

Until the last five years, study of microcapsules formed by complex coacervation has been approached almost entirely on an empirical basis. Only recently has it been possible to study microcapsule dissolution and important parameters such as wall thickness (1), optimum coacervation pH (2), consumption of cross-linking agents (3), and electron microscopy to determine surface

characteristics (4). Diffusion or leaching through the gelatin-acacia shell wall has been shown to be the rate limiting step at least for a segment of the dissolution (2). This gelatin-acacia coating formed through complex coacervation and cross-linked with formaldehyde or gluteraldehyde is responsible for the sustained release characteristics of the dosage form since the dissolution media must diffuse through the shell wall, dissolve the encapsulated drug and the drug dissolved in the solvent must permeate out through the shell wall into the total dissolution fluid.

Because dissolution of the drug from microcapsules is often limited by the structure and nature of the shell wall, of prime interest would be the construction of an acacia-gelatin coacervate film for diffusion studies. The film would have to be extremely thin, similar in width to that of a microcapsule shell wall, readily reproducible and essentially free from any structural defects. Production of such a film would possibly allow for a more theoretical approach and evaluation of micro-encapsulated systems.

It was postulated that the optimum conditions for production of a coacervate film suitable for diffusion studies would be similar to those of encapsulation.

Because of this, the following parameters in the coacervation procedure were investigated and changed as listed.

(1) Initial colloid concentrations were 1, 3 and 5% (w/v).

(2) The temperature of the original solutions was varied from 40° to 60°.

(3) The pH of the original acacia and gelatin solutions were 6.5, 7.0 and 7.5.

(4) The formaldehyde was added at three different times: before lowering the temperature, while the temperature was lowered, and after the temperature was lowered.

(5) The formaldehyde was added in concentrations of 1, 5 and 10 mls. per 100 mls. of coacervate solution.

(6) The concentration of isopropanol was varied from 30 to 70% (v/v).

(7) The container for the coacervate film was pyrex, teflon or aluminum.

(8) The film was air dried or oven dried at 40°, 50°, 60°.

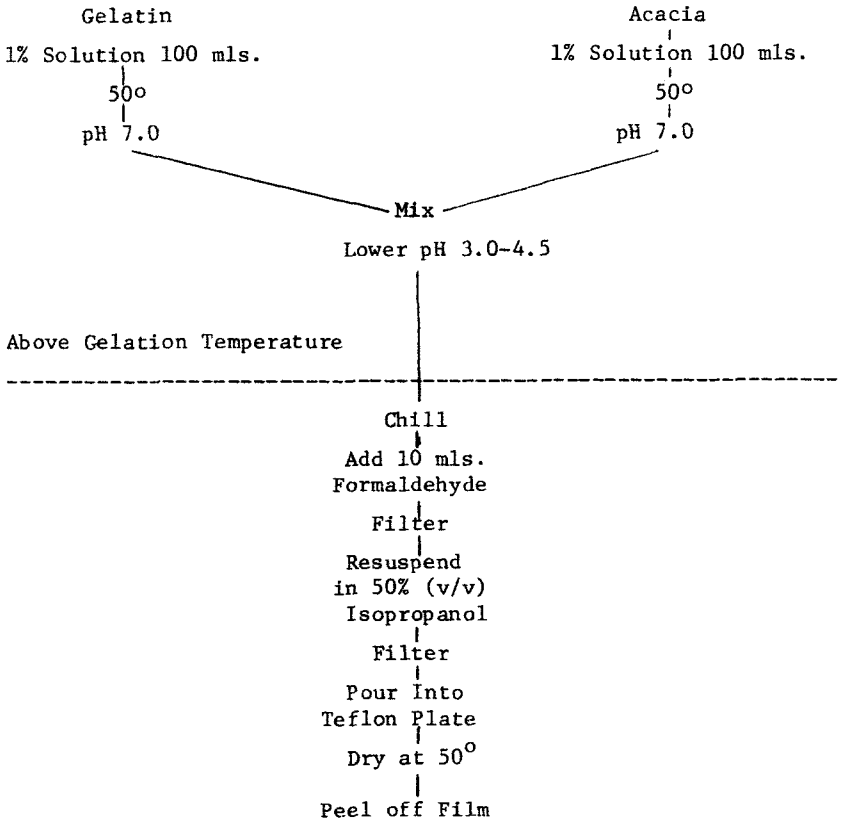
Results and Discussion

Scheme I illustrates the mixing procedure and amounts of substances that produced apparent optimum conditions for development of the coacervate film. They are:

(1) 1% gelatin and acacia. If more concentrated solutions were used, the system tended to become lumpy and difficult to filter.

SCHEME I

PROCESS FOR PRODUCTION OF A COACERVATE FILM



(2) A beginning temperature of 50° appeared satisfactory although temperatures from 40° to 60° appeared not to alter the film characteristics.

(3) An initial pH of 7.0 for each solution was satisfactory.

(4) The time of formaldehyde addition appeared not to influence the coacervate.

(5) Ten milliliters of formaldehyde cross-linked the coacervate mixture sufficiently.

(6) A concentration of 50% (v/v) isopropanol in water removed excess water rapidly, yet did not destroy the integrity of the coacervate film as did 60% (v/v).

(7) The film was most easily removed from a flat teflon coated sheet rather than a pyrex or aluminum sheet.

(8) A drying temperature of 50^{o} dried the coacervate film with minimal defects within 10 hours.

These conditions produced a coacervate film which could be cut into two square centimeter sections suitable for diffusion studies. The average film thickness of twenty-five samples was 95.61 μ ± 5.91 μ. Although the film would often have defects, the individual sections for diffusion studies did not. These coacervate film models appear to be viable for study of diffusion characteristics through microcapsule shell walls.

Since colloidal silica has been shown to be useful in production of free-flowing microcapsules (2), it was added to the film producing process after the pH of the coacervate mixture was lowered to cause coacervation. When colloidal silica was added, the average of twenty-five film thickness measurements was 99.61 μ ± 7.63 μ, approximately that of the film without colloidal silica. Both films appeared free from structural defects when observed with a stereo-microscope.

Future electron microscopic studies may prove useful in further verifying that the film produced is free from voids, sub-microscopic cracks or other structural defects.

Although the film discussed here is relatively thick when compared to that calculated for coacervate shell walls, it appears to warrant study as a diffusional model. Future reports shall discuss the usefulness of this model and its applicability to microcapsules produced by complex coacervation.

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