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REVIEW ARTICLE

Microencapsulation

LOUIS A. LUZZI

Keyphrases ☐ Microencapsulation—review ☐ Coacervation simple, complex—microencapsulation ☐ Phase separation—microencapsulation ☐ Interfacial polymerization—microencapsulation ☐ Electrostatic methods—microencapsulation of aerosols ☐ Pharmaceutical applications—microcapsules

Microencapsulation may be thought of as a method of wrapping small entities in individual, protective coatings. These coatings may be designed to protect, separate, or aid in storage and handling. Alternatively, the coatings may be constructed so that the encapsulated material is released under prescribed conditions to control or prolong the action from the microscopic-size capsules. The conditions for release may be made dependent upon moisture, pH, physical force, or combinations thereof. The mechanism for release may be associated with leaching, erosion, rupture, or other such actions, depending upon wall construction.

Microencapsulation encompasses both science and technology. A great deal has been written concerning current applications and future possibilities for encapsulating those materials whose original activities, actions, or stabilities may be altered or controlled by packaging in microcapsules. The technology of microencapsulation, involving several varied disciplines, is advancing rapidly, but the application of the principles involved has not yet approached its full potential. Knowledge from several disciplines is often essential to the technology of microencapsulation. For example, it may be necessary for pharmacology and therapeutics to join with colloidal and polymer chemistry for the encapsulation of medicinals.

Much of the available information pertaining to microcapsules and microencapsulation is found in the patent literature. Many applications of microencapsulation, employing varied and ingenious techniques, are patented. However, as is typical with patent literature, control and testing data as well as completeness of details essential for reproducibility are either lacking or alluded to in ambiguous terms. Definitive literature in these areas is limited and will probably remain so for some time, due to security measures on the part of those companies holding patent rights.

In this review of microencapsulation, an attempt will be made to bring together the published information from the scientific, patent, and company-prepared literature. In cases in which the scientific or patent literature is accompanied by company brochures, only the former literature will be discussed and the latter will be referenced.

Microcapsules are measured in microns and usually fall into the range of from several to approximately 200 μ (1). Some of the literature (2) alludes to microcapsules as a form produced by a specific mechanism which yields discretely packaged materials regardless of size, as opposed to discrete, microscopic packages of material. For this paper, microcapsules are defined as being discrete packages of material in the size range of 0.5–200 μ (3), and the term applies to all small, discrete packages produced by any number of techniques. Figures 1–3 illustrate microcapsules in different stages of preparation.

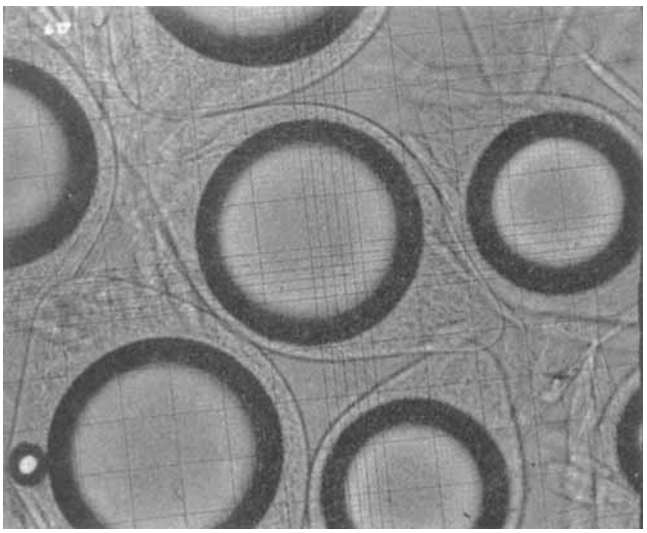

Figure 1—*Microcapsules of individual oil droplets before drying. (Courtesy of The National Cash Register Co.)*

SURVEY OF MICROENCAPSULATION METHODS

The processes of microencapsulation have been used to encase particles of liquids, solids, or gases. These particles must be immersible in the liquid phase containing the material that will ultimately form the capsule wall. The first practical use of microencapsulation appears in United States patents issued to Green and Schleicher (4–6). The principles of microencapsulation enumerated in these patents involve both simple and complex coacervation. Coacervation, as a method of microencapsulation, was also claimed in two other patents by Green and Schleicher (7) and by Green (8); these patents were filed at the same time but issued several years later.

Coacervation—The term "coacervation" has been used by chemists to describe the salting out of or phase separation of lyophilic solids into liquid droplets rather than into solid aggregates (9). The term was introduced into colloidal chemistry by Bungenberg de Jong and Kruyt (10) to describe the flocculation or separation of liquids from solution where at least one of the liquids contained a colloidal solute.

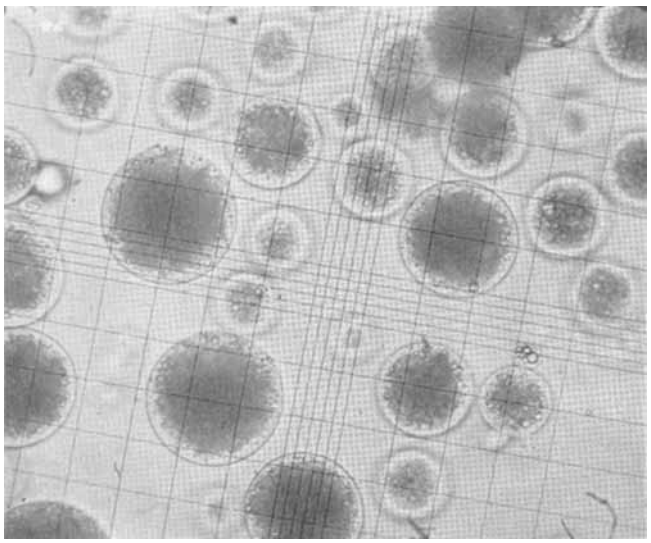

Figure 2—*Capsules within a capsule or aggregate microcapsules containing a liquid, before drying. (Courtesy of The National Cash Register Co.)*

Coacervation has been subdivided into two categories: simple coacervation and complex coacervation. Briefly, simple coacervation usually deals with systems containing only one colloidal solute, while complex coacervation usually deals with systems containing more than one colloid (11).

Simple coacervation is a process involving the addition of a strongly hydrophilic substance to a solution of a colloid. This added substance causes two phases to be formed, one phase rich in colloidal droplets and the other poor in such droplets. This process depends primarily on the degree of hydration produced. For example, addition of alcohol or sodium sulfate, as typical hydrophilic substances, to an aqueous solution of gelatin can lead to phase formation. When suitable conditions, including the presence of suitable nuclei, are prevalent, microcapsules may result.

Complex coacervation (Fig. 4) is primarily dependent on pH. It has been reported that in gum arabic–gelatin systems, complex coacervation occurred and microcapsules formed at pH values below the isoelectric point (IEP) of the gelatin but would not occur above this pH. At pH values below the IEP of gelatin, it becomes positively charged while acacia particles retain their negative charge regardless of pH. The same was found to be true of other systems containing two dispersed colloids, one of which was ampholytic (12).

Two mechanisms have been suggested for the formation of microcapsules by these methods (13): (*a*) individual coacervate droplets may be drawn to and coalesce about particles immiscible in the system, or (*b*) a single coacervate droplet may encompass one or a group of immiscible nuclei. Either or both mechanisms may be operative in a given system. However, unpublished data seem to indicate that, in certain cases, complex coacervate systems may be controlled to yield reproducible "compound capsules." That is, capsules may be formed which contain smaller, previously formed capsules from the same mother liquid, without first removing the smaller capsules or rejuvenating the liquid.

Phase Separation—This technique involves the dispersion of a polymer or copolymer in a solvent system in which the nucleus material is not soluble. Another liquid, which is miscible with the solvent system but which must be a nonsolvent for the polymer and nuclei, may be added. The rate of stirring, subsequent dispersion of the polymer-rich phase, and the rate of addition of the nonsolvent may be controlled to regulate the porosity of the capsule wall.

Several other methods of microencapsulation have been reported. These include interfacial polymerization, electrostatic methods, mechanical processes, and vacuum metalization.

Interfacial Polymerization—Microencapsulation by this method is a process whereby a monomer is made to polymerize at the interface of two immiscible substances. If the internal phase is a liquid, it is possible to disperse or solubilize the monomer in this phase and to

emulsify the mixture in the external phase until the desired particle size is reached. At this point, a crosslinking agent may be added to the external phase. Since there is usually some migration of the monomer from the internal to the external phase, and since it is preferred that the crosslinking agent not transfer to the internal phase, the bulk of any polymerization will take place at the interface (15).

An interesting dual-walled capsule formulation embodying a combination of coacervation and interfacial polymerization was disclosed by Brynko and Scarpelli (16). They prepared dual-walled oil-containing capsules whose inner wall consisted of polymerized styrene–divinylbenzene monomer with an outer wall of a gelatin–acacia coacervate shell. The monomer was dissolved in the internal phase, and polymerization took place during and after coacervation. The individual processes were controlled by temperature adjustment.

Electrostatic Methods—Preparation of microcapsules by these methods (17, 18) involve a bringing together of the wall material and the material to be encapsulated when both are aerosols. The material must be liquid during the encapsulation stage and must be capable of wetting the core material. Should the internal phase be liquid during the process, then it must have the higher interfacial tension to ensure encapsulation. The two aerosols must be oppositely charged; this can be accomplished prior to the mixing of the two. Three chambers are used in this process, with two of the chambers being atomization chambers and the third a mixing chamber. Oppositely charged ions are generated and directed into the two atomization chambers and are deposited on the liquid drops while they are being atomized. The capsules are allowed to cool in order to solidify the coating and then are collected by an appropriate aerosol collection system.

Mechanical Methods—One mechanical method (19) for producing microcapsules involves the use of counter-rotating disks. The inner rotating disk produces small particles of the core material. These particles are projected toward a point on the outer counter-rotating disk, which is lined with liquid coating material and has a row of orifices. When a sufficient weight of core material has collected at a particular orifice, centrifugal force separates the core and wall-forming material from the rotating cylinder, thus completing capsule formation. The amount of wall material applied is related to the initial concentration of the wall solution and the rate at which the solution flows onto the outer disk.

Another method (20) involves the dripping of the material to be encapsulated onto a continuous film of the liquified wall material and subsequent collection of the capsules. Here, again, the accumulated weight of core material causes the film to separate, with subsequent capsule formation (Fig. 5).

Still another method for the mechanical coating of small particles is the Wurster fluidized-bed coating technique (21–23). Figure 6 shows that the apparatus may consist of a vertical, somewhat conical column. A gas, carrying the coating material, is introduced at the base or constricted part of the column at a velocity high enough to suspend the particles. The gas velocity

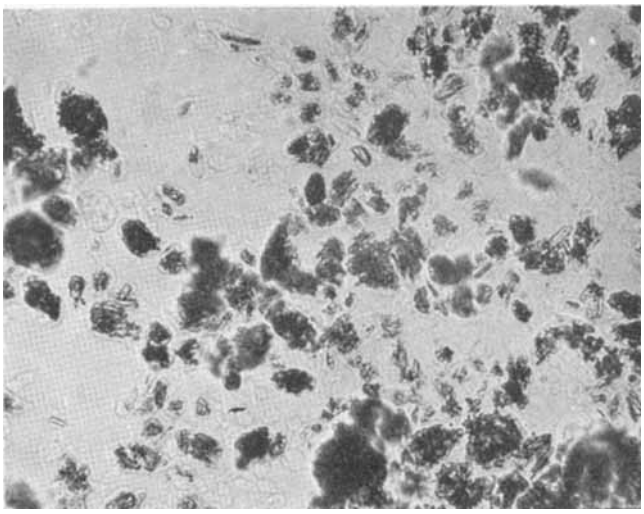

Figure 3—*Microencapsulated solid before drying.*

in the flared part of the column is greatly decreased, so the particles cannot be supported in this region and they fall outward and downward into the constricted region where they are again lifted by the gas flow. The wall material is dissolved in a solvent (usually volatile) and is sprayed onto the supported particles, in a fine mist, from a nozzle located near the bottom of the column. The solution coats the suspended particles, and heated air drives off the solvent. When the particles are sufficiently dry, the air flow is cut off and the coated product falls to the bottom of the apparatus for collection. The amount of wall material applied is generally proportional to the atomizing time, since the coating material is sprayed at a uniform rate and the particles

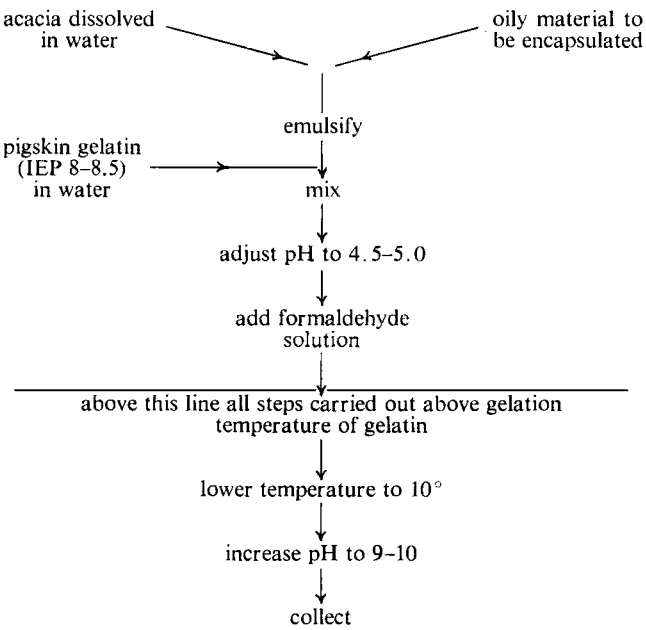

Figure 4—*Flow diagram of a typical method of manufacture of microcapsules* via *complex coacervation. Emulsification may be carried out with or without gelatin present. The particle size of the emulsified oil may be controlled, thus affecting the size of the ultimate capsule. Adjustment of pH to 4.5 causes coacervate droplets to form and encapsulate the emulsified oil. Formaldehyde addition, lowering of temperature, and increase in pH all fix the coacervate droplets in place about nuclei.*

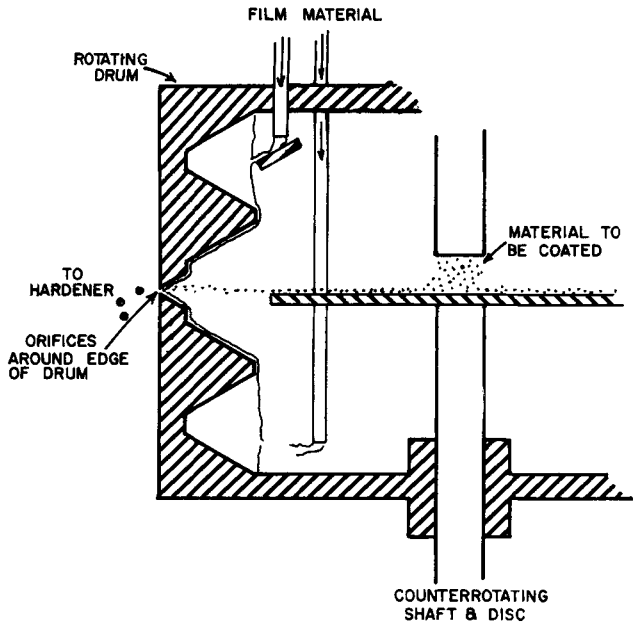

Figure 5—*Schematic of a counter-rotating, multiorifice apparatus for the coating of particles.*

are uniformly exposed to the spray. The time and air velocity required to coat the particles depend upon: (*a*) the starting surface area of the particles to be coated (the smaller the particle, the greater the surface area per pound of material to be coated and, therefore, the longer the time needed to coat); (*b*) the desired thickness of the coating; (*c*) the weight of particles coated per batch; and (*d*) the rate of flow of the coating liquid.

Vacuum Metalization—Although not directly applicable to pharmaceuticals when using metallic substances as the coating material, this process presents a very interesting methodology (24, 25). The apparatus (Fig. 7) consists of a container in which a vacuum can be pulled and which is equipped with a heated metal vaporization mechanism, a refrigerated hopper, and an inclined refrigerated vibrating tray. The particles to be coated are fed onto the tray and, in their cooled state, condense the metal vapors emerging from the heated crucible. The thickness of the coating may be regulated by controlling the rate at which the particles descend the inclined tray. Other factors which may be controlled to regulate wall thickness are the rate of metal vaporization and its consequent condensation.

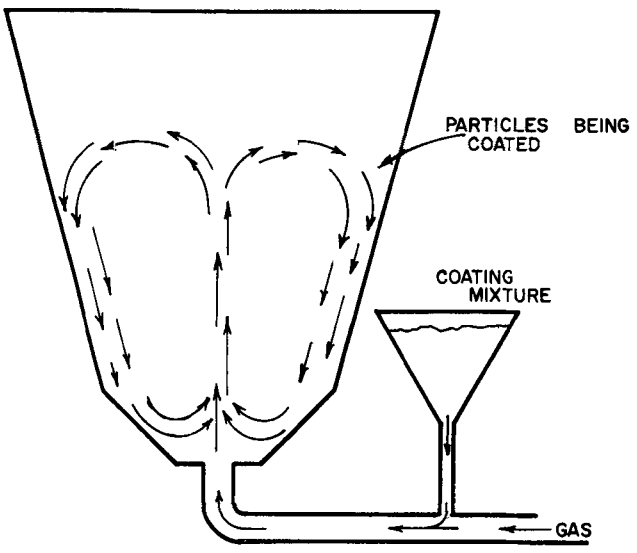

Figure 6—*Schematic of the Wurster coating apparatus.*

Many more devices have been reported. However, most of the principles have been discussed here. The specific mechanisms not mentioned are usually part of, or a combination of, several of those discussed.

PREPARATION OF MICROCAPSULES

Bungenberg de Jong (26) described many coacervate systems along with the behavior of coacervate droplets under a variety of conditions. Although he did not attempt the technique of microencapsulation, his descriptions and observations are the bases for the current technology of microencapsulation *via* coacervation. The first practical use of the process of coacervation was made by Wagner (3), Green and Schleicher (4), and Green (27, 28). Two of the early patents (3, 4) indicated that various oils, some of which contained dissolved dyes, had been encapsulated in gelatin–acacia microcapsules.

One procedure (4) consisted of dissolving 20 g. of acacia in 160 g. of water and emulsifying into this 80 g. of trichlorodiphenyl containing 3–6%, by weight, of color reactant materials. Emulsification was continued until the oil droplet size was from 2 to 5 μ. Next, 20 g. of gelatin was dissolved in 160 g. of water and mixed with the emulsion. This mixture of colloids and oil was then diluted by adding approximately 525 g. of water, at which time (the patent states) coacervation occurred and the gelatin–acacia complex formed about the oil droplets; all ingredients were kept at 50°. The mass was then cooled by pouring it into a quantity of cold (0°) water. The mixture was agitated and allowed to stand for 1 hr. at not more than 25°. The pH was adjusted to between 7 and 9 with sodium hydroxide, and the material was left in this state for at least 30 min. The capsules were hardened by adding 20 g. of formaldehyde solution USP and mixed at 3° or lower for about 10 min. Since the ultimate use of this material was for the preparation of "carbonless carbon paper,"[1] the capsules were not dried but the water content of the mixture was adjusted to suit this application.

In another patent (5), Green and Schleicher, again using similar materials, related that encapsulation may be brought about by adjusting pH and by controlling the degree of hydration of pigskin gelatin through salt addition. Using the pH adjustment method, the oily material was emulsified into an acacia solution; a solution of pigskin gelatin, with an IEP of pH 8, was added to the emulsion. Then, the pH of the mixture was brought to 6.5 with a 20% w/w solution of sodium hydroxide. Three hundred grams of this mixture was diluted with 700 g. of water at 50°. The pH of the diluted mixture was then lowered to approximately 4.5 with diluted acetic acid. It was during this step that the coacervate droplets formed and were deposited about

[1] The National Cash Register Co., Dayton, Ohio.

the oil droplets. While still at 50°, 2.19 g. of formaldehyde solution was added to help fix in place the coacervate droplets. The mixture was cooled to 10° and, subsequently, the pH was brought to 9. The cooling and pH adjustment further immobilized the formed shell.

Another method of microencapsulation is given in the same patent and describes coacervation by salt addition. In this case, the emulsion, containing 100 parts of 10% w/w gelatin and 20 parts of oil but no acacia, is treated in a similar manner, except that coacervation is induced by slowly adding, with stirring, a strongly hydrophilic salt solution. In this instance, 1.51 l. of a 20% solution of sodium sulfate was added at 50°. The mixture was then placed in 37.85 l. of 7% sodium sulfate solution at about 20°. The material was filtered and washed to remove the salt and was later treated with formaldehyde solution.

In later patents, Green and Schleicher (7) and Green (8) presented schematic diagrams for the preparation of microcapsules by both simple and complex coacervate systems. They also offered further explanation of these reactions and included an enumeration of other core materials consisting of naturally occurring and synthetic oils. A list of anions and cations arranged according to their relative hydrophilic nature was given to aid in determining the efficiency of various salts which may be used for simple coacervate systems.

In other patents involving coacervation of phase separation, several inventors added to the technology of microencapsulation. Materials other than, and in addition to, gelatin, albumin, casein, pectin, acacia, *etc.*, have been used. Solids as well as oils have been encapsulated, wall materials have been altered, sealing coats have been applied, and various combinations of natural and synthetic materials have been used as coating agents. The following is a sampling of the many variations perpetrated to attain microcapsules having various "improved" characteristics. An attempt will be made, in this section, to discuss patent information in a chronological manner, using filing dates as a guide.

Brynko and Scarpelli (16), in their patented process of making dual-walled capsules, dissolved two monomers, dichlorodiphenyl monomer and styrene monomer, in an internal oil phase. The oil phase was emulsified into an aqueous phase containing acacia, gelatin, and (to act as the catalyst for the monomers) potassium persulfate. The initial pH of the emulsion was 6.5 and the temperature was 55°. The pH was subsequently lowered and the temperature brought to 15°. Polymerization of the monomers began with the initial mixing of the phases and was substantially completed at the interface by the time coacervation had been accomplished. To harden the capsule walls, formaldehyde solution was added and the pH was raised to 10. Agglomeration of capsules was controlled by the addition of a maleic anhydride copolymer such as the polyvinylmethyl ether–maleic anhydride copolymer.

Brynko and Scarpelli (29) also reported that dual-walled capsules have been formed by causing deposition, *via* coacervation, of a lower molecular weight copolymer followed by an addition of a higher molecular weight copolymer. They reported a mixture of polyethylene–maleic anhydride copolymer, of approximate 1000–2000 molecular weight, in an aqueous solution containing gelatin and acacia at 35° and at pH 9. The material to be encapsulated was dispersed in the mixture and the pH was lowered to 4.8. A wall thickness of about 5 μ was found when coacervation was completed using the prescribed quantities of materials. The pH was then raised to about 6.8 to allow for the addition of an aqueous medium containing polyethylene–maleic anhydride copolymer having a molecular weight of 60,000–70,000. At pH 6.8, decoacervation took place and, consequently, it was important that the time during which the mixture was at this pH was at a minimum. Upon addition of the higher molecular weight copolymer, the pH was lowered to approximately 5. The resultant deposition yielded capsules with a total wall thickness of about 100 μ. When the mixture was cooled to 13°, the walls became rigid and solid but were still in a reversible state; formaldehyde, glutaraldehyde, or a similar crosslinking material was used to fix the wall material.

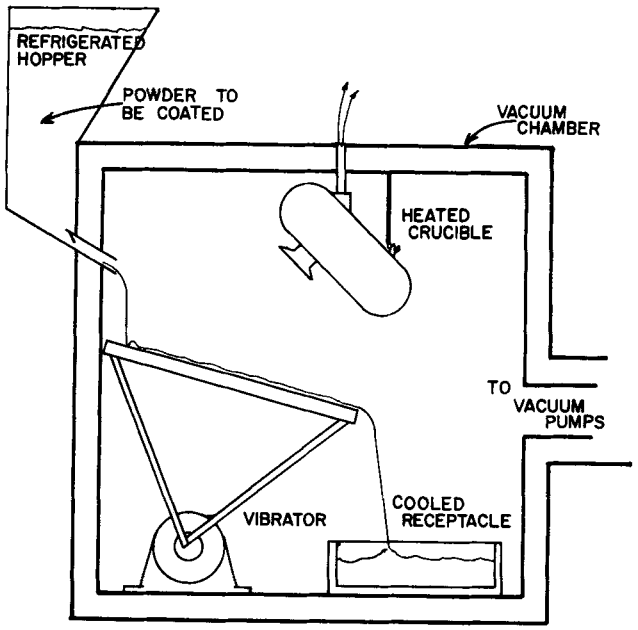

Figure 7—*Vacuum metalization apparatus for encapsulation.*

In another patent (30), fractionated gelatin along with acacia was used as the wall-forming material. Fractionation was accomplished by heating a solution of pigskin gelatin (IEP 8) at pH 7 and treating this with ethyl alcohol. Two distinct layers formed, one rising to the top and the other sinking. The lower layer was collected, dried, and comminuted. The powdered gelatin fraction, along with acacia, was dissolved in water, and capsules were formed by complex coacervation. Discrete capsules were collected and were found to be more pervious to light than capsules formed using nonfractionated gelatin.

Jensen (31) reported a method for encapsulation of water-soluble solid materials. The solid material was first coated with a liquefied lipid material by one of several mechanical methods. The coated solid was then encapsulated, using either simple or complex coacer-

Table I—Effect of pH on Diffusion Rate of Dye

pH of Material prior to Spray Drying	Diffusion Rate of Dye, % dye released/min.
4.00	0.125
5.00	0.125
6.00	0.128
7.25	0.180
8.50	0.302

vation or a partially hydrolyzed maleic anhydride copolymer. The solubility of the partially hydrolyzed copolymer was found to vary in different hydroalcoholic systems; the solubility was also found to decrease with the addition of selected salts. For example, completely hydrolyzed styrene–maleic anhydride copolymer was found to be about 2% soluble in water but at least 20% soluble in a 50–50 mixture of methanol and water. When the partially hydrolyzed copolymer was used, phase separation and consequent encapsulation of suspended material were brought about by the addition of an appropriate solvent or a salt such as magnesium sulfate. The sulfate salt was found to be effective over a wide concentration range. An adjustment of pH, either up or down depending on the polymer, was necessary to reduce the solubility of the wall material, thereby ensuring irreversibility.

Another method for the encapsulation of hydrophilic materials that involves precoating was disclosed by Heistand *et al.* (32). In this case, the precoating procedure was carried out from nonaqueous systems. For example, 50% hydrolyzed styrene–maleic anhydride copolymer was dissolved in a nonaqueous liquid. Into this an aqueous solution of the desired core material was emulsified. A third liquid, soluble in the organic liquid but not a solvent for the polymer, was added to induce phase separation and encapsulation of the suspended aqueous phase. The precoat was hardened, separated, and dried. The resultant precoated material was then suspended in an aqueous system from which encapsulation was brought about by any of several previously mentioned methods.

In a patent granted to Jensen (33), styrene–maleic anhydride copolymers and the hydrolyzed species of these copolymers were used as part of the negatively charged species to effect encapsulation *via* complex coacervation. It is stated that encapsulation by this method produces a shell which is less permeable than that obtained using, for example, gelatin and acacia. The gelation or cooling step may be eliminated when using this combination of materials.

Another method of preparing less permeable microcapsules was patented by Jensen (34) and involves controlling pH during the drying procedure. This included a spray-drying process which was used to obtain a free-flowing powder form of microcapsules and which was carried out at pH values between 4 and 6. It is stated in the patent that although the reason for the decrease in permeability was unknown and unexpected, nevertheless there existed an optimum between pH 4 and 6. Table I is a presentation of some of the data generated for this patent. The data were collected from 1 g. of dry product having a gelatin–acacia shell and suspended in 250 ml. of chloroform and stirred at a constant rate. The rate of diffusion of an encapsulated dye was measured spectrophotometrically using filtered aliquots of the chloroform suspension (Table I).

Jensen and Wagner (35) also were granted a patent in which they described the preparation of microcapsules using a partially hydrolyzed styrene–maleic acid copolymer. The method for the preparation of the acid copolymer was disclosed in this case.

In a patent entitled "Encapsulation in Natural Products" (36), the lipophilic material to be encapsulated was dispersed in a solution of egg albumin and, in order to bring about encapsulation, was heated to between 70 and 90°. In examples given in this patent, other techniques that aid coagulation were cited. These included addition of formaldehyde solution, alternations of ratios, variations of temperature and time, and use of additional polymers. The inventor stated that one advantage of this process was that it was particularly suitable for volatile substances since only moderately high temperatures were necessary.

Capsules with a wall material consisting of acacia and low viscosity ethylcellulose (ratio not more than 2:1) and gelatin were disclosed in a patent granted to Maierson (37). The process of encapsulation follows that of Green and Schleicher (5) and Green (6), differing only in the inclusion of ethylcellulose in the lipid phase. It was claimed that this modification of the process causes ethylcellulose to be deposited at the inside of the capsule walls, thereby plugging pores which may be present in the walls. Deposition of the ethylcellulose was said to be brought about by the presence of an aqueous phase. The film of ethylcellulose continues to deposit during coacervation and acts as host for acacia–gelatin droplets.

A cyclic process (38) for the manufacture of microcapsules that may contain acetylsalicylic acid and which employs nonaqueous dispersion media was disclosed in a patent issued to Miller and Anderson. Given as "Example I" of encapsulation in this patent is the following:

"This example utilizes (a) cyclohexane as the solvent vehicle, (b) butyl rubber . . . to maintain the wall material solution as a separate phase, (c) aspirin of a particle size . . . , and (d) ethylcellulose . . . solution in a 20% alcohol/toluene solvent as a wall material.

"Into a 600 ml. vessel, there are introduced, with agitation sufficient to produce liquid entities of ethylcellulose–cyclohexane solution of several microns average drop size at 80°, 200 grams of a 3% by weight, solution of the specified butyl rubber in cyclohexane, 4 grams of the specified ethylcellulose, and 48 grams of the specified particulate size acetylsalicylic acid, to form a system which is heated to 80°." (38)

When the desired dispersion had been reached, the system was cooled and the wall began to form at about 70°. The cooling was carried to room temperature. The capsules were removed and the remaining liquid reconstituted to its original proportions of starting ingredients. The capsules were recovered, in an appropriate manner, and dried.

Anderson *et al.* (39) also patented a method of encapsulation for aspirin using ethylcellulose. In this system, the aspirin particles were first wetted with an aqueous buffering solution of monobasic potassium phosphate previously adjusted to pH 2.3 with phosphoric acid. The aspirin particles were dried and the encapsulation procedure begun.

Ethylcellulose, acetic anhydride, and polyethylene were dispersed in cyclohexane at room temperature and solubilized by raising the temperature to 80°. At this point, the buffered aspirin particles were dispersed with continued agitation, and the temperature was lowered to approximately 25°. The capsules thus formed were separated from the insoluble polyethylene particles by washing through a screen. Polyethylene was used in this system as a phase separation inducing material, which caused no hydrolysis of aspirin as may have been the case with water-soluble materials.

When the phase separation of a polymer is used as the method of coating small particles, difficulties are sometimes encountered in recovering discretely coated nuclei. To overcome this, Rowe (40) incorporated mineral silicates into the system and thus minimized adhesion and coalescence of capsules. Generally speaking, when phase separation of polymers is to be the method of encapsulation, an organic solvent solution of the polymer is prepared, the particles to be coated are dispersed in it, and an organic nonsolvent for both the polymer and particles is added to the dispersion. A polymer-rich dispersed phase separates during the addition of the nonsolvent; this phase, while dispersed, may migrate to and coat suspended particles. It was found that incorporation of the mineral silicate (40) (talc was preferred) into the system during the addition of the nonsolvent minimized coalescence.

Another method of preventing capsules from aggregating during the isolation or drying step was patented by Maierson (41). In this method, cationic surfactants were added to redispersed capsules prior to drying. More than one surfactant was added, in varied sequences, to achieve optimum particle dispersion.

Ranney (42) compiled techniques from the U. S. patent literature pertaining to microencapsulated products. The techniques were abstracted from 81 U. S. patents, some of which have been presented here and some of which are yet to be discussed. He also included numerous flow charts and schematics obtained from the literature.

STUDIES OF MICROENCAPSULATION SYSTEMS

The most widely known application of microcapsules to date is, of course, manifest in the copying material produced by The National Cash Register Co. Their major product, in this area, is record paper commonly known as "carbonless carbon paper." Several methods of microencapsulation are utilized to encapsulate the system of leuco dyes used in this process. In all cases, however, the dyes are dissolved in an oily base prior to encapsulation. The formed capsules are coated or spread on paper along with a material which will cause color formation of the leuco dyes when the capsules are ruptured and contact between reactants is possible. This is not only the major application but, as mentioned earlier, is the first to become widely used in a commercial product. As noted, the technology has been widely patented and there has been a rapid diversification of application. Materials ranging from volatile oils to solids and semisolids are now being encapsulated. The materials used as encapsulating agents are just as varied, ranging from the gelatin–acacia complexes to ethylcellulose, hexamethylenediamine, and combinations of two or more of these or similar materials. In spite of the wealth of technology, and with one or two exceptions, microcapsules and the microencapsulation processes remain a curiosity. Figure 8 illustrates some of the characteristics of microcapsules. Numerous potential applications have been advanced in various patents and elsewhere (1, 43, 44) and have served to stimulate exploration of the area.

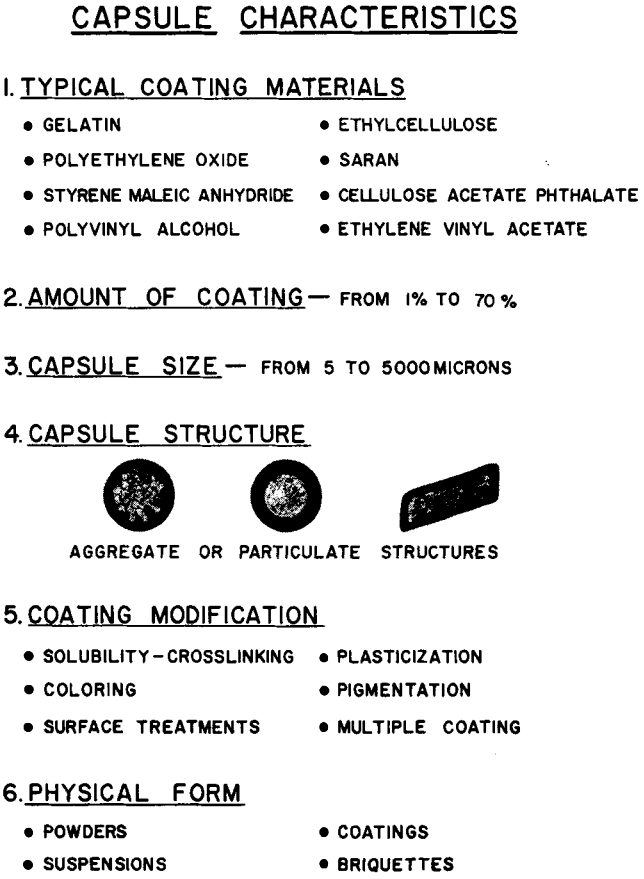

Figure 8—*Some capsule characteristics. (Courtesy of The National Cash Register Co.)*

The discussion to this point has primarily involved the patent literature. As such, it was descriptive in areas of technology but lacked depth of detail due to the nature of the literature covered. Several definitive treatments of restricted areas of microencapsulation have appeared in the literature. The object of an important, continuing, in-depth study (45–52) has been to encapsulate enzymes in semipermeable microcapsules for use in enzyme-replacement therapy. Thus far, these investigators have reported several successes using both shunt systems and, in certain cases, interperitoneal injection. They have encapsulated catalase,

Table II—Effect of Acid Value of Encapsulated Oil on Permeability of Microcapsule Wall[a]

Acid in Oil, %	Acid Value of Oil	Oil Extracted in 60 Min., ml.	Oil Extracted as Total Weight of Sample, %
0	0	0.012	1.02
1	2.15	0.012	1.02
2	4.22	0.061	5.18
3	6.08	0.091	7.70
4	8.24	0.248	21.08
5	10.47	0.320	27.20

[a] Reprinted, with permission, from L. A. Luzzi and R. J. Gerraughty, *J. Pharm. Sci.*, **53**, 431(1964).

urease, and erythrocyte hemolysates as well as detoxicants useful in conjunction with the experimental enzyme therapy.

Various encapsulation methods have been used by these investigators in attempts to achieve workable systems. Microcapsules have been prepared with walls of nylon, collodion, and heparin-complexed collodion. The nylon microcapsules are of special interest, since neither the methods by which they may be prepared nor the products themselves have, as yet, been discussed in this presentation. The nylon monomer, 1,6-hexanediamine, was dissolved in water along with a solution of the material to be encapsulated. This was emulsified into a mixture of chloroform and cyclohexane until the desired particle size was reached. At this point, a suitable polymerizing agent, such as sebacyl chloride, which had been dissolved in some of the external phase of the emulsion, was added. As there was migration of the nylon monomer across the interface, and since a polymerizing agent was present in the external phase, polymerization of the nylon took place in the immediate vicinity of the aqueous droplet. Improved capsules, in the sense that they existed individually by virtue of strong negative charges, were achieved when 4,4′-diamino-2,2′-diphenyldisulfonic acid was substituted for 50% of the nylon monomer.

Luzzi *et al.* (53) modified this technique to produce a sustained-release pharmaceutical dosage form. In this work, nylon was used to encapsulate a barbiturate. Particle-size range of the resultant free-flowing powder was noted, and kinetic data were given for the release of medication from tablets formulated in different manners.

Table III—Effect of Final pH on Permeability of Capsule Walls when a Solid Barbiturate Has Been Encapsulated *via* Complex Coacervation[a]

Final pH	After 0.5 Hr. in Gastric Fluid[b]	After 1 Hr. in Intestinal Fluid	After 2 Hr. in Intestinal Fluid	Total in Gastric and Intestinal Fluids
6.5	27.0	14.7	23.5	50.5
7.0	23.7	28.4	29.3	53.0
7.5	29.4	13.1	22.4	51.8
8.0	28.6	17.7	27.2	55.8
8.8	36.7	33.7	36.0	72.7

[a] Reprinted, with permission, from L. A. Luzzi and R. J. Gerraughty, *J. Pharm. Sci.*, **56**, 634(1967). [b] All values expressed as percent of encapsulated phase.

In other work by Luzzi and Gerraughty (54), some selected oils used in pharmacy were encapsulated and evaluated for their effect on capsule permeability (Table II). The capsules were prepared by complex coacervation, using gelatin and acacia, and contained oils with a variety of acid and saponification values and surfactant properties. In additional publications by the same authors (55, 56), a similar encapsulating system, modified for the encapsulation of solids, was evaluated. Manufacturing variables such as starting pH, starting temperature, ratio of encapsulated material to wall material, quantity of denaturant, and final pH (Table III) were examined to determine the effect on capsule formation. Techniques of altering and controlling the release of drugs from microcapsules were also studied.

Phares and Sperandio (57) used a simple coacervate encapsulating system to investigate the possibility of coating pharmaceuticals. They investigated the encapsulation of five solids and two liquids, with emphasis on regulation of coating thickness and on controlling the volume of coacervate. These authors (58) also investigated the preparation of phase diagrams for coacervate systems, using parameters of physical measurement rather than chemcial analysis methods which had previously been used.

Very basic work has been and is being carried out in the area of phase separation by Veis and coworkers (59–63). Although microencapsulation was not cited as the objective in these references, the information presented is important for an understanding of the area. These authors have explored phase separation in complex and simple coacervate systems, both with and without fractionated gelatin. In some cases, mathematical models were prepared; in others, the degree of separation of polymeric material was examined.

ADDITIONAL PRESENT AND FUTURE APPLICATIONS

Although wide ranging applications have been found for microcapsules, their potential use in pharmaceuticals has not yet been realized. The following brief overview of a few current and projected applications may suffice to stimulate further the reader's imagination.

The first application was, as mentioned, the preparation of "carbonless carbon paper." Many other uses for these capsules have since followed. The encapsulation of magnetizable materials was disclosed by Schleicher and Boughman (64). The encapsulated material may be permanently magnetized or may be magnetized by magnetic fields applied to the capsules. When the encapsulated and magnetizable materials are light-opaque platelets, light transmission through the area covered by these capsules may be controlled by the direction of the magnetic field. This type of application has potential in fields such as computerology, printing, data processing, copying, and light shuttering (Fig. 9).

Another application for microcapsules may be found when it is desired to apply a thin film of a volatile or partially volatile mixture on surfaces. One such application (65, 66) involves the encapsulation of ad-

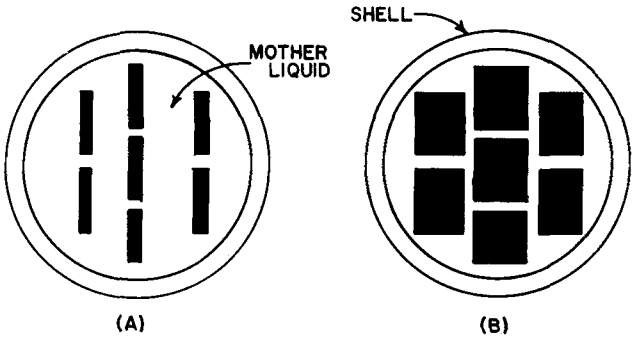

Figure 9—*Schematic of encapsulated magnetic pigments in different magnetic fields.*

hesives and subsequent distribution of the encapsulated adhesive on a surface. In the encapsulated form, the adhesive is nontacky and remains so until the capsules are ruptured. Various adhesive systems have been advanced and include heat reactivatable, resin-catalyst, solvent reactivatable, and totally encapsulated systems.

Another application (67) using films of microcapsules involves absorbent material which may be used for cleaning and wiping. In this case, the pressure applied during use releases an encapsulated soil-removing liquid. Similar products are becoming increasingly popular in the advertising media for fragrances and foods.

Other microencapsulated products, such as aspirin, have been marketed, and the potential for products seems to be unlimited. This is due to the variety of techniques that exists for encapsulating particles as a means of packaging, separating, and/or storing materials on a microscopic level for later release under controlled conditions. Pharmaceutical applications such as taste-masking of bitter drugs, formulation of prolonged-action medicinals, separation of incompatible materials, protection of moisture- and light-sensitive drugs, and formulations for enzyme-replacement therapy are areas currently receiving considerable attention.

Other areas, allied to pharmaceuticals, which are being investigated include agricultural chemicals and foods. In agriculture, microcapsules of insecticides, fungicides, and various microorganisms, for example, have been made in attempts to increase the longevity of action of the encapsulated material.

The food industry is using microcapsules as containers for maintaining the quality of fats, oils, and flavors. The encapsulated materials are released during the preparation of the meal or during ingestion.

Perhaps the most imaginative area for the application of encapsulated materials is in aerospace studies. Cosmic dosimeters utilizing encapsulated live bacteria are already in use. Measurement of survival of bacteria during a space trip can indicate how much cosmic radiation was encountered. Another possibility in the area of space travel may be in the construction of urethan-type shelters. This application depends on the encapsulation of a polymer which foams when the capsules are broken. This and other applications may be found in many of the references cited to this point; however, no attempt has been made to exhaust this type of reference. References 68–81 have been included in the list so that the interested reader may pursue the topic further.

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RESEARCH ARTICLES

Thermodynamic Analysis of Structure–Activity Relationships of Drugs: Prediction of Optimal Structure

TAKERU HIGUCHI and STANLEY S. DAVIS*

Abstract □ A new quantitative and comprehensive approach relating structures of congeneric drugs to their relative biological activities is presented. The analysis is derived on the basis that structure–activity relationships represent a family, a different situation applying to each phenomenon such as drug absorption, drug transport, drug transformation, and drug excretion. The present treatment considers the relationship under equilibrium or quasiequilibrium conditions, thus permitting rigorous thermodynamic treatment. On the basis of the effect of structural changes on the distributive tendencies of the drug in various body tissues, including the receptor site, relationships have been derived which are surprisingly in good agreement with available experimental data. The approach suggests a rational way to predict the degree of lipophilicity which would result in maximal activity.

Keyphrases □ Structure–activity relationships, drugs—optimal structure prediction □ Thermodynamic analysis—structure–activity relationships □ Equilibrium conditions, model compartments—thermodynamic activity, drugs □ Energy change—aqueous–lipid partitioning

Persistent efforts have been made over many decades to bring some satisfactory order to the correlation of the relative activities of drugs with their molecular structure. The last few years have seen a great upsurge in interest in this direction. In this publication, the authors: (*a*) review many of the earlier hypotheses and theories dealing with structure–activity relationships, and (*b*) present a new formulation of the problem based on thermodynamics.

The proposed approach, which will be treated in depth later in this paper, assumes that any observed biological activity in the animal or any test system usually involves one or more time-independent situations and a large number of time-dependent processes such as drug absorption, drug transport, drug transformation, and drug excretion. Since structural alterations affect each of these differently, it would appear highly unlikely that any single relationship can account for the observed situation. The present treatment has been largely limited to analysis of the effects of structural changes on the time-invariant activity of drugs.

As a general approximation, overall interaction of a drug molecule with its receptor site appears to be resolvable into two parts. The first is highly specific in nature and is presumably responsible for the "lock and