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COACERVATION-PHASE SEPARATION TECHNOLOGY

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DEFINITIONS

The earliest known appearance of the word, phase, was in 1812 (Onions, 1933). An appropriate definition of the word for this chapter is 'a homogeneous, physically distinct, and mechanically separable portion of matter that is present in a non-homogeneous, physical-chemical system and that may be a single compound or a mixture,' (Gove, 1963).

Phase separation is a broad term that may be applied to various processes such as the formation of a solid or liquid phase from a solution. Examples are the crystallization of a salt or the precipitation of a polymer as the result of the removal of some solvent from solution. The new phase is physically distinct and has different properties compared with its solution and can be separated by mechanical means.

The word coacervate was first noted in 1623 (Onions, 1933). This word may be defined in the present context as 'an aggregate of colloidal droplets (as of two hydrophilic sols or of a sol and ions of opposite charge) held together by electrostatic attractive forces,' (Gove, 1963).

Coacervation is a term used to describe the formation of a coacervate related to phase separation and has been applied to the separation of a colloid from a solution into a phase rich in the colloid called the coacervate and the remaining phase which is poor in colloid (Bungenberg de Jong, 1949a). The coacervate has certain properties that distinguish it from the original solution. The coacervate will form a separate liquid layer, but with stirring may form droplets suspended in the polymer-poor phase; furthermore it is usually more viscous, more concentrated and often has the property of binding or adsorbing onto, or engulfing a solid or liquid which

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may be added in to the system.

Coacervation has also been defined as the partial miscibility of two or more optically isotropic liquids, at least one of which is in the colloidal state. It may also be defined as the production by coagulation of a hydrophilic sol of a liquid phase which often appears as viscous drops instead of forming a continuous liquid phase (Considine, 1983). Luzzi (1976) indicated that a solid precipitate is not formed, but a polymer phase consisting of liquid droplets. Bungenberg de Jong (1949a) indicated that simple coacervation is concerned with non-ionized groups on the macromolecule and complex coacervation is concerned with the charges on the macromolecule and the formation of salt bonds. Luzzi (1976) and Deasy (1984a) indicate that simple coacervation usually deals with systems containing only one colloidal solute and complex coacervation involves systems containing more than one colloid, the solvent being water. Arshady (1990a) uses the term coacervation to include the use of both water and non-aqueous systems and describes simple coacervation and complex coacervation in terms of one or two polymers in aqueous systems, respectively. Another definition of a coacervate proposed by Ecanow *et al.* (1990) is that phase most dissimilar to water in its physical chemical properties. Deasy (1984a) has pointed out that the solvent is continuous on both sides of the interface and that the polymer or macromolecule is able to diffuse between the two phases.

Some authors separate the discussion of microencapsulation by coacervation, which includes the use of temperature change or incompatible solvent addition, from other phase separation methods such as the use of emulsification and/or solvent removal to prepare a polymer-rich phase (Kondo, 1979a; Arshady 1990a,b; Watts *et al.*, 1990). Other authors include all these processes in the term coacervation-phase separation to indicate that a new phase, a polymer-rich phase, is being formed (Luzzi, 1976; Deasy, 1984a,b).

In any case, a process is applied to a polymer solution, usually dilute, to reduce solubility in the system to such a degree that appropriate phase separation of the polymer takes place, that is the formation of a polymer-rich phase. This polymer-rich phase may be used to treat pharmaceuticals and other substances. Alternatively, the formation of the colloid-rich phase may result in flocculation and the colloid is present in a higher dispersed state and is usually not satisfactory for encapsulation (Bungenberg de Jong, 1949a).

HISTORY

The term coacervation is derived from the latin acervus, meaning aggregation, and the prefix co to indicate union of colloidal particles. Bungenberg

de Jong and Kruyt described the term in 1929 and 1930, as noted by Bungenberg de Jong (1949a). Two chapters, 'Crystallization - Coacervation - Flocculation' and 'Complex Colloidal Systems' describing the early work of coacervation, were prepared by Bungenberg de Jong (1949a,b). The term was used to indicate the formation of colloid rich liquids brought about by various processes which caused phase separation in aqueous systems of macromolecules or colloids in solution.

In 1954, Green and associates of the National Cash Register Company researched the coacervation process using gelatin and gelatin-acacia for commercial purposes. This led to the publication of a number of patents for the preparation of carbonless carbon paper. The result of the coacervation process was the formation of microcapsules containing a colourless dye precursor. The microcapsules were attached to the underside of the paper, and the dye was released upon pressure from pencil or pen and reacted with an acid clay which coated the top surface of the subsequent page; a copy was formed as a result (Deasy, 1984a; Kondo, 1979b).

A brief history of the process using phase separation by emulsification and/or solvent evaporation/extraction is provided by Arshady (1990b), who indicates that early examples include the formation of microspheres/microcapsules of cellulose beads by Wieland and Determan in 1968, and that of dye-loaded polystyrene microcapsules by Vranken and Claeys in 1970. An extensive list of early patents is provided by Kondo (1979a).

The preparation of microcapsules is the single, most important use of coacervation-phase separation because microcapsules are widely used in many industries such as printing, food, aerospace, agriculture, cosmetics, and especially pharmaceuticals. Other methods of microencapsulation have been investigated and are used extensively. The two other principal methods of microencapsulation are chemical processes which include interfacial polymerization and *in situ* polymerization and also mechanical processes which include, for example, air suspension coating and spray drying (Kondo, 1979c; Deasy, 1984c).

REVIEWS

While it is the purpose of this chapter to inform the reader of recent technology related to coacervation-phase separation, it should be pointed out that there are a number of reviews on coacervation-phase separation in both journals and textbooks. Most textbooks with a title containing the word microencapsulation or controlled release include a chapter or two on coacervation and/or phase separation, and usually other chapters dealing with topics such as different methods of preparing microcapsules and

various applications. Journal reviews specifically related to coacervation-phase separation include those of Arshady (1990a,b), Madan (1978), Watts *et al.* (1990), Tice and Gilley (1985), Van Oss (1988–89). Journal reviews which include some discussion of coacervation-phase separation include those of Jalil and Nixon (1990a), Thies (1975, 1982), Luzzi (1970), Nixon (1985). Complete chapters on coacervation-phase separation in textbooks are: Kondo (1979a), Bakan (1980), Calanchi and Maccari (1980), Gutcho (1979), Deasy (1984a,b), Donbrow (1992), Fong (1988), Flory (1953), Veis (1970a), Nixon and Harris (1986), Wong and Nixon (1986). Finally, textbooks which include some discussion of coacervation-phase separation have sections prepared by Sparks (1984), Speiser (1976), Luzzi (1976), Hui *et al.* (1987), Kato (1983), Oppenheim (1986), Benoit and Puisieux (1986), Bakan (1986), and Luzzi and Palmieri (1984).

GENERAL PROCESS

A general description of coacervation-phase separation is outlined below. It should be noted that a large number of changes can be made in the process.

Step 1

In order to produce a suitable product such as microcapsules or microspheres by the methods of coacervation-phase separation, it is necessary to select the polymer or macromolecule which will provide the appropriate coating or matrix characteristics desired in the final product, such as an enteric coating or a product to control the release of the drug. The polymer is dissolved in a suitable solvent so that it is usually fully solvated.

Step 2

If it is desired to encapsulate a core such as a drug or chemical, it may be added to the continually stirred polymer solution to form, preferably, a dispersion of the core in the polymer solution. The solvent for the polymer is selected, preferably so that it does not dissolve the core.

Step 3

One of many processes, such as the addition of a non-solvent for the polymer, is used to bring about coacervation-phase separation of the poly-

mer. This process promotes the formation of a new phase 'the coacervate' in a coacervation process. With stirring; coacervate droplets form which encapsulate the core to form microcapsules. It should be noted that most of the solvent used to dissolve the polymer is now the polymer-poor phase and forms the suspending medium in which the core and the coacervate droplets are stirred; this liquid is sometimes called the manufacturing phase. In the case of solvent removal, for example by evaporation, the polymer phase is enriched in polymer and it will eventually deposit on the core. In this system, because the solvent for the polymer has been removed, it may be necessary to provide another liquid, such as liquid paraffin or water which does not evaporate appreciably and is used to suspend the core and the polymer enriched phase.

Step 4

The polymer-rich droplets containing the drug are further desolvated by a process similar to that noted above, or a different process. The polymer may also be hardened by a number of methods such as thermal desolvation or crosslinking to form a product, microcapsules for example, which preferably does not aggregate.

Step 5

The microcapsules are then collected and may be rinsed with an appropriate liquid to remove unwanted solvents and excipients (Bakan, 1980; Deasy, 1984a).

PROCESSES

In order to bring about coacervation-phase separation, a number of processes have been employed. These have been developed and are being improved in order to meet the many requirements of producing microcapsules or microspheres with appropriate characteristics. Some of the factors which must be considered in the process include:

- Solubility of the polymer
- Solubility of the drug
- Heat stability of drug and polymer
- Proper size range of microcapsules or product
- Formation of coacervate or concentrated polymer solution with suitable characteristics such as appropriate viscosity, deposition onto and adherence to the core

- Appropriate shape characteristics
- Sensitivity of enzymes, biological products or drugs to the process

As a result of the characteristics of the polymer, the properties of the core and the desired features of the final product, which is usually microcapsules or microspheres, a number of processes have been developed to effect coacervation-phase separation. The following discussion is an attempt to organize the various processes and is based on the solubility of the polymer, the number of polymers which are expected to form the coating material and the type of process used in the procedure.

Polymer solubility. The solvent used to dissolve the polymer is water or an organic liquid. In order for coacervation-phase separation to take place, it is first necessary to dissolve the polymer in an appropriate solvent so that it can be induced to separate in a more viscous, but still fluid state, in order that it can surround or mix with the core and then be hardened. While most polymers are either soluble in water, such as gelatin, or in an organic solvent, e.g. ethyl acetate, such as ethylcellulose, some polymers, e.g. cellulose acetate phthalate, are soluble in acetone and also in alkaline water.

Number of polymers. In aqueous systems one or two water-soluble polymers are frequently used to form the polymer wall or matrix of the product. Usually, only a single polymer is used to form the wall or the matrix of the microcapsule when the polymer is soluble in the organic liquid. The intentional incorporation of two organic soluble polymers within the same coat or matrix of the microcapsules is infrequent.

It should be noted that polymers may also be used to induce coacervation-phase separation, to improve the process such as minimizing aggregation, or to stabilize an emulsion during the formation of microcapsules, but not be incorporated into the microcapsule coat. Polymers may also be used to gel the interior, that is the core, of liquid-filled microcapsules (Kondo, 1979a).

Processes

I A single wall-forming polymer soluble in water

- addition of a miscible liquid, a non-solvent for the polymer
- addition of a water-soluble salt
- change of temperature
- addition of an incompatible or non-wall-forming polymer
- adjustment of pH
- addition of reacting ions

II Two or more wall-forming polymers soluble in water

- pH adjustment
- dilution and/or temperature change

- addition of an incompatible or non-wall-forming polymer
- three wall-forming polymers

III A single wall-forming polymer soluble in an organic liquid

- addition of a miscible liquid, a non-solvent for the polymer
- change of temperature
- addition of an incompatible or non-wall-forming polymer
- evaporation with a miscible liquid, a non-solvent for the polymer
- evaporation with an immiscible polar liquid, a non-solvent for the polymer
- evaporation or removal with an immiscible organic liquid, a non-solvent for the polymer

IV Two wall-forming polymers soluble in organic liquids
V One wall-forming polymer soluble in water and one soluble in an organic liquid

While emphasis is placed on the above classification, it would appear that the properties of the core material are not important. This is not true as the core, whether a solid, a mixture of solids, a liquid, a solution, a suspension or an emulsion, for example, may alter or inhibit the process of coacervation-phase separation. A suitable process must be selected in order to obtain a satisfactory product in terms of maximum utilization of the core and appropriate characteristics of the product.

In many cases it is not necessary to have a core present - empty microcapsules are formed. In other cases microcapsules are not readily formed unless there is a core present to promote deposition of the polymer. Only a few procedures which do not pertain to pharmacy will be described in order to exemplify different procedures or materials. Coacervation-phase separation is also used extensively in a number of other fields, such as photography, agriculture, food and biology.

I A single wall-forming polymer soluble in water

Addition of a miscible liquid, a non-solvent for the polymer

When ethanol is added to an aqueous solution of gelatin, there is a competition for the water molecules, and some of the water is removed from the gelatin. The partially dehydrated polymer begins to aggregate and a phase rich in gelatin, the coacervate, separates from solution. The addition of excess ethanol causes the formation of a gelatinous mass which is not satisfactory for microencapsulation. As ethanol is added, the coacervate is

formed and tends to envelop water-insoluble powders or liquids. Phase diagrams are useful to describe the appropriate concentrations to select for coacervation (Kondo, 1979a, Deasy, 1984a).

As an example, rose oil has been encapsulated by this process above room temperature. A limited amount of ethanol was added, and the temperature was decreased to harden the gelatin microcapsules. After separation the microcapsules were washed with ethanol and dried. A number of polymers other than gelatin may be used, such as agar, pectin, methylcellulose and polyvinyl alcohol, and a number of other hydrophilic organic liquids have been employed - namely acetone, dioxane, isopropanol (Kondo, 1979a). Other modifications of this method include temperature control, pH adjustment and hardening with formalin (Khalil *et al.*, 1968; Nixon *et al.*, 1968). The core material to be encapsulated should have a low solubility in water in order to obtain an appropriate yield of product and may be either liquid or solid.

A useful development of this process is the formation of nanoparticles which are so named because their size is in the nanometer range. Because of their small size, they may be considered as useful drug delivery devices for parenteral purposes. The preparation of nanoparticles involves the treatment of a solution of gelatin containing a suitable surfactant, at appropriate temperature and pH with ethanol, so that the coacervate region is just reached, as indicated by an increase in turbidity. The coacervate is redissolved so that the molecules exist in the 'rolling up region'. To prevent aggregation of the nanoparticles, the mixture is homogenized. The rolled up gelatin can entrap the core material and then the nanoparticles are hardened with an agent such as glutaraldehyde (Marty *et al.*, 1978; Kreuter, 1978).

Addition of a water-soluble salt

Gelatin and other hydrophilic colloids may be treated with various salts such as sodium sulfate which tend to desolvate the colloid, effecting coacervation. This process tends to require a high concentration of salt, 20–30%, which should be removed by treatment with water. Salts with different water-binding capacity according to the Hofmeister series may be used. It is usually necessary to harden the microcapsules by temperature change, pH adjustment or treatment with formaldehyde to obtain a satisfactory product (Khalil *et al.*, 1968; Deasy, 1984a).

Change of temperature

It has been indicated in a number of reviews that temperature change will promote coacervation-phase separation (Madan, 1978; Sparks 1984). The

phase separation is believed to be brought about as a result of a decrease in solubility of the polymer. Thus, a decrease in temperature will promote phase separation of gelatin from solution while an increase of temperature will effect a phase separation for methylcellulose, ethyl hydroxyethylcellulose and hydroxy propylcellulose (Sparks, 1984).

Temperature change is more often used in conjunction with other physicochemical factors such as the use of non-solvents and pH adjustment to effect the appropriate coacervation condition. For example, a dispersion of a drug, aspirin, in gelatin was added to mineral oil then phase separation was promoted by a reduction in temperature then isopropyl alcohol was added and the product was hardened with formaldehyde (Paradissis and Parrott, 1968).

Addition of an incompatible or non-wall-forming polymer

The addition of a polymer which has a high affinity for water has been used to induce coacervation-phase separation of the coating polymer, gelatin. Thus, a core was incorporated in a gelatin solution containing 10 to 25% polyethylene glycol to cause phase separation (Kondo, 1979a). Starch has also been noted to induce phase separation when gelatin is used as the wall-forming material (Madan, 1978). A low concentration of the non-wall-forming polymer may also aid in the control of the viscosity of the solution.

Adjustment of pH

There are a number of polymers which are soluble in water and which possess either or both acidic and basic groups in their structure. Thus, an alteration of the pH causes a change in the ionization of the polymer, leading to insolubility. This effects a phase change and under the appropriate conditions, cores, either liquid or solid, suspended in the polymer solution can be encapsulated when the pH is adjusted. The polymer solution containing the suspended core is allowed to drop into a buffered solution and encapsulation takes place; alternatively, the pH of the aqueous polymer solution containing core is slowly changed. The water-insoluble drug sulfadiazine was encapsulated by permitting an alkaline solution of cellulose acetate phthalate containing the drug to drop into a solution of acetic acid (Milovanovic and Nairn, 1986).

A number of polymers such as casein, phthalylated gelatin, a copolymer of methacrylic acid and methylacrylate have been used to encapsulate various core materials such as photographic materials, solvents and oils.

Addition of reacting ions

Cores of biologically active cells in a suspension of a sodium alginate have been encapsulated successfully by permitting the mixture to flow dropwise into a dilute solution of $CaCl_2$. The calcium ions caused immediate gelling of each droplet. The microcapsules were collected and subsequently treated with a polylysine solution to provide a permanent, semi-permeable membrane. In this process the calcium ions react with the alginate ions to produce a colloid-rich phase entrapping the core material (Lim and Moss, 1981).

II Two or more wall-forming polymers soluble in water

pH adjustment

Under suitable conditions, phase separation will occur with a positively charged colloid and a negatively charged colloid in an aqueous medium. This process is usually called complex coacervation. The polymer-rich phase may be used to entrap a core material, if present, and thus produce microcapsules. The most frequent type of this coacervation process is conducted with gelatin and acacia. A 50:50 mixture of a dilute solution of gelatin and gum arabic (acacia) at about 40°C is mixed and the pH is adjusted to 4. This pH is below the isoelectric point of gelatin, and thus it is positively charged while acacia is still negatively charged. The new phase is the coacervate, which has a colloid composition of about 20% and a composition ratio of about 1:1 of the two polymers. The system is cooled, then formaldehyde is added to rigidize the microcapsule. Other polyanionic colloids such as sodium alginate, or polyvinyl methyl ether–maleic anhydride copolymer have been used to form the complex coacervate, although acacia has been the most extensively studied (Kondo, 1979a).

Dilution and/or temperature change

Variations of inducing phase separation of the complex coacervate include not only adjustment of pH, briefly described above, but also dilution of a concentrated solution of gelatin $\geqslant 6\%$ with warm water or by beginning the process at a low temperature (10°C) and increasing the temperature so that the coacervate is formed. The efficient formation of the gelatin–acacia coacervate and its composition depends upon polymer and salt concentration, pH and temperature, each of which must be controlled or adjusted throughout the process (Kondo, 1979a).

Addition of an incompatible or non-wall-forming polymer

Liquid paraffin was encapsulated by first emulsifying it with a solution of acacia and then treating it with an aqueous solution of gelatin containing a non-ionic polymer, polyethylene oxide. The gelatin concentration, the pH and temperature were adjusted for efficient complex coacervation. The use of polyethylene oxide aids in the induction of coacervation over a wider pH range (Jizomoto, 1984).

Three wall-forming polymers

Finally, it should be noted that systems employing three water-soluble polymers have been investigated; for example, gum arabic as the polyanion and gelatin and haemoglobin as the polycations. In this process the pH is lowered to 5 and the coacervate is comprised of haemoglobin and gum arabic. When the pH is lowered to below 4.3, coacervates of gelatin and gum arabic enclose the first coacervate drops. As a result, capsules with two walls are formed (Kondo, 1979a).

III A single wall-forming polymer soluble in an organic liquid

Addition of a miscible liquid, a non-solvent for the polymer

In this process, the polymer is dissolved in an appropriate organic solvent, then a non-solvent, which is miscible with the polymer solvent, is used to induce phase separation. The non-solvent may be organic or an aqueous liquid (Kondo, 1979a). Frequently, low polymer concentrations are used, along with gradual phase separation to promote appropriate encapsulation. This permits the polymer solution to deposit onto the core and at the same time, flow evenly. The formation of high polymer concentrations tends to provide a demixing effect. The demixing effect and coacervation are best explained by phase diagrams. In Fig. 1 the line AKB represents the formation of a new phase. If the original concentration of polymer is on the SD, and heptane is added, a coacervate is formed; however, if the original concentration is on the line DP and heptane is added, then the polymer tends to come out of solution in a form that is not satisfactory for coating (Kondo, 1979a).

An example of this process is the encapsulation of magnesium hydroxide with ethylcellulose, using dichloromethane as the solvent and effecting phase separation with *n*-hexane as the non-solvent (Kasai and Koishi, 1977). Aqueous solutions of dyes have been encapsulated by this process. The

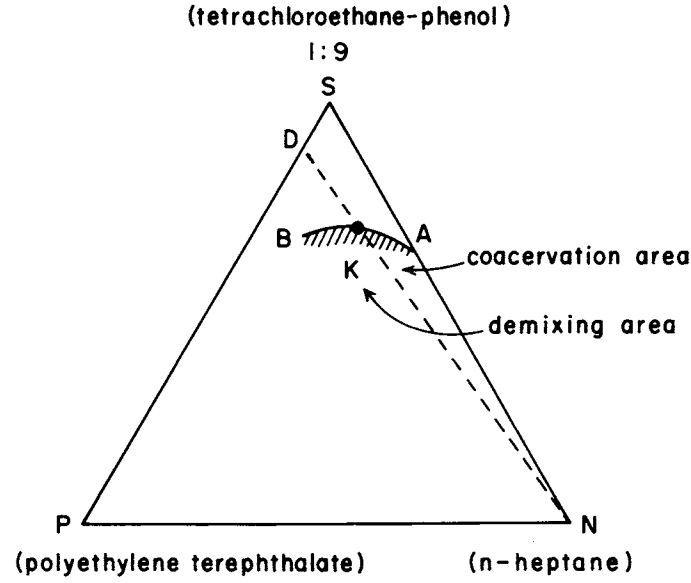

Fig. 1 Ternary diagram showing the phase-separation region of a mixture of polyethylene terephthalate, phenol, and heptane: AB, binodal curve; K, critical point. Reproduced with permission from Kondo (1979a), *Microcapsule Processing and Technology*, p. 96. Marcel Dekker, Inc., New York.

aqueous solution was dispersed in a solution of ethylcellulose dissolved in toluene containing a surface-active agent to assist emulsification. The miscible non-solvent, petroleum ether, was added to induce phase separation of the polymer onto the aqueous droplet (Reyes, 1965). Kondo (1979a) provides an extensive list of polymers, solvents and non-solvents. Some of the polymers are ethylcellulose, cellulose acetate butyrate, polyethylene and polyisobutyl methacrylate. The removal of the residual solvent from the product may be accomplished by washing with more non-solvent or by drying.

Change of temperature

This method of inducing phase separation depends upon the difference in solubility of the coating polymer as the temperature changes. For example, ethylcellulose is dissolved in the solvent, cyclohexane, at about 80°C and as the solution is allowed to cool the coacervate which is formed surrounds the core material which is dispersed throughout the system by appropriate

stirring. This process was described by Fanger *et al.* (1970) who reported that after cooling to harden the product, an aggregated product was formed. This system has been studied in detail by Jalsenjak *et al.* (1976). It was found that the procedure was sensitive to minor changes in the procedure. Stirring speed, the vessel geometry and the rate of cooling affected the size distribution of the product, the amount of aggregation, surface characteristics and porosity.

Addition of an incompatible polymer or non-wall-forming polymer

This method of preparing microcapsules by coacervation is similar to the one previously described, in that while temperature is a main factor used to effect phase separation, an incompatible polymer is added to the system in order to aid in the induction of coacervation and/or to minimize the aggregation of microcapsules so that a more uniform product is obtained. As an example of this method, a suspension of the core, aspirin, in a solution of ethylcellulose and polyethylene of low molecular weight in cyclohexane was prepared at 80°C. Upon cooling slowly to room temperature the ethylcellulose separates from solution to surround the core. The polyethylene precipitates from solution in the form of fine particles. The purpose of the polyethylene is not clear, but may aid in the coacervation of the ethylcellulose and also minimize the coalescence of microcapsules prior to hardening of the walls (Kondo, 1979a).

Other incompatible polymers are butyl rubber, polybutadiene, and polydimethylsiloxane. Polyisobutylene, another polymer, apparently acts as a protective colloid and minimizes the formation of agglomerates of ethylcellulose (Deasy, 1984b). Polyisobutylene also promotes the formation of smooth, non-aggregated droplets and it has been shown that it is not incorporated into the wall (Benita and Donbrow, 1980).

After the capsules have been hardened, it is necessary to remove the incompatible polymer. This is readily accomplished, if the polymer remains in solution as the temperature is lowered, by filtration and rinsing the product, or by sieving if the incompatible polymer has a different particle size than the microcapsules.

Evaporation, with a miscible liquid, a non-solvent for the polymer

In this process the polymer is dissolved in an appropriate solvent and then another liquid, the suspending vehicle which has a higher boiling point and which is miscible with the polymer solvent is added. However, this liquid is a non-solvent for the polymer. Prior to evaporation the system is one phase, not including the core which may be added to the polymer solution

either before or after mixing with the miscible liquid. During evaporation the polymer separates from solution forming liquid droplets, which are dispersed in the suspending liquid and these coat the core material (Fong, 1988).

An example of this process is the microencapsulation of drug ion-exchange resin complex. The core was dispersed in a solution of polyisobutylene dissolved in cyclohexane, and light liquid paraffin was added. A solution of ethylcellulose in ethylacetate was then added and evaporation allowed to proceed. The microcapsules were treated with cyclohexane, filtered and washed to remove the suspending liquid (Moldenhauer and Nairn, 1990).

Evaporation with an immiscible polar liquid, a non-solvent for the polymer

The core is dissolved or dispersed in an organic liquid, which contains the dissolved polymer and which has a relatively high vapour pressure and is immiscible with water. This mixture is dispersed in water, the immiscible liquid a non-solvent for the polymer, usually contains surface-active agents or a soluble viscosity agent which aid the formation and stabilization of the resulting oil/water (o/w) emulsion. The organic solvent is removed using heat or by reducing pressure. As the organic solvent is removed, the polymer solution becomes concentrated and phase separation of the polymer occurs with the result that the dispersed or dissolved core is entrapped in the polymer matrix (Hui *et al.*, 1987).

As an example of the above, sulfathiazole was dispersed in a solution of ethylcellulose in chloroform. This mixture was then dispersed in an aqueous solution of sodium lauryl sulfate to form an emulsion. After stirring for several hours, the organic solvent evaporated, resulting in the formation of ethylcellulose microcapsules. Other polymers used in this process include polylactic acid, polystyrene, and a large number of hydrophobic polymers (Kondo, 1979a; Deasy, 1984a).

The yield of microencapsulated products is high if the core material has a low solubility in water, otherwise the core will partition into the aqueous phase. The partitioning effect can be decreased if the aqueous phase contains salt, which decreases the solubility of the core in the aqueous phase, or by adjusting the pH to decrease the water solubility of the drug. Improved yields of drug can be achieved if the organic solvent has some solubility in water. These solvents then cause rapid deposition of the polymer at the interface, thus forming a barrier that decreases the rate of partitioning of the core into the aqueous phase (Watts *et al.*, 1990).

If the core is an aqueous solution or suspension, it is first dispersed in

the polymer solution to give a water/oil (w/o) emulsion and when this is added to the aqueous solution containing the surface-active agent and/or viscosity agent, a water/oil/water (w/o/w) emulsion is formed. The capsule size is influenced by factors such as the viscosity of the starting liquid, agitation speed, and the temperature. It has been suggested that if suitable surfactants are used to prepare the dispersion of the aqueous phase in the polymer solution, small capsules may be prepared with a size of $\approx 10\,\mu m$ (Kondo, 1979a).

An example of this process is the encapsulation of an aqueous solution of an enzyme. This solution is added to a 5 or 10% solution of a polystyrene dissolved in benzene and a primary emulsion is formed by means of a homogenizer. This primary w/o emulsion is then dispersed in an aqueous solution containing a viscosity agent such as gelatin to form the w/o/w emulsion. The temperature is raised to 40°C with constant stirring until the benzene dissolves in the aqueous layer and is removed by evaporation. The polymer is deposited around the aqueous enzyme solution to form the shell wall (Kondo, 1979a).

One difficulty with the process is the time it takes to remove the solvent from the polymer solution, as it is immiscible with the water phase even if the preparation is subjected to heating and reduced pressure. Other techniques used to remove the polymer solvent include freeze drying or adding a solvent that is miscible with water and the polymer solvent but a non-solvent for the polymer (Kondo, 1979a).

A modification of the above process has been called the interfacial deposition technique. In this particular process, *n*-heptane was emulsified in an aqueous solution of Pluronic F68, an emulsifier, to give an o/w emulsion. A solution of dichloromethane containing either poly (L-lactide) or poly (DL-lactide) was added dropwise to the emulsion which was stirred under partial vacuum. The polymer deposited at the surface of the *n*-heptane droplets to yield small microcapsules containing water (Makino *et al.*, 1985).

Evaporation or removal with an immiscible organic liquid, a non-solvent for the polymer

This process is especially useful for the preparation of microencapsulated, water-soluble compounds. The drug is dissolved or dispersed in the solution of the organic polymer and this is then dispersed into another organic liquid, usually mineral oil; as a result, an oil/oil (o/o) emulsion or separate phase is formed. The inner phase contains the drug and the polymer and the outer phase is mineral oil. The solvent for the polymer may be partially extracted by the mineral oil and/or may be allowed to evaporate. The

resulting microcapsules are filtered and washed with a non-solvent which removes the solvent for the polymer and the mineral oil.

A number of drugs and vaccines have been prepared in microcapsule form in cellulose acetate phthalate in this manner. For example, the drug or vaccine is dispersed in mineral oil, with or without sorbitan monooleate, with stirring and then an acetone-ethanol solution of cellulose acetate phthalate is added. The polymer separates and entraps the drug; after some evaporation has taken place, the mixture is treated with chloroform, filtered and further treated with chloroform (Maharaj *et al.*, 1984; Beyger and Nairn, 1986).

Some investigators, after decanting the excess mineral oil from an ethylcellulose ethylacetate system, have placed the product directly in soft gelatin capsules (D'Onofrio *et al.*, 1979).

IV Two wall-forming polymers soluble in organic solvents

This method has been investigated by Itoh *et al.* (1980) in which a mixture of ethylcellulose and polylactic acid was used to form the wall of the product. The drug sulfamethizole was suspended in the solution of the two polymers which were dissolved in ethylacetate. The miscible non-solvent, pentane, was added dropwise until phase separation occurred and microcapsules were obtained and washed.

V One wall-forming polymer soluble in water and one soluble in an organic liquid

This process, developed by Morris and Warburton (1980, 1982), provides microcapsules that possess three walls. An aqueous acacia solution was dispersed into a solution of polychloroprene in xylene or ethylcellulose in ethylacetate to yield a w/o emulsion. This preparation was then dispersed into an acacia solution to yield a w/o/w emulsion. The organic solvent was allowed to evaporate by bubbling air through the multiple emulsion or removed by dialysis to give microcapsules with a polymeric wall surrounding a solution of acacia. Subsequent evaporation of water leads to the formation of microcapsules with three walls.

CONSIDERATIONS PRIOR TO PROCESSING

The successful preparation of a microencapsulated product depends on the core, the encapsulating polymer and the process of coacervation-phase

separation. Once the core has been selected, the formulator will have a choice of a few polymers for a specific pharmaceutical purpose. A consideration of the process must then be made. The selection of the process for the preparation of a suitable product depends upon a number of factors, but principally upon the solubility of the coating polymer and the solubility of the core.

Wall polymer. The polymer used to encapsulate the core is often called the wall polymer and in some cases the polymer will form a wall around a large, solid particle or a liquid drop. However, in other cases the encapsulation polymer may be dispersed throughout the microcapsule providing a matrix type of preparation containing core particles. Finally, the core may be homogeneously or molecularly dispersed throughout the polymer. Almost any non-toxic polymer which is soluble in a solvent can be used to encapsulate pharmaceuticals. Consideration must be given to the intended use of the product such as taste masking, controlled release, enteric coating, biodegradability and modifying the form of a drug, that is from liquid to solid. The polymer should be selected on the basis of its physical and chemical characteristics, its suitability for encapsulating the desired compound and the process which will be used (Luzzi, 1976). A number of properties of polymers have been suggested for the purpose of microencapsulation. These include a cohesive film - a film that adheres to, and is compatible with, the core material and provides the desired properties such as strength, flexibility, impermeability, optical properties, stability, moisture sorption, and solubility. Normal applications require the coat to be from 2 to 30% by weight and this corresponds to a thickness range from 0.1 to 200 μm. However, the amount of coat can vary from 1 to 70% by weight. As noted above, some or a good part of the polymer may be distributed throughout the microcapsule (Bakan, 1980).

Information about appropriate wall polymers may be obtained not only from the literature on coacervation-phase separation, but also from data on cast or free films. These films, however, are not only usually thicker than films enclosing microencapsulated drug particles, but the deposition of cast or free films is considered to be different from the formation of a film by coacervation-phase separation technique, and therefore their properties will usually be somewhat different.

Deasy (1984d) has listed a number of commonly used film formers or polymers for microencapsulation and related uses. The table includes polymers from natural sources, such as gelatin, semi-synthetic polymers such as ethylcellulose, synthetic polymers such as polystyrene and copolymers such as poly(lactic-acid-co-glycolic acid). The release mechanisms of several of these polymers is also given.

Polymer solvents. Once the polymer has been chosen, its solubility characteristics may be determined. The solvent must dissolve the polymer. If the polymer is water soluble, then water may be used to prepare a solution of the polymer; if the polymer is soluble in organic solvents, then a selection of the solvent to be used must be made. Occasionally, a solvent pair will be used. Other considerations for the selection of the organic solvent should be miscibility with another liquid which may be used as a non-solvent, or immiscibility with another liquid, which may be used as the suspending liquid or manufacturing vehicle phase. Furthermore, the polymer solvent should generally not dissolve the core, which may be polar such as water or water-soluble drugs or non-polar such as mineral oil or organic soluble drugs. Other properties to be considered are volatility, toxicity, reaction with the drug and ease of removal from the final product. The polymer-rich phase should have some affinity for the core in order to be adsorbed onto the surface and be fluid enough to encapsulate the core. It is suggested that the process effecting the formation of the polymer-rich phase be slow, and start with a low concentration of polymer. High polymer concentrations generally provide a more rapid phase separation which may be too viscous to provide an appropriate coating of the core. Agglomeration of microcapsules is believed to be caused by the presence of some polymer solvent remaining in the wall. This problem is particularly important when all the solvent is present during the process and until the microcapsules are separated from the suspending liquid. Agglomeration tends to be less when an immiscible liquid is used as the suspending medium because the droplets are appropriately separated in the system. Agglomeration may also minimized by some methods described below (Fong, 1988).

Core. Equal consideration must be given to the core material and its solubility. Types of cores include: (a) no core for the purpose of preparing empty or blank microcapsules; (b) a solid core, e.g., aspirin; (c) a liquid core, e.g., cod liver oil; (d) an active product dissolved in a liquid, e.g., an enzyme in water; (e) on active product dispersed in a liquid, e.g. sulfadiazine in mineral oil; (f) a drug complex, e.g., a drug ion-exchange complex. In order to achieve a high yield of product in terms of active component, it is usually desirable that the core has a low solubility in the polymer solvent or a suspending liquid, used for microencapsulation. However, modifications can be made in the process to improve the yield of the drug product. For example, it may be possible to arrange the conditions in such a way that even if the core material is soluble in the polymer solvent, it has lower solubility than the polymer. In this case the core will come out of solution first and then be encapsulated as phase separation of the polymer takes place. If the above condition is not satisfied, the process of

encapsulation will be inefficient and the product will consist of non-encapsulated core and empty microcapsules and microcapsules containing some core (Fong, 1988).

Solid cores are used more often than liquid cores. One reason for this is that the particle size may be more readily controlled. Large-size cores frequently have only one core particle per microcapsule (Moldenhauer and Nairn, 1990) providing a membrane type of microcapsule. Cores of smaller size may have several particles per microcapsule, either due to agglomeration of core particles before microencapsulation, or as a result of the formation of aggregates of coacervate droplets containing core particles. This leads to a matrix type of microcapsule. Finally, if the core dissolves in the polymer solvent, then provided crystallization or precipitation of the core does not take place, the microcapsule may contain a molecular dispersion of the core in the polymer phase. The shape of the core particle frequently will control the shape of the final product, particularly if the core to coat ratio is high. Thus, grinding, milling and spheronization may be considered in order to obtain the appropriate core size and shape. In addition, polymorphs of a drug may be considered in order to obtain a shape that is more amenable to encapsulation (Deasy, 1984d).

Wall-forming polymers soluble in water

Wall polymer. Wall polymers include acacia, alginate, carboxymethylcellulose, gelatin, polyethylene glycol, poly (vinyl alcohol), albumin, carbupol and pectin. Appropriate polymers may be used singly or in pairs as described below.

Cores – water-soluble. In general, water-soluble solids or liquids are not encapsulated to a great extent when water-soluble polymers are used because the core will be distributed between the aqueous polymer-rich phase and the aqueous polymer-poor phase. There are, however, techniques that may be used to encapsulate water-soluble compounds with water-soluble polymers (Harris, 1981).

1. Make the water-soluble core such as KCl insoluble in water through the use of waxes such as carnauba.
2. While the control of pH is important for water-soluble polymers such as gelatin, it also may be used to alter the solubility of many drugs which are weak acids or bases. Thus, the solubility of salicylic acid is decreased in acid solution and may be a candidate for encapsulation by water-soluble polymers.
3. Preparing water-insoluble cores by first making microcapsules using a water-insoluble polymer and then providing a second coat with a water-soluble coating.

Cores – solid. The encapsulation of a number of solid core materials by means of simple coacervation has been studied in an organized manner by Okada *et al.* (1985a). The ability of different core particles to be encapsulated with gelatin was studied as a function of different miscible non-solvents, and other manufacturing parameters. The effect of solubility, zeta potential and the adsorption of gelatin was related to the ability of the product to be encapsulated. Low solubility, high gelatin adsorption and zeta potential play a significant role in the ability of the process to encapsulate the core.

Cores – liquid. Research has also been carried out on the encapsulation of liquids with water-soluble polymers. Gelatin–acacia microcapsules containing oils or oils containing a drug were prepared by employing polyethylene glycol or polyethylene oxide as the incompatible or non-wall-forming polymer. After cooling, the microcapsules formed were cross-linked with glutaraldehyde (Jizomoto, 1984). Jizomoto also showed that the minimum concentration of the polymer polyethylene glycol (or polyethylene oxide) necessary for complex coacervation depended upon the molecular weight. The molecular weight may be related to the chemical potential and the excluded volume of the polymer used to effect coacervation (Jizomoto, 1985).

Process variables. The total polymer concentration has been shown to be related to droplet size. The mean diameter of the coacervate droplets of gelatin–Carbopol 941 microspheres increased from 50 μm to 135 μm as the concentration of polymers increased fivefold (El Gindy and El Egakey, 1981a,b). Similar results have been described by Mortada *et al.* (1987a) for the gelatin–Gantrez system.

El Gindy and El Egakey (1981a) showed that the droplet size decreased as the speed of rotation increased for the gelatin–Carbopol system; at a speed of 600–650 r.p.m. the mode was about 35 μm, while at 100–150 r.p.m. the mode was approximately 85 μm.

In order to minimize aggregation in the complex coacervate system, gelatin–acacia, Maierson (1969) added a surfactant to the prepared microcapsules, and as a result of steric and charge effects, microcapsules were kept apart and aggregation minimized.

A single wall-forming polymer soluble in an organic liquid

Addition of a miscible liquid, a non-solvent for the polymer

Wall polymer. Wall-forming polymers include acrylates, cellulose acetate, cellulose acetate butyrate, ethylcellulose, poly(lactic acid), poly(lactic-co-

glycolide), polystyrene, polyvinyl acetate, polyvinyl chloride and other polymers (Fong, 1988).

Control of agglomeration. Fong (1988) described a number of patents regarding agglomeration. Agglomeration of poly(lactic acid) microcapsules prepared from a dispersion of drug particles in a solution of the polymer using a non-solvent was minimized by conducting the phase separation at a temperature of −65°C using a dry ice bath. The use of low temperatures made the wall of the microcapsules sufficiently firm during the phase separation process, so that adhesion of the microcapsules was avoided. Another technique for minimizing the agglomeration of microcapsules employs talc. During the addition of the non-solvent, talc, a mineral silicate is added to minimize the adhesion and coalescence of the microcapsules. It is suggested that the talc forms a barrier against adhesion between the microcapsules. Talc has been used to minimize agglomeration in other patents. Polyisobutylene has been used to minimize aggregation of microcapsules prepared from Eudragit RS (Chun and Shin, 1988) and from Eudragit RS100 (Chattaraj *et al.*, 1991).

Polymer solvent. The polymer solvent must be miscible with the non-solvent and should not dissolve the core. The choice of a solvent for a particular polymer can have an effect on the product and its properties. A methacrylate polymer, Eudragit RLPM, has been used to encapsulate riboflavin. When the polymer is dissolved in benzene and then treated with petroleum ether as the non-solvent, phase separation occurs, with the result that large polymeric droplets are formed which adsorb on the surface of the vitamin as a thick, uniform coat. The product provides a slow release of riboflavin. This is in contrast to the use of isopropanol as the solvent which, after treatment with non-solvent, provides smaller coacervate droplets, a thinner coat and faster release (El Sayed *et al.*, 1982).

Non-solvent. The miscible non-solvent should effect phase separation of the polymer and not dissolve the core material. The non-solvent should be easily removed by evaporation or by rinsing with a volatile solvent possessing similar properties to the non-solvent. Both polar and non-polar non-solvents have been used in the formation of microcapsules. Fong (1988) preferred polar non-solvents such as isopropanol and isobutanol to non-polar, non-solvents such as heptane in low temperature microencapsulation. He found that a combination of non-solvents, e.g. propylene glycol and isopropanol, produces larger microcapsules (100–125 μm) than those prepared from isopropanol alone (25–50 μm). In some cases, it is easier to control the wall thickness when the appropriate non-solvent is used to prepare polystyrene microcapsules (Iso *et al.*, 1985a,b).

Core. Generally, the core should be insoluble in both the solvent for the polymer and the non-solvent. A wide variety of cores have been encapsulated by this method, including antibacterial and anticancer agents, steroids, vitamins, antacids, and pharmaceuticals (Fong, 1988). Products with two walls have also been encapsulated (Hiestand, 1966). Methods have been used to encapsulate cores which are soluble in the solvent. For example, soluble thioridazine as the free base was soluble in the polymer solvent, but after converting to the pamoate salt it was insoluble in both the polymer solvent and the non-solvent. Another method for encapsulating a soluble core is to begin phase separation of the polymer before adding the core particles. As an example, after a solution of styrene maleic acid copolymer in ethanol was prepared, the non-solvent isopropyl ether was added until turbidity was first noticed. The drug methylprednisone was then added and the rest of the isopropyl ether was added to complete the process (Fong, 1988).

The non-solvent method of inducing phase separation has been used to prepare products which have two polymers to alter the release of the core. Itoh and Nakano (1980) coated matrix particles composed of an evaporated product of drug and cellulose acetate with ethylcellulose. In a patent, Fong (1988) describes the preparation of microcapsules with a double wall of polylactic acid prepared by essentially repeating the process.

Change of temparature

Wall polymer. The polymer selected for this process must have a low solubility at room temperature and a high solubility at elevated temperature where it is completely dissolved. Few polymers possess this property, for example, ethylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose, methylcellulose (Fong, 1988). The molecular weight of the ethylcellulose affects some of the properties of the final product. Deasy *et al.* (1980) showed that a higher molecular weight of ethylcellulose (100 cp, 0.1 Pa s) gave finer microcapsules and slower drug dissolution than those microcapsules prepared with lower molecular weight ethylcellulose (10 cp, 0.01 Pa s).

Control of agglomeration. Koida *et al.* (1983) found that the agglomeration of microcapsules was affected by the molecular weight. For example, microcapsules in the 149–250 μm size range increased as the molecular weight of the ethylcellulose increased. Agglomeration of microcapsules can be minimized by vigorous agitation, slow cooling near the coacervation temperature and washing with cold solvent (Deasy *et al.*, 1980). Several aliphatic solvents at low temperature, 10°C, have been used to minimize aggregation: pentane, hexane or octane and also cyclohexane (Morse *et al.*, 1978). The

addition of a polymer for the purpose of minimizing aggregation has been investigated. Both butyl rubber and polyethylene have been investigated, however, polyisobutylene has been studied more intensely. Samejima *et al.* (1982) indicated that polyisobutylene prevented aggregation of microcapsules and found it to be equally as effective as butyl rubber and much better than polyethylene. Donbrow and Benita (1977) and Benita and Donbrow (1980) indicated the beneficial effects of polyisobutylene in preventing aggregation and suggested that it was adsorbed onto the surface of the ethylcellulose droplet, probably functioning as a protective colloid. Ethylene vinyl acetate copolymer has also been shown to alter the particle size and perhaps the aggregation of ethylcellulose microcapsules (Lin *et al.*, 1985).

Control of particle size. The particle size of the coacervate drops was shown to decrease as the viscosity of the medium increased as a result of higher concentrations of polyisobutylene in the preparation of ethylcellulose microcapsules in cyclohexane by temperature change (Benita and Donbrow, 1980).

Core. Fong (1988) has provided a list of cores that have been encapsulated by this method; these include aspirin, vitamin C, sodium salicylate, chloramphenicol, isoniazid, phenethicillin potassium, sodium phenobarbital, niacinamide and riboflavin. The core compounds should have a low solubility in the solvent at the coacervation temperature. In addition, the compounds should be stable at the temperature employed. Koida *et al.* (1986) found that the efficacy of encapsulation was also related to low solubility of the core material.

Addition of an incompatible or non-wall-forming polymer

Incompatible polymers. The incompatible polymer is chosen on the basis of its higher solubility in the solvent than the coating polymer, thus there will be a tendency for the coating polymer to come out of solution first and coat the core, resulting in a core that is surrounded by one polymer only. Polymers that have been used are frequently low molecular weight liquids, mainly polybutadiene, methacrylic polymer and polydimethyl siloxane. It has been indicated that the advantage of using an incompatible polymer is that certain properties of the coacervation phase, namely the viscosity and relative volume, can be controlled. If the viscosity of the coacervation phase is too high, proper coating of the core cannot occur (Fong, 1988). Extensive studies on the system poly(DL-lactic-co-glycolic acid) copolymer dissolved in methylene chloride using silicone oil have been made by Ruiz *et al.* (1989).

Wall polymers. Some polymers used to form the walls are ethylcellulose,

polymethylmethacrylate, polystyrene and poly (lactic-co-glycolide). The wall material may be hardened by adding a non-solvent for the polymer, for example microcapsules of methylene blue hydrochloride prepared from the wall polymer ethylcellulose dissolved in toluene employing the incompatible polymer polybutadiene were hardened by treatment with hexane. Other techniques include solvent evaporation and chemical cross-linking (Fong, 1988).

Control of agglomeration. It has been suggested that agglomeration can be minimized when solvent evaporation is used to harden the wall by using excess liquid paraffin and/or low temperatures during the microencapsulation process (Fong, 1988).

Solvent. The solvent must dissolve the wall polymer, the incompatible polymer and it should also be miscible with the washing non-solvent and should not dissolve the core.

Washing solvent. The function of the washing solvent is to remove the polymer solvent from the microcapsules and any incompatible polymer. Consequently, the washing solvent should be miscible with the polymer solvent, dissolve the incompatible polymer and not dissolve the core material or the polymer wall material.

Core material. Some examples of core materials encapsulated by this method include antibiotics, pharmaceuticals, polypeptides and dyes (Fong, 1988).

Evaporation with a miscible liquid, a non-solvent for the polymer

Wall polymer. Polymers include primarily ethylcellulose, polyethylene, ethylene acrylic copolymers and vinyl polymers (Fong, 1988).

Polymer solvent. The polymer solvent should have a relatively high vapour pressure so that it is readily evaporated. Polymer solvents include aliphatic and aromatic hydrocarbons, ketones, ethers, alcohols and esters.

Miscible liquid, a non-solvent for the polymer. The miscible liquid should not dissolve the core or the polymer, but should be miscible in the concentration used with the polymer and solvent, thus at the beginning of the process the mixture is homogeneous. Furthermore, this liquid should have a low vapour pressure so that during evaporation it will function as the suspending liquid. Examples of suspending liquids include hydrocarbons with a high boiling point, silicone fluid and polyethylene glycols (Fong, 1988).

Control of agglomeration. Moldenhauer and Nairn (1990) indicated that polyisobutylene has other effects, in addition to its protective colloidal action, namely, increasing the viscosity of the system, thereby suspending

the core more uniformly, especially larger particle sizes, and decreasing the rate of evaporation, thereby the rate of surface nucleation of the polymer. It has also been suggested that the use of the suspending medium, light liquid paraffin, in this case actually initiates the coacervation process by removing some of the solvent from the polymer.

Coat structure. The rate of evaporation has an effect on the coat structure and thereby the rate of release of the microencapsulated drug (Moldenhauer and Nairn, 1991). Intermediate rates of evaporation provide a dense coat of uniform thickness and a smooth surface, whereas fast evaporation rates produce an irregular, smooth, porous coat and slow rates of evaporation produce a sponge-like coat.

Evaporation with an immiscible polar liquid, a non-solvent for the polymer

Core. The most important factor in selecting a core material is that it has a low solubility in the polar liquid, usually water, otherwise some of the core will partition into the aqueous external phase. A number of cores have been encapsulated, as listed by Fong (1988), such as antibiotics, antineoplastics, anaesthetics, insulin, steroids and other pharmaceuticals. Water-soluble drugs are generally not successfully encapsulated by this method; for example, salicylic acid, theophylline or caffeine could not be encapsulated with polylactic acid from a preparation of the drug in methylene chloride (Bodmeier and McGinity, 1987a).

Several methods have been used to encapsulate water-soluble or partially water-soluble drugs. Weak bases or weak acids in their salt form may be converted to their non-ionic form, thereby reducing their solubility. Chemical modification of a compound can be used to reduce its water solubility, thereby making it easier to encapsulate by this method. The addition of an inorganic salt to the aqueous phase will reduce the solubility of the core. Alternatively, some of the core can be added to the external aqueous phase in order to decrease the partition of the drug from the core to the external aqueous phase. For example, the addition of tetracaine to the non-solvent more than doubled the drug content of the microspheres (Wakiyama *et al.*, 1981). Other examples of loading in the external aqueous phase with drug in order to obtain a high drug content in the microcapsule include a saturated solution of quinidine sulfate (Bodmeier and McGinity, 1987b), and cisplatin (Spenlehauer *et al.*, 1988).

The solubility of the core in the solvent for the polymer will have an effect on the nature of the final product. If the core material is soluble in the polymer solvent, then the encapsulated product will tend to have a homogeneous structure, as both the core and the polymer will come out of

solution as the solvent is evaporated. If the core material is insoluble in the polymer solution, then thought should be given to the particle size before beginning the encapsulation process and milling or micronization should be considered. When the polymer comes out of solution, it will surround the core particles, leading to a heterogeneous product. Finally, large cores have been encapsulated by this method with the result that a membrane covers the drug. This type of product is different from the two types described above which are either homogeneous or heterogeneous in nature. The rate of release from the single core will tend to be constant while that from the monolithic type of microcapsule will tend to decrease with time. Blank microcapsules, that is microcapsules without a core, may also be prepared (Fong, 1988).

The core loading will affect the ratio of polymer to core, the size of the microcapsule, and the rate of release of the core material. The rate of release of dibucaine (Wakiyama *et al.*, 1982), butamben, tetracaine (Wakiyama *et al.*, 1981), ketotifen, and hydrocortisone acetate (Fong, 1988) all increase as the core loading increases. The maximum fraction of core loading depends upon the properties of the microencapsulation system, but may range from 0.4 to 0.75; for example, thioridazine and ketotifen were encapsulated at a fraction of 0.5 to 0.6 (Fong, 1988).

As mentioned in the process section, aqueous solutions have been encapsulated with considerable success, leading to a w/o/w system; however, a water-soluble compound will tend to diffuse into the outer aqueous phase. The loss of water to the external aqueous phase is reduced by using humectants such as glycerin (Fong, 1988). Gelatin has also been used as an internal stabilizer (Kondo, 1979a).

Wall polymers. The polymer selected for this process must be insoluble in water. Some examples include ethylcellulose, polystyrene and cellulose acetate butyrate which are used to prepare microcapsules. A number of biodegradable polymers have been used to prepare microspheres of pharmaceuticals; these include homopolymers and copolymers of lactic acid, glycolic acid, β-hydroxybutyric acid and caprolactam (Fong, 1988). This phenomenon occurs with poly(DL-lactide) (Spenlehauer *et al.*, 1986). Generally, particle size increases with polymer concentration.

The concentration of the wall-forming polymer solution, that is the polymer to solvent ratio, has an effect on the *in vitro* release rate of the core material. The release of the core material decreased when the initial concentration of the polymer solution was increased. The significance of this factor depends upon the drug that is used as the core. When thioridazine was used as the core material, the effect was appreciable as the initial polymer concentration in the process was raised from 5 to 10%.

However, only a small change was noticed when the core was hydrocortisone acetate. It has been suggested that the formation of homogeneous microcapsules containing thioridazine, which is soluble in the polymer solution, was more readily affected by the initial polymer concentration in the solvent than for the hydrocortisone acetate which was not soluble in the polymer solution, and thus formed heterogeneous microcapsules (Fong *et al.*, 1986).

Polymer solvents. The solvent for the wall-forming polymer should be immiscible or have only a low solubility in water. Its boiling point must be lower than that of water so that it will evaporate faster than the external phase water. A solvent frequently used in this microencapsulation process is methylene chloride because of its high vapour pressure and because it is a good solvent for many polymers. Methylene chloride is, however, toxic and considerable amounts can remain in the product even after drying. Weight losses of up to 3.5% were determined by thermogravimetric analysis and chlorine content analyses (Benoit *et al.*, 1986). Other solvents for polymers include chloroform, carbon tetrachloride, ethylene chloride, ethyl ether, benzene and methyl acetate (Fong, 1988).

Aqueous phase. The solubility of the polymer solvent in the aqueous phase has been shown to have a significant effect on drug loading. A study of solvent effects on the entrapment of quinidine sulfate showed that high loading was achieved with the solvent methylene chloride, which had the greatest water solubility, whereas very poor loading was achieved using chloroform, which has a lower water solubility. It is suggested that solvents with high water solubility effect rapid deposition of polymer at the droplet interface, creating a barrier at the interface, thus minimizing drug diffusion out of the microsphere to the outer phase water. Alternatively, if water-miscible polymer solvents are used to dissolve the drug and polymer, agglomerates of polymer are formed on mixing. Mixtures of polymer solvents with different water solubilities can be used to obtain microspheres (Bodmeier and McGinity, 1988).

Surfactants and emulsifying agents. The emulsifying agent should be selected so that an emulsion of the appropriate particle size is readily formed, and it stabilizes the emulsion during removal of the volatile polymer solvent preventing coalescence of the droplets. As this method of phase separation involves the formation of an o/w emulsion, the proper HLB (hydrophile–lipophile balance) value is 8 to 18. The specific emulsifying agent and its concentration should be determined by trial and error.

Salts of fatty acids, particularly sodium or potassium oleate, have been found to be useful for the preparation of microcapsules, including polymers

that are subject to biodegradation. As an example, sodium oleate produced high yields of biodegradable microspheres which were free of agglomeration. The fraction of the drug incorporated was 80–99%, and core loading was up to 0.5 of the weight of the microsphere. The size of the microspheres was less than 150 μm diameter, which will pass through a 20 gauge needle (Fong *et al.*, 1986). It is necessary to consider the pH of the aqueous phase if the surface active agents are subject to different degrees of ionization as a result of different pK values. It will be necessary to maintain a pH at least two to three units above the pK_a of the fatty acid in order for it to be properly ionized.

Surface-active agents, both anionic and non-ionic with an HLB of at least 10 at a concentration of 0.1–1% have been used to prepare microcapsules by this method (Morishita *et al.*, 1976). Watts *et al.* (1990) have listed a number of surface-active agents: polysorbate 80, sodium oleate and sodium dodecyl sulfate. The use of polysorbate 80 in the aqueous phase at a concentration of 2% produced a small reduction in the content of quinidine in the microcapsules. This was attributed to not only an increased solubility of the drug in the aqueous phase, but also to stabilization of the polymer droplet interface which reduced the rate of solvent loss, thereby reducing the polymer deposition rate and permitting a greater loss of drug from the partially formed microcapsules before a suitable hardened barrier could be formed (Bodmeier and McGinity, 1987b). Low yields of small microcapsules may be obtained if surface-active agents are used, e.g. sodium lauryl sulfate (Jaffe, 1981).

Emulsifiers such as gelatin and polyvinyl alcohol at a concentration of 0.5–2.0% may be used to form o/w emulsions (Morishita *et al.*, 1976). Emulsifiers have other effects on the preparation of microspheres as a result of enhanced solubilization. Lomustine and progesterone crystals were formed on the microsphere surface and in the aqueous phase as a result of using polyvinyl alcohol and methylcellulose. The crystals were eliminated and drug loading improved when the emulsifier was removed half way through the evaporation step (Benita *et al.*, 1984). The use of emulsifiers can alter the rate of release of drugs from the microsphere. For example, the use of a gelatin solution which provides a lower solubility for insulin showed only a 26% burst effect, compared with a solution of polyvinyl alcohol which provides a higher solubility for the insulin, resulting in an 88% burst effect. The difference in the burst effect has been attributed to the difference in the solubility of insulin in the hydrophilic colloidal solution (Kwong *et al.*, 1986).

Wakiyama *et al.* (1982) investigated the effect of acid-processed gelatin and alkaline-processed gelatin as an emulsifying agent on the yield and efficiency of microencapsulation of basic amino drugs. A greater efficiency of

drug incorporation was achieved when alkaline-processed gelatin was used, perhaps owing to the fact that alkaline-processed gelatin gave a pH of 7.5, promoting the formation of the non-ionized form of dibucaine (pK_a 1.6 and 8.3) and thus its greater uptake by the solvent as a result of the greater o/w partition coefficient. When the pH of the aqueous phase was raised to 8.6, a greater fraction of the dibucaine was in the non-ionized form and a greater incorporation of drug was observed.

The use of hydrophilic colloids to stabilize the emulsion may have an effect on the shape or particle size of the final product. For example, the use of methylcellulose 400 and polyvinyl alcohol as a stabilizer for the external aqueous phase resulted in oval-shaped microcapsules; most of the products were, however, spherical (Cavalier *et al.*, 1986). In other experiments microsphere size was dependent on the type and concentration of the emulsifying agent; for example, microsphere size increased with increasing polyvinyl alcohol concentration (Benita *et al.* 1984). Other researchers have obtained smaller microspheres with a 1% sodium alginate solution which had a higher viscosity than a 1 or 2% gelatin solution (Wakiyama *et al.*, 1981; Kojima *et al.*, 1984). In some cases high concentrations of gelatin decreased aggregation (Wakiyama *et al.*, 1982).

Solvent evaporation. Solvent evaporation may be accomplished by stirring the emulsion in an apparatus where the surface is exposed to air. Forced air or nitrogen may be used to promote a more rapid evaporation rate. Heat and reduced pressure may also be used but should be controlled at such a rate that microcapsules with a smooth surface are obtained if desired. Heat and low pressure may cause foaming of the emulsion system which should be avoided, particularly at the early stages of phase separation (Fong, 1988).

Stirring rate. After the emulsion containing the particles with appropriate size has been formed and before evaporation has begun, the stirring rate should be such that there is minimum aggregation of the droplets until the microspheres are hardened. The main factors that control the particle size are speed, equipment and the concentration of the polymer in the dispersed phase and the concentration of the hydrophilic polymer or surfactant in the aqueous phase. Particle size tends to decrease and the size range is narrowed as the mixing speed increases (Benita *et al.*, 1984). Stirring speeds of 800–1600 r.p.m. have been used when either gelatin or polyvinyl alcohol have been used as the emulsifier. At 900 r.p.m., small holes were observed in the microspheres, while at 500 r.p.m. they were absent (Nozawa and Higashide, 1978).

Reactor design. The use of baffles minimizes the vortex which can lead to

microsphere aggregation and, in addition, droplet breakup occurs with the result that the average size of the microcapsules is decreased and the microsphere yield is increased (Bodmeier and McGinity, 1987c).

Evaporation or removal with an immiscible organic liquid, a non-solvent for the polymer

Core. The core should have a minimal solubility in the immiscible organic liquid in order that most of the core is encapsulated. Tartrazine has been encapsulated with cellulose acetate trimellitate (Sanghvi and Nairn, 1991) when evaporation of the polymer solvent is not permitted. When evaporation is allowed to proceed, several pharmaceuticals have been encapsulated: tetracycline, loperamide, metoclopramide, hydrochloride and also biological material (Maharaj *et al.*, 1984) and drug-resin complexes (Sprockel and Price, 1990).

Wall polymers. The polymers used in this process should not dissolve in the suspending medium, for example, ethylcellulose dissolved in acetone was dispersed in a non-volatile hydrocarbon liquid (Dispersol 81515) (Yoshida, 1972). Another example is cellulose acetate phthalate dissolved in a mixture of acetone and ethanol, 95%, and then added to mineral oil (Beyger and Nairn, 1986). The size of the microcapsules increased from an average diameter of 140 μm to 295 μm when the concentration of the polymer, Eudragit RS was increased two and a half times. The reasons for this increase in size are attributed to the increase in viscosity of the dispersed phase as a result of higher polymer concentration and an increase of polymer inside the droplets affecting a larger volume (Pongpaibul *et al.*, 1984).

Polymer solvents. In order to avoid evaporation, the use of polymer solvent should be selected so that it has some solubility in the immiscible organic liquid, thus avoiding the use of temperature and the destruction of heat labile drugs. The removal of acetone, which has limited solubility in mineral oil, effects the phase separation of the polymer cellulose acetate trimellitate and subsequently microcapsules are formed (Sanghvi and Nairn, 1991, 1992).

Surfactants. The use of surfactants with low HLB values increases the region of the phase diagram where microcapsules were formed. The use of these surfactants tends to give a smooth surface on the microcapsules and at 3% concentration gives smaller microcapsules. Surfactants with a higher hydrophilic lipophilic balance value decrease the region on the triangular phase where microcapsules could be produced (Sanghvi and Nairn, 1991).

Immiscible organic liquid. Mineral oil is used extensively in this process of phase separation. It has been used in preparation of microcapsules with the

following polymers: polymethyl methacrylate (Sprockel and Price, 1990), cellulose acetate phthalate (Beyger and Nairn, 1986), and ethylcellulose (Kaeser-Liard *et al.*, 1984).

THEORY AND MECHANISM

This section is concerned with some physical and chemical parameters, mechanisms and theories and/or experimental evidence which support the various concepts for coacervation-phase separation and deposition of the coacervate onto the core. As a result, this section is split into three parts:

1. A single wall-forming polymer soluble in water
2. Two wall-forming polymers soluble in water
3. A single wall-forming polymer soluble in an organic liquid

A single wall-forming polymer soluble in water

Phase diagrams

In order to prepare a satisfactory solution of a water-soluble polymer, it is necessary to disperse the polymer in water and allow it to become fully hydrated, perhaps using appropriate temperature conditions, addition of a small amount of non-solvent and/or mechanical means.

Coacervate-phase separation is induced by a number of techniques such as addition of a water miscible solvent, the non-solvent, which is not a solvent for the polymer, or a salt that binds a considerable amount of water thus removing it from the polymer. This process can best be illustrated by three component phase diagrams. The components usually are polymer, solvent and the agent which effects coacervation such as salt or ethanol. An example is given in Fig. 2 for gelatin, water and ethanol (Nixon *et al.*, 1966). It can be seen that a dilute solution of gelatin in water, say 10%, will form a single phase. As ethanol is added, the two-phase region is encountered and the polymer-rich phase, the coacervate, is produced which encapsulates the core material if present. The polymer-poor phase functions as the medium to suspend both the coacervate and core which is being encapsulated. At pH values distant from the isoionic point, flocculation occurs in the presence of ethanol because the gelatin is fully stretched and is unable to entrap the occlusion liquid. The flocculation region is generally not satisfactory for encapsulation. The concentrations in the various regions in this system were studied by using refractive index and specific gravity (Khalil *et al.*, 1968; Nixon *et al.*, 1966). Rigidization of the coat may

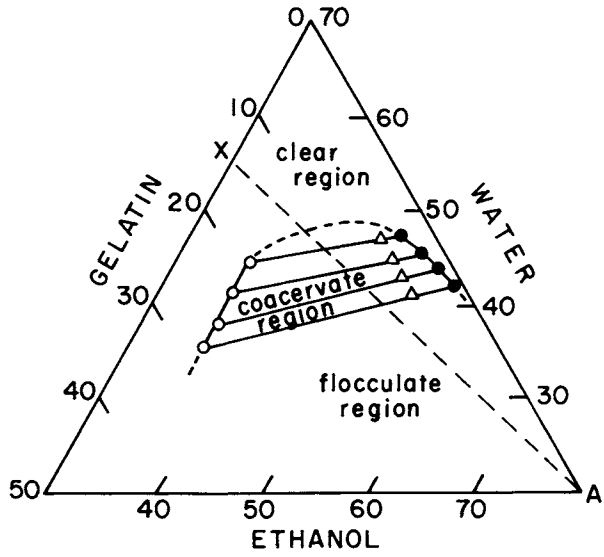

Fig. 2 The composition of coacervate and corresponding equilibrium liquid. ○ Coacervate; ● equilibrium liquid; △ total mixture. Reproduced with permission from Nixon *et al.* (1966), *J. Pharm. Pharmacol.* **18**, 409–416. The Royal Pharmaceutical Society of Great Britain, London.

be effected by temperature change, use of a cross-linking agent and/or the use of appropriate non-solvent for the coat.

Phase diagrams are also useful for preparing nanoparticles which are in the nanometre size range. For example, one method of preparing nanoparticles from gelatin or albumin is to desolvate the polymer with a salt which is highly hydrated, thus causing the coacervate to form. Then the protein is just resolvated with a small amount of water or isopropanol. In this procedure the phase diagrams are prepared using light scattering to measure the onset of coacervation and thus the appropriate conditions to achieve nanoencapsulation. The nanoparticles can be rigidized with a suitable cross-linking agent such as glutaraldehyde (Oppenheim, 1986). Thus, phase diagrams are useful for preparing nanoparticles which form in the precoacervation region, microcapsules or microspheres which separate in the coacervation region, and purification of the protein in the flocculation region when excess salt is added to the system (Oppenheim, 1986).

Hydrogen ion concentration

Khalil *et al.* (1968) investigated the role of pH in the coacervation of gelatin. Since gelatin exists as a randomly coiled configuration in solution, the shape of these coils is influenced, by the ionization of the acidic and basic groups. A stretched configuration is predominant when the gelatin is mainly in the anionic or cationic form. A random coiled structure is favoured at the isoionic point as a result of inter- and intra-molecular attractive forces. The role of pH as it affects coacervation was explained by two factors which appear to influence coacervation of polyelectrolyte systems, namely inter- and intra-molecular attractive coulombic forces, and hydration. The authors postulate that the first of these effects favours phase separation and formation of floccules while the second promotes redispersion of the molecular species. A proper balance between these factors promotes the formation of a colloid-rich isotropic liquid phase which is the coacervate. At the isoionic point there is a balance between the attractive forces of the oppositely charged sites and the hydration effect. The authors found that at the isoionic point, a coacervate was readily obtained when ethanol was added. As pH values move away from the isoionic point, attractive forces decrease and hydration of the gelatin increases; both of these tend to prevent coacervation. At pH values considerably different from the isoionic point, flocculation occurs upon addition of ethanol as the molecule is stretched and cannot entrap sufficient water. At intermediate pH values, a viscous gel is formed. There is more flexibility in the gelatin chain but insufficient water is entrapped to form a coacervate.

When sodium sulfate is used as the coacervating agent, the ions in solution shield the charges on the gelatin material and thus the forces of repulsion are modified by the added salt. At pH values on the acidic side of the isoionic point of gelatin the sulfate ions are associated with the positively charged groups and coacervation proceeds satisfactorily.

Microcapsule formation

Madan (1978) has suggested that deposition of the polymer onto a core may take place as a result of:

1. Molecular interaction between the colloidal macromolecular particles,
2. Coacervate droplets may coalesce about the core particles,
3. Single droplets may encompass one, or a group of core particles.

An examination of the surface characteristics of microcapsules of gelatin, prepared by coacervation using ethanol or Na_2SO_4, showed that the dried microcapsules had no cracks or fissures. The smoother surfaces of the

microcapsules produced using ethanol showed marked surface folding, attributed to vacuole formation in the coacervate droplet, which increased with time, allowing for the formation of the coacervate coat. As a result of these observations, Nixon and Matthews (1976) proposed that microcapsules prepared by coacervation resulted from the merger of several smaller microcapsules.

Encapsulation of liquids

Several microencapsulation procedures involve the encapsulation of immiscible liquids which may, or may not, contain a drug dissolved, dispersed or emulsified in the liquid. In order for the process of microencapsulation to proceed properly, the coacervate must engulf the liquid drop and then be hardened. In this system there are three immiscible phases present - the liquid core, the coacervate and the polymer-poor phase. Torza and Mason (1970), both theoretically and experimentally, investigated the interfacial phenomenon of systems that contain three liquids which are immiscible and indicated the spreading coefficient necessary for a coacervate droplet (liquid 3) to surround the core liquid (liquid 1) when both are in an immiscible continuous phase, the polymer-poor phase (liquid 2). The three spreading coefficients for the three-phase system are:

$$S_1 = \sigma_{23} - (\sigma_{12} + \sigma_{13})$$

$$S_2 = \sigma_{13} - (\sigma_{12} + \sigma_{23})$$

$$S_3 = \sigma_{12} - (\sigma_{13} + \sigma_{23})$$

In order to consider the process it is assumed that $\sigma_{12} > \sigma_{23}$ thus $S_1 < 0$, and thus only three possible sets of values of S exist. These correspond to complete engulfing, partial engulfing and non-engulfing of the liquid core. Complete engulfing occurs under the condition that $S_1 < 0$, $S_2 < 0$, $S_3 > 0$. As the interfacial tension between the polymer-rich phase, that is the coacervate, and the polymer-poor phase is low and if the interfacial tension between the core and the continuous medium is higher than between the core and the coacervate-rich phase, then the above requirements are satisfied and engulfing will occur. Torza and Mason (1970) conducted a number of experiments using different liquids and found that of 20 systems studied, only five did not correspond with the theory. The method of engulfing was determined with a high-speed movie camera and was shown to involve two competitive processes - spreading and penetration. This theory may apply to any coacervate system involving liquids.

In a study of the microencapsulation of oil droplets with or without a drug, clofibrate or chlormethiazole, using gelatin with an isoelectric point

of 4.85 in the presence and absence of a surface-active agent, Siddiqui and Taylor (1983) were able to relate the ionic charge on the coacervate, which was negative, and the spreading coefficient of the liquid substrate. The surface active agents cetrimide, sodium lauryl sulfate or a double salt hexadecyltrimethylammonium lauryl sulfate were used in the process. Spreading coefficients calculated from interfacial tension values indicate that the coacervate should spread more easily in the presence of the double salt, and less so in the presence of either of the other two surfactants. It was noted that conditions for measuring the spreading coefficient and microencapsulation were not identical. Measurements of the charge size on the dispersed particles showed that the oil droplets and coacervate droplets can be expected to have opposite charges, except in the presence of sodium lauryl sulfate. Microencapsulation was satisfactory with both the double salt and cetrimide, but not with sodium lauryl sulfate. The authors suggest that some cetrimide may enter the coacervate phase and subsequently microcapsules tend to agglomerate. Addition of sodium lauryl sulfate at this stage tended to prevent agglomeration. The authors suggest that the use of the double salt enhances the attachment of the coacervate to the oil droplet surface. In fact, this double salt produces the smoothest microcapsule and permits a slower release of the drug from the oil droplets.

Adsorption studies

By electrophoresis and adsorption studies of gelatin and various core materials using six different kinds of coacervating agents, Okada *et al.* (1985a) were able to show that suitable encapsulation by gelatin is affected by the affinity between the core material and the coacervate phase. If a large amount of gelatin is adsorbed prior to coacervation, then encapsulation is successful.

In a subsequent paper Okada *et al.* (1985b) showed that carboquone could not be encapsulated with gelatin unless methanol or sodium sulfate solution was used as the coacervate inducing agent. If, however, the drug is recrystallized from a solution of an ionic polymer and if the pH of the solution is appropriate, then the drug can be encapsulated using many coacervating inducing agents. It was shown that the electrostatic attraction found between the gelatin and the polymer attached to the drug has an important role.

An incompatible or non-wall-forming polymer

Instead of using alcohols of low molecular weight to cause coacervation, Jizomoto (1985) used polyethylene glycol or polyethylene oxide. Both these

polymers have the same general structural formula, but the former name is usually used for polymers with molecular weights $\leqslant 20\,000$ and the latter for those greater than tens of thousands. Polyethylene oxide or polyethylene glycol was added to aqueous gelatin 2.2% with stirring at 40°C at various pH values to influence phase separation. The phase diagram shows that the addition of a small quantity of polyethylene oxide or polyethylene glycol causes phase separation over a wider pH range and this phenomenon is largely dependent on molecular weight. A plot of the log of minimum concentration of polyethylene glycol or polyethylene oxide required to effect phase separation against the log of molecular weight at pH 8.7 gives a straight line. Elemental analysis of the coacervate is identical with that of gelatin; thus the phase separation induced by the addition of polyethylene oxide or polyethylene glycol is caused by an incompatibility. After reviewing the theory proposed by Bailey and Callard (1959) which suggests that water molecules are orientated with respect to polymer chain and the postulation of Kagemoto *et al.* (1967) that the parameter ascribed to the interaction between the oxygen atoms of the ether bonding in polyethylene oxide chain and the water molecules is proportional to a function of the molecular weight, Jizomoto suggests that the effect of polyethylene oxide or polyethylene glycol on phase separation in relation to molecular weight cannot be explained by dehydration. Blow and coworkers (1978) suggested that polyethylene oxide causes a decrease in 'free water' but in the present experiments, polyethylene oxide concentration to bring 'free water' to zero was not appreciably influenced by molecular weight. Therefore, the dependence of phase separation on molecular weight cannot be explained by the concept 'free water'. The author used a simplified equation of the chemical potential expressed in terms of molalities of two polymers, the solvent and the exclusion volumes as described by Edomond and Ogston (1968). Calculations were made to estimate the minimum concentration of the polymers required to cause phase separation. The author concludes that the excluded volume should make the main contribution to the induction of phase separation.

Two wall-forming polymers soluble in water

Effect of ionic charge

Complex coacervation may be brought about in water by the combination of two polymers, one with a positive charge and the other with a negative charge. The most common polymers used are gelatin, which is dissolved in water and the pH is adjusted so that it is below the isoelectric point, and acacia which is negatively charged because of the ionization of its carboxyl

groups. The combination leads to a coacervate, which is polymer rich, and the other phase which is polymer poor (Luzzi, 1976). The interaction between the two polymers is also influenced by temperature and the presence of salts (Madan, 1978).

Theory

In a series of papers Nakajima and Sato (1972) reported upon the phase relationships and theory of complex coacervation of the sulfated polyvinyl alcohol–aminoacetalysed polyvinyl alcohol system. Phase relationships were examined for the polymer salt, water and sodium bromide. The experimental results were interpreted by the use of a theoretical equation for the free energy of mixing by taking into account the entropy and enthalpy contributions ascribed to a non-ionic polymer solution and the electrostatic free energy expression as derived by Voorn (1956). In two subsequent papers, Sato and Nakajima (1974a,b) investigated the effects of chain length of the polyelectrolytes, the thermodynamic interaction between the polymer and water and the number of charges of polyelectrolyte chain on the complex coacervate on the basis of a free energy equation. Conditions for the formation of coacervate droplets as a function of charge density and polymer concentration were also discussed.

Burgess and Carless (1984) investigated the electrophoretic mobility profile of polyions and showed that these profiles can be used to determine if complex coacervation will occur between two polyions. Furthermore, they showed that the pH range of coacervate, the pH of optimum coacervation and the salt tolerance of the system can be predicted. They also showed that the maximum coacervate volume occurred at the electrical equivalence pH, that is when the charges on the two polyions are equal and opposite.

A practical analysis of complex coacervate systems has been published by Burgess (1990) who reviewed several theories which are now briefly described. Overbeek and Voorn (1957) postulated that the coacervation which takes place between gelatin and acacia is a competition between ionic attractive forces, which tend to bring the polyions together, and entropy effects, which promote the dispersion. The coacervate phase binds water between the loops of the polymer chains. The water in the coacervate contributes to the entropy and permits a number of arrangements of polymers. As a result the coacervate is fluid. Another theory which attempts to explain complex coacervation is the 'dilute phase aggregate model', developed by Veis and Aranyi (1960) to take into account the formation of complex coacervation when the product of the charge density and the molecular weight is low. The model postulates that complex coacervation occurs in

two steps, as oppositely charged gelatins fuse, aggregate, and then rearrange to form the coacervation phase. The rearrangement occurs slowly and is formed by the gain in configuration entropy. Several differences between the two theories are described by Burgess (1990). Burgess and Carless (1985, 1986b) confirmed the two-step process and detected the presence of small aggregates by light scattering. Tainaka (1979, 1980) modified the Veis and Aranyi theory to indicate that the aggregate pairs in the dilute phase did not have specific charge pairing. Again, the dilute phase aggregates condense to form the coacervate, but the aggregates are present in both the dilute and coacervate phases. The aggregates overlap with each other in the coacervate phase and, as a result, there is a gain in electrostatic energy due to the increase in ion density in the overlapped domain. High molecular weights and highly charged densities of the polyions enhance the attractive forces effecting phase separation. The Tainaka theory explains the suppression of coacervates at high polymer concentration as stabilization of aggregate structures at high concentration. Burgess (1990) concluded that, while the Tainaka model is not all-inclusive, as it does not explain the reduction of coacervation at low ionic strength, it is not as restricted as other theories and thus, at present, is the best general theory.

Polar bonding

A recent paper by Van Oss (1988–1989) presents a somewhat different classification of coacervation, complex coacervation and flocculation based on polar (hydrogen) bonding components of interfacial interactions. Van Oss (1988–1989) has reviewed the classification for coacervation (simple) and complex coacervation for the system of gelatin and acacia (Table 1). A theoretical analysis of cohesion and adhesion in terms of the Lifshitz–van der Waals, or apolar, components and Lewis acid–base, or polar, components of free energy between two different bodies 1,2, through a liquid 3, indicates interfacial (hydrophobic) attraction when $\Delta G_{132} < 0$ and interfacial ('hydration pressure' mediating) repulsions when $\Delta G_{132} > 0$. As a result of this theory, Van Oss provides a table which indicates the mechanisms and conditions for coacervation (simple) and complex coacervation. He indicates that coacervation (simple) takes place when polar and/or apolar repulsion between the two solutes, where one or both must be a polymer dissolved in the same solvent, results in phase separation. Complex coacervation takes place when there is electrostatic or polar attraction between two polymers of opposite charge (or of opposite signs of Lewis acid–base behaviour). Examples of coacervation (simple) due to polar interactions are negatively charged gelatin and gum arabic, agar and ethanol, polyvinyl alcohol and polyethylene glycol, the solvent in all cases being water.

Table 1 Comparison of coacervation (simple) and complex coacervation using a mixture of gelatin and acacia given by Bungenberg de Jong, adapted from Van Oss (1988–89)

Property	Coacervation (simple)	Complex coacervation
pH	> Isoelectric point for gelatin	< Isoelectric point for gelatin
Concentration of original solutions	Occurs with concentrated solutions	Occurs with dilute solution
Indifferent salts	Tend to promote coacervation Place in lyotropic series is important	Tend to suppress coacervation Place in lyotropic series is minor Valency is important
DC field	Drops show no disintegration	Drops show disintegration
Composition of liquid layer	Each layer contains essentially one species	The coacervate layer is rich in the colloid which is a ratio of about one to one
Principal condition	Water deficit in the system	Different charge between the two species

Coacervation (simple) due to apolar interactions includes cellulose acetate and ethanol dissolved in chloroform, polyisobutylene and polystyrene in benzene. Complex coacervation always takes place in water and some examples resulting from electrostatic interaction are positively charged gelatin and negatively charged gum arabic, and positively charged gelatin and nucleic acid. Examples of polar (Lewis acid-base) interaction include polyacrylic acid and polyvinyl methylether.

Borue and Erukhimovich (1990) developed a microscopic statistical theory of symmetrical polyelectrolyte complexes. The complex was shown to form a polymer globule and the equilibrium density, the width of the surface layer and the surface tension were calculated as a function of salt concentration. Complex coacervation is considered as a precipitation of polymer globules due to a minimization of surface energy. The theory is based on the Lifshitz–Grosberg theory of polymer globules and the authors' previous work concerning the equation of state of polyelectrolyte solutions.

Particle size

In a study of the encapsulation of hydrophobic compounds such as stearyl alcohol by complex coacervation with gelatin–acacia, Madan *et al.* (1972) found that only particles below 250 μm diameter could be encapsulated. It was proposed that the mechanism for encapsulation in this system was either a single coacervate droplet which encompasses a group of immiscible nuclei or individual coacervate droplets adsorbed to, or coalesced around the particles. Photomicrographs of 163 μm particles indicate that encapsulation takes place by aggregation or coalescence of several droplets (with diameters usually under 40 μm) to surround the core stearyl alcohol particles. Larger particles were incompletely covered. The authors suggest that the affinity of the coacervate droplets for the core material is not great. They suggest that the velocity difference between the core particles and the coacervate droplets, as the mixture is stirred, tends to prevent the aggregation of droplets around the core particles. In addition, the probability that a sufficient number of coacervate droplets will aggregate and coalesce to surround a core particle decreases as the particle size increases. Experimental studies showed that larger particles could be encapsulated if the concentration of the coacervate was increased. In order to improve the encapsulation process, the stearyl alcohol was melted in an acacia solution and then congealed. The acacia is adsorbed more strongly to liquid stearyl alcohol than to the solid form. The adsorbed acacia then reacts directly with the gelatin in the encapsulation process to form the microcapsules.

Thermodynamics

Veis (1975) described the thermodynamics of phase separation in a mixture of oppositely charged polyelectrolytes. He indicated that homogeneous solutions will be formed as long as a plot of ΔG_M, the free energy of mixing of a solute and solvent, versus ϕ_2, the volume fraction of the polymer, has a single minimum. However, if X_{12}, the interaction parameter, which is proportional to the interaction energy per mole of solvent molecules, is sufficiently large and positive two minima will be present in the plot and any mixture prepared between these two will separate into two phases. Mathematical analysis shows that for polymers of moderate size, phase separation will occur at low solute volume fraction if X_{12} is slightly greater than 0.5.

The thermodynamics of mixing of two dissimilar polymers in a single solvent are also discussed. The author discusses two cases. In the first case the polymeric ions have a very high charge density and phase separation occurs to give essentially solvated coprecipitates in equilibrium with an extremely dilute phase. These precipitates are the basis of certain membranes. The other case is that in which the polyions are of a moderate charge density and phase separation is driven by the more favourable electrostatic interaction in the concentrated phase. In this example, both phases contain both ionic polymers, as is the case for the gelatin–acacia interaction.

Based on two experimental findings, namely charge equivalence in the coacervate phase and molecular weight pairing in the coacervate phase, the author suggests the possibility of two mechanisms for the formation of the coacervate based on an unfavourable entropy change ΔGentropic > 0 and a favourable electrostatic free energy change ΔG electrostatic < 0 for the reaction:

$$P^+OH^- + H^+Q^- \rightarrow [PQ]Agg + H_2O$$

where P^+ is the cationic polymer, Q^- is the anionic polymer and [PQ]Agg is the aggregate.

The aggregation may take two forms: the two molecules with the centres of gravity overlapped, or two molecules with explicit ladder-like charge pairing. The author argues in favour of the ladder type formation, based on the molecular weight pairing and the suppression of coacervation observed in most polydispersed mixtures. This new aggregate, PQ, behaves as a new component which should obey the basic Florey–Huggins polymer binding mixture phase separation rule.

Surfactant effects

The influence of cationic, anionic and non-ionic surfactants on complex coacervate volume and droplet size has been researched by Duquemin and Nixon (1985). The coacervate was prepared by dissolving the surfactant in the acacia solution and then adding an equal quantity of gelatin solution at the optimum pH of coacervation, 4.35. It was found that the per cent coacervate weight decreased with increasing concentration of sodium lauryl sulfate. At high surfactant concentrations, 0.20 and 0.35%, and at a low colloid concentration, 1%, formation of the coacervate was prevented. It was postulated that the additional ions from the surfactant prevented or restricted electrostatic attraction between the gelatin and acacia polyions. The effect of increasing concentration of cetrimide on the per cent coacervate by weight is not so clear and depends on the concentration of the colloid. At low concentration of the surfactant, there is a slight increase in weight and this has been attributed to an increase in water content of the coacervate. At a high colloid concentration, 4 and 5%, and high surfactant concentration, 0.075%, there is an appreciable decrease in the concentration of the coacervate. The authors suggest that this is due to the suppression of coacervation because the process is less energetically favourable. The effect of polysorbate 20 on coacervate weight is similar to that produced by cetrimide. It is suggested that steric hindrance of the large surfactant molecules suppresses coacervation.

A single wall-forming polymer soluble in an organic liquid

Solubility effects

Use of a non-solvent. After the polymer is dissolved in an appropriate organic solvent, phase separation may be induced in a number of ways. For example a second organic solvent which is miscible with the solvent for the polymer, but at the same time is a non-solvent for the polymer may be added. The solubility of the polymer is now decreased and separates under appropriate conditions as a polymer-rich phase which is also able to surround the core. The polymer-rich phase may be hardened by further treatment with the miscible non-solvent (Luzzi, 1976).

Relation between polymer composition, solvent and non-solvent. The mechanism of coacervate formation in a non-aqueous system has been investigated by Ruiz *et al.* (1989). Microcapsules of poly (DL-lactic acid-co-glycolic acid) were prepared by dissolving the polymer in methylene chloride and then adding various quantities of silicone oil to effect phase separation. The phase separation phenomenon was observed by taking photomicro-

graphs after increasing quantities of the incompatible polymer were added. At the first step when the amount of phase inducer is low (1–5%), a pseudo-emulsion of the silicone liquid is formed. During the second step when more silicone oil is added, the beginning of the phase separation appears. The coacervate droplets appear to be unstable and merge together then break apart. In the third step the added quantity of silicone oil is sufficient to permit a stable dispersion of polymer coacervate droplets; this step is called the stability window. Finally, the fourth step occurs after further addition of silicone oil, which causes extensive aggregation of the coacervate droplets.

Four polymers with different compositions of lactic acid (LA) and glycolic acid (GA) were studied. The polymers with the highest percentage of lactic acid had the largest stability window, and required the largest amounts of silicone oil to reach that region. The polymer with the lowest content of lactic acid, namely 50% LA and 50% GA, is the least hydrophobic among the polymers studied and did not easily dissolve in the solvent and required only small amounts of silicone oil to effect phase separation, accounting for the small stability window. Silicone oil with a low viscosity did not yield a stability window with four polymers tested; however, silicone oils with higher viscosity, up to 12 500, increase the size of the stability window for all polymers. The stability window was increased by increasing the solubility of the poly(DL-lactic acid-co-glycolic acid) polymer in the solvent by the addition of methanol. As a result, more silicone oil was needed to reach the stability window, and thus to induce the appearance of the polymer droplets. The width of the stability window can be altered by changing the viscosity of the silicone oil and modifying the solvent for the polymer by adding a suitable percentage of a better solvent.

Shively and McNickle (1991) considered the effect of various solvent compositions on the coacervation process. Ternary phase diagrams were prepared using a biodegradable block copolymer prepared from tartaric acid and 1,10-decanediol, and ethanol and water, with or without NaCl. Microcapsules of kaolin or hydrocortisone-21-acetate were prepared by adding the core to an ethanol solution of the polymer and then titrating with the aqueous non-solvent. The microcapsules were then filtered and dried. At high polymer concentrations in the non-plait region, minimal or no solvent interaction occurred and the polymer was in the coiled configuration. In the plait region at low polymer concentration, the ionic strength of the non-solvent showed an effect on the coacervate, the adhesive forces were greater than the cohesive forces, and the polymer adopted a more linear configuration. Surface tension measurements, when the solvent composition was 30% water and 70% alcohol (non-plait) or 50% alcohol and 50% water (plait), showed that the area per polymer molecule decreased in post-coacervation compared with the precoacervation region. These

results agree with the theory that the coacervation results in the reduction of the surface free energy of a system through a reduction of the molecular surface area. Analysis of the surface tension versus polymer composition graphs shows that coacervate phases resulting from 30% water, 70% ethanol compared with 50% water, 50% ethanol were very different suggesting differences in molecular configuration and interaction properties. Thus, the authors speculate that microcapsules made with different coacervation conditions would have different properties, such as diffusion or morphology. It was found that microcapsules produced with non-plait conditions had considerably slower rates of release of the drug and had rough and irregular surfaces compared with microcapsules prepared with plait conditions.

Solubility parameters. Robinson (1989) determined the solubility of ethylcellulose Type N10 in 122 solvents qualitatively and in 36 solvents quantitatively. The contribution of dispersive, polar and hydrogen-bonding intermolecular forces was determined and plotted on two-dimensional and triangular solubility graphs. The influence of dipole–dipole interactions on the solubility of ethylcellulose was shown by plotting the fractional polarity of the solvent against the solubility parameter. The diagram shows that ethylcellulose is soluble over a range of polarity from 0 to 0.75, but it is not soluble in solvents with either a low or high solubility parameter. In order to show the effect of the relative fractional contributions of the hydrogen bonding, polar and dispersion components, a triangular solubility diagram was prepared. The solvents were classified on their hydrogen bonding ability: weak, medium, and strong. The three areas of solubility overlap and they define a region which determines the intermolecular forces appropriate to dissolve ethylcellulose. Ethylcellulose occupies a central position within the defined solubility regions. The triangular diagram is useful for determining good solvents and non-solvents for microencapsulation purposes. Coacervation was observed after cooling a solution of ethylcellulose in a poor solvent which had a solubility parameter near, or just outside, the solubility region for the polymer. Gelation occurs after cooling with liquids usually considered non-solvents for the polymer and their solubility parameters are well outside the solubility region and have higher interaction parameters. Flocculation was observed after cooling solutions of the polymer in polar solvents where large values of the interaction parameters occur.

The selection of appropriate solvents and non-solvents may be ascertained through the use of solubility parameters. In a study by Moldenhauer and Nairn (1992), it was shown that microcapsules could be prepared by phase separation using a number of solvent–non-solvent pairs. The solubility parameter map was prepared using a number of solvents, both singly and in mixtures, to provide regions where the polymer ethylcellulose was

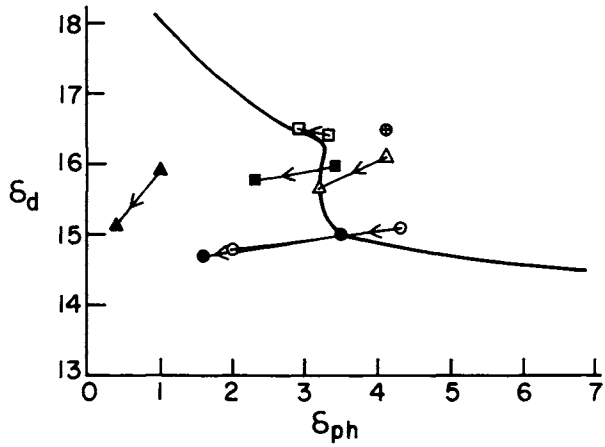

Fig. 3 Solubility parameter map for ethylcellulose showing the solubility border and the initial and final microencapsulation solubility parameters: □ using ethyl acetate and cyclohexane; ⊕ using methyl ethyl ketone and cyclohexane; ▲ using toluene and light liquid paraffin; ■ using ethyl acetate, cyclohexane and light liquid paraffin; △ using methyl ethyl ketone, cyclohexane and light liquid paraffin; ● using ethyl acetate and light liquid paraffin; and ○ using methyl ethyl ketone and light liquid paraffin. Reproduced with permission from Moldenhauer and Nairn (1992), *J. Controlled Release* **22**, 205–218. Elsevier Science Publishers BV, The Netherlands.

soluble (that is, gave clear solutions at definite concentrations) and regions where the polymer was insoluble (that is, where clear solutions were not obtained). This information was then used to prepare microcapsules of theophylline ion-exchange resin beads coated with ethylcellulose using a number of solvents. Partial evaporation of the solvent in a mixture leads to a change in solubility parameters effecting phase separation. These authors experimentally corroborated Robinson's (1989) studies that microencapsulation systems should be near the limit of ethylcellulose solubility where coacervation will occur and showed that microcapsules could be prepared by controlled evaporation of a solvent–non-solvent pair for ethylcellulose. The total amount evaporated was the same in all experiments. As evaporation of the solvent and non-solvent took place, the solubility parameter of the mixture generally changed, owing to the different vapour pressures, into a poor solvent for the polymer. The composition of the solvent pair, both before and after evaporation, was related to the phase diagrams and the solubility parameter map. Well-formed microcapsules were prepared from solvent–non-solvent pairs whose solubility parameters changed during evaporation from the soluble region to just at the other side or at the edge

of the solubility region on the solubility parameter map. Even though different solvent mixtures were used, ethyl acetate or methyl ethyl ketone as solvents and non-solvents cyclohexane and light liquid paraffin, the solubility parameters were similar and evaporation produced microcapsules with similar characteristics (see Fig. 3).

Experiments conducted with solvents that had a poor solubility parameter for ethylcellulose yielded either no coat or a coat of poor quality. Evaporation of solvent pairs which had similar vapour pressures and which were in the solution region of the solubility parameter map did not change their solubility parameter during evaporation, and microencapsulation did not take place. Solubility parameter maps provide information about a number of solvent–non-solvent pairs whereas a phase diagram provides information about only one solvent–non-solvent pair.

Wall formation

The mechanism of wall film formation of ethylcellulose onto magnesium aluminium hydroxide hydrate was investigated by Kasai and Koishi (1977). Four different experiments were carried out in order to investigate the phenomenon of microencapsulation. With increasing amounts of ethylcellulose, in dichloromethane, added to the core and also addition of water, it was shown that the surface properties of the core changed from hydrophilic to hydrophobic, likely as a result of adsorption of the ethylcellulose onto the surface of the core. Photographs of ethylcellulose coacervate drops formed by the addition of increasing volumes of *n*-hexane to the ethylcellulose solution show an increase in size of the coacervate drops which corresponds to an increase in the weight of ethylcellulose in the coacervate. The authors indicate that the smaller-sized coacervate droplets are likely to be suitable for microencapsulation, and the larger-size coacervate droplets are not. The authors also relate the surface structure of the microcapsules to the weight of ethylcellulose coacervate as a result of the addition of non-solvent.

The authors then suggest possible cross-sectional models for the deposition of ethylcellulose coacervate drops on the core and in the final state of the walls as shown in Fig. 4. It is noted in Fig. 4 that there is compression of the ethylcellulose on the core material and this is supported by the fact that despite an increase in percentage ethylcellulose concentration in the microcapsules from 27 to 46%, the wall thickness range is almost constant within the range of 15–17.5 μm. In conclusion, the authors postulate a model for deposition of ethylcellulose coacervate based on the amount of coacervate on the core, as a result of increasing amounts of non-solvent added, scanning electron microscopy of the microcapsule surface, photographs of the coacervate droplets and the region of constant wall thickness.

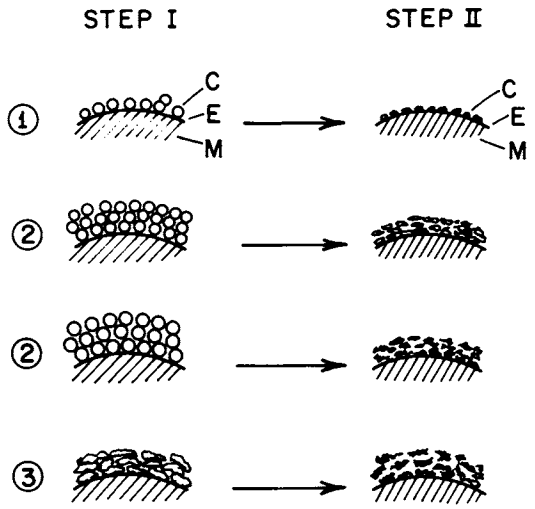

Fig. 4 Possible cross-sectional models for the deposition of ethylcellulose coacervate drops on the core material and the final state of microcapsule walls. Key: step I: coacervate drops deposited at first; step II: final walls; ① ② and ③: different stages, C, E, and M, coacervate drops, ethylcellulose adsorbed initially on the core material, and the core material. Reproduced with permission from Kasai and Koishi (1977), *Chem. Pharm. Bull.* **25**(2), 314–320. Pharamaceutical Society of Japan.

Incompatible or non-wall-forming polymers

A number of papers have been written about the effect of polyisobutylene on the coacervation of ethylcellulose and the formation of microcapsules. In an early paper Donbrow and Benita (1977) describe ethylcellulose coacervation by dissolving the polymer in cyclohexane and slowly cooling with controlled agitation. Phase separation occurs over 24 h to yield a lower phase of coacervate droplets and a clear upper layer containing polyisobutylene. The authors noted the non-linear increase in volume of the coacervate with polyisobutylene concentration. At the same time, a decrease in the particle size of the coacervate droplets was related to the increase in phase coacervation volume effected by the change in polyisobutylene concentration. They attributed the rise in phase coacervation volume with polyisobutylene concentration to an increase in the volume of adsorbed solvated polyisobutylene. The adsorbed layer minimizes agglomeration of the droplets rather than the mixing of their solvated polyisobutylene layers. They suggest that polyisobutylene acts as a protective colloid in the coacervation process and prevents the formation of large aggregates of ethylcellulose. A free-flowing powder was obtained on drying when polyisobutylene was

employed; however, in the absence of polyisobutylene an aggregate mass was produced. Benita and Donbrow (1980) extended their research on the role of polyisobutylene and its effect on coacervation. Microanalysis indicated that polyisobutylene was not coprecipitated with the washed ethylcellulose coacervate droplets and thus functions as a stabilizer by adsorption. The increase in phase coacervation volume with increasing polyisobutylene concentration was explained by a decrease in sedimentation rate as a result of combined effects of the smaller size of the droplet and the higher viscosity of the medium. The final phase coacervation volume is determined less by the ethylcellulose close-packed volume than by the repulsion forces between the stabilized droplets. During the cooling process in order to solidify the coacervate drops, the adsorbed layer of polyisobutylene increases the surface viscosity and it is expected that the rate of surface nucleation of the ethylcellulose decreases, thus explaining the formation of the smooth surface, characteristic of a structure of amorphous nature. The process would be promoted by an increase in adsorption of polyisobutylene and surface viscosity as the temperature falls. The authors concluded that polyisobutylene, a linear polymer, acts by forming a high-energy barrier as a result of adsorption of anchor groups on the surface of the droplet; the rest of the polyisobutylene molecule, bound by either looped segments or segments, is directed toward the outside of the coacervate droplet. This arrangement provides steric stabilization as a result of repulsion of solvated polymer chains.

The mechanism of aggregation prevention by polyisobutylene was studied using Eudragit RS or RL as the wall polymer, tetrahydrofuran as the solvent and cyclohexane as the non-solvent (Donbrow *et al.*, 1990). Phase diagrams, phase volume ratios of the system and photomicrographs of various stages of microencapsulation were presented. The presence of polyisobutylene permits the formation of two liquid phases, which is an unstable emulsion and a significant volume fraction is occupied by the wall polymer phase. During addition of the non-solvent cyclohexane, the solvent tetrahydrofuran is removed from the wall polymer phase and its volume fraction decreases. The dispersed concentrated wall polymer phase remains fluid during deposition onto the core surface and then gelling occurs and the system is then composed of two liquids and one gel. If polyisobutylene is not present a viscous coacervate rapidly separates, which is adhesive, during the slower desolvation stage as the composition of the solvent changes, and in this case liquid and gel are formed. The authors suggest that secondary dispersion phase phenomena are more readily controlled in the two liquid dispersion compared with liquid gel dispersion and the polyisobutylene permits steric stability. The effect of polyisobutylene molecular weight was also investigated. Polyisobutylene (mol. wt 50 000) did not permit the

formation of microcapsules, but yielded matricized core particles. This was attributed to the formation of a low volume wall-polymer phase of high viscosity, even prior to non-solvent addition, which was not able to provide an appropriate coating similar to the condition of the gel formed in the absence of polyisobutylene. Polyisobutylene of higher molecular weight gave two incompatible fluid phases which progress through the appropriate changes on addition of cyclohexane to give microcapsules. Polyisobutylene solutions at a constant viscosity but using higher molecular weight polymers, that is, using smaller concentrations of polyisobutylene, gave smaller phase volumes at initial condition and smaller droplet diameters.

The influence of coacervation inducing agents, namely butyl rubber, polyethylene and polyisobutylene, was studied by Samejima *et al.* (1982). The core was ascorbic acid and the coat of ethylcellulose was deposited on the core drug as a result of temperature reduction from a solution of the polymer in cyclohexane. Scanning electron microscopy of the resulting microcapsule showed that the surface of ascorbic acid was poorly covered when butyl rubber was used as the coacervation inducing agent, a smooth coat with small holes was produced when polyethylene was used and a smooth surface with few holes was obtained with polyisobutylene. The wall thickness was in the range from 0.75 to 3.72 μm and was in the order butyl rubber < none < polyethylene < polyisobutylene. The authors suggested that the factors of smoothness and wall thickness influenced the dissolution rate in the order, butyl rubber > none > polyethylene > polyisobutylene. In conclusion, polyisobutylene is adsorbed on the coacervate wall which is on the surface of the crystal and functions as a stabilizer, preventing the agglomeration of single microcapsules into aggregates.

Viscosity and surface tension effects on microsphere size

The influence of viscosity and surface tension on the particle size of microspheres prepared by emulsification was investigated by Sanghvi and Nairn (1992). The microspheres were prepared by dissolving different amounts of polymer, cellulose acetate trimellitate, in solutions of acetone and ethanol and adding this solution to the external phase composed of mixtures of light and heavy mineral oil. The viscosities of the two phases were determined both before and after mixing and the interfacial tension between the two phases was also determined. The interfacial tension ranged up to 7 dynes cm^{-1} but did not affect the particle size appreciably. It was found that as the viscosity ratio of the internal phase to the external phase both before and after mixing increased, the particle size of the microspheres slowly increased from about 100 μm to about 200 μm until a minimum viscosity ratio of approximately 10 before mixing and approximately 1000

after mixing was achieved; subsequently there was a very rapid increase in the size to about 700 μm. The data were related to the theory of drop deformation as described by Becher (1965) and the ease with which particles coalesce (Gopal, 1968).

In a subsequent paper Sanghvi and Nairn (1993) were able to control the particle size of the cellulose acetate trimellitate microspheres by adjusting the ratio of the polymer to solvent concentration and by adjusting the internal phase volume fraction. The amount of polymer has a direct influence on the viscosity of the internal phase, and hence the viscosity ratio of the internal to external phase as described above. The phase volume ratio affects the particle size of the microsphere as it changes the probability of two droplets colliding and forming a larger droplet.

COACERVATION-PHASE SEPARATION USING A SINGLE WALL-FORMING POLYMER SOLUBLE IN WATER

This section and the next two are generally grouped according to the expected number of polymers in the wall and their solubility. Within each of these sections the polymers are arranged alphabetically and within these sections chronologically grouped according to the authors.

Acacia

Acacia (gum arabic) has been used to encapsulate oil drops such as lemon and polybutadiene. It has been reported that the coacervation process was more satisfactory if acacia was treated with acidic and basic ion-exchange resins to produce a salt-free form (Schnoering and Schoen, 1970).

Albumin

Research by Ishizaka *et al.* (1981) describes the preparation of egg albumin microcapsules and microspheres by dispersing a solution of the albumin, containing a core material, in isooctane containing sorbitan trioleate and then heating to about 80°C to cause denaturation of the albumin. It was found that the size distribution of the albumin microspheres was strongly affected by the surface-active agent concentration, mechanical agitation and albumin concentration.

Serum albumin microcapsules have been prepared by dispersing poly(acrylonitrile) beads of specific sieve fractions into a bovine serum albumin solution adjusted to pH 5.0 (Ishizaka *et al.*, 1985). Isopropyl

alcohol was added to the suspension to form the coacervate drops at 25°C. Vigorous stirring was employed to prevent the formation of multinuclear microcapsules. Subsequently, the suspension was heated to 70°C to harden the microcapsule wall. Coacervation of serum albumin was observed and a three component phase diagram was prepared. The optimum concentration for microcapsule formation was also provided on the phase diagram. Low concentrations of isopropyl alcohol were not appropriate for microcapsules, but 30% was found to be satisfactory. The characteristics of the product depended upon the total surface area of the core beads and the albumin concentration. At high surface areas of the core and low albumin concentrations, non-spherical and multinuclear microcapsules were obtained.

Several patents have been published by Ecanow and Ecanow (1983) describing the coacervate formed from albumin and lecithin for parenteral purposes. A composition containing albumin, urea, sodium chloride and lecithin solutes was prepared and stored at 4°C to give a coacervate which was then treated with cholesterol, $CaCl_2$ and KCl and the pH adjusted to 7.3 and made isotonic. After storage for 6 days, two phases are formed. It is suggested that it be used as synthetic whole blood.

In a subsequent patent, Ecanow (1988a) used human serum albumin for the solubilization and parenteral delivery of a drug dispersion. Butanol was added to a solution of egg lecithin and after shaking the middle phase was removed. To this phase, human serum albumin was added and dissolved. After storage in the cold, diazepam was added to the colloid-rich phase. The colloid-poor phase was then added and the mixture emulsified and the pH adjusted to 7.3–7.4.

Polymerized albumin and lecithin have been used to form a coacervate of erythromycin, and the dried particles used in oral products such as tablets, capsules and syrups (Ecanow, 1988b). Ecanow (1991) also described a coacervate containing egg albumin and egg lecithin which could be used for different routes of administration. In one example, bovine insulin was incorporated into the coacervate of egg albumin and then administered to rats. This resulted in a decrease in glucose blood levels whereas the unencapsulated insulin had no effect.

Simple coacervation with albumin has also been studied to prepare microcapsules of the core, namely sulfamethoxydiazine or acrylonitrile styrene copolymer resin beads. It was found that the time for 50% release increased from 6 min to 73 min when the drug was encapsulated with albumin (Ku and Kim, 1987).

Alginate

Sodium alginate has been occasionally used to prepare microcapsules. Salib *et al.* (1978) dispersed various drugs such as chloramphenicol or sulfadiazine in the sodium alginate solution and this mixture was added to an aqueous calcium chloride solution. Calcium alginate is formed and deposited around the drug particles. Loss of drug which was less than 16% occurred during the microencapsulation process.

Carboxymethylcellulose

Carboxymethylcellulose sodium has been used in the preparation of microcapsules by coacervation. In order to prepare microcapsules of indomethacin, the drug was dispersed in the aqueous polymer solution and this was added to an aluminium sulfate solution. Drug loss during the preparation of the microcapsules was minimal. The release of the drug followed an apparent zero process and there was a four- to eight-fold reduction in the release rate compared with the uncoated drug. The zero-order rate constant could be related to the coating ratio (Salib *et al.*, 1989).

Cellulose acetate phthalate

Cellulose acetate phthalate has been used to prepare microcapsules of phenacetin as described by Merkle and Speiser (1973). The polymer was dissolved in an aqueous solution containing a stoichiometrically equivalent quantity of Na_2HPO_4. The stirred solution was maintained at 60°C and the drug was added then the coacervating agent, a solution of sodium sulfate at 60°C. Subsequently, the solution was slowly cooled to 20°C, followed by rapid cooling to 5°C. The polymer was rigidized by treatment with a dilute solution of acetic acid. A triangular phase diagram was prepared representing polymer, water and total salt which included the Na_2HPO_4, the solvating agent, and Na_2SO_4, the coacervating agent. It was found that the amount of drug in the microcapsule had no appreciable effect on the particle size distribution of the microcapsule but did influence the release rates of the drug, suggesting that diffusion of the drug through the microcapsule wall is the controlling step. In order to obtain better utilization of the polymer, a technique was developed for the continuous addition of sodium sulfate during cooling of the system to produce microcapsules. The encapsulation process is able to produce microcapsules of varying drug-to-shell ratios by maintaining the polymer concentration and altering the amount of drug used. The rate of drug release increases as the

drug content increases. In contrast, all batches of capsules plasticized by washing with a dilute solution of glycerin for a short period showed identical release rates, despite different drug contents; the authors now suggest that the release rate is controlled by dissolution of the drug in the microcapsule.

Another method of preparing microcapsules using the polymer cellulose acetate phthalate-containing pharmaceuticals with low water solubility was described by Milovanovic and Nairn (1986). Solutions were prepared by dissolving the polymer in dilute solutions of Na_2HPO_4 and heating to 60°C. Various quantities of the drug sulfadiazine, polyoxyethylene 20 sorbitan monooleate and, if necessary, a viscosity agent such as glycerin, Avicel pH 105 or hydroxypropyl methylcellulose were added to the polymer solution. The stirred suspension was added dropwise to the aqueous hardening solution of diluted acetic acid. A suitable viscosity of the solution to suspend the drug was obtained by using a 2.5% cellulose acetate phthalate solution. Addition of the above-mentioned viscosity agents to this solution did not alter the core:coat ratio, the particle size appreciably, or the percentage of drug incorporated, 81–94%, but the disintegration time was decreased when glycerin was used. The size of the microcapsules tended to increase, the core to coat ratio increased, and the disintegration time decreased as the amount of drug incorporated into the microcapsule increased.

Microcapsules of water-insoluble liquids such as vitamin A palmitate have also been prepared using cellulose acetate phthalate (Anon., 1988).

Gelatin

Phares and Sperandio (1964) showed that a number of insoluble particles, liquids and solids, could be encapsulated with gelatin using sodium sulfate as the coacervation-inducing agent. A phase diagram for the system gelatin, water and sodium sulfate was prepared to show the region of encapsulation.

As a result of the preparation of phase diagrams (Nixon *et al.*, 1966), suitable compositions within the coacervate region were selected for preparing microcapsules. Subsequently, an improved method for preparing microcapsules by simple coacervation methods using gelatin was accomplished by Nixon *et al.* (1968). The drug, sulfamerazine, was dispersed in either ethanol or 20% w/w sodium sulfate and added to the isoelectric gelatin solution. The mixture was stirred and maintained at 40°C. Both lime-pretreated and acid-processed gelatin were studied. After further treatment with the coacervating agent, the product was washed with isopropanol and hardened with a formalin-isopropanol mixture. This method produced

the best results. In an alternative procedure for hardening the microcapsule, the product was cooled to 5 or 10°C, washed and dried; this method produced a cake. In a third method, the microcapsules were spray dried, but the product was not satisfactory because most of the drug was not encapsulated. The size of the drug particles to be coated did not hinder the coacervation process. It was found that encapsulation was successful if the drug particles were dispersed in the gelatin solution before coacervation or added to the system when coacervation was complete. The authors suggested that encapsulation can occur by two methods: the dispersed particles functioning as nuclei around which the coacervate drops form, or the coacervate droplets surround the drug particles. The recovery of the microcapsules was based on hardening the coacervate shell by dehydration. Isopropanol with its milder dehydrating effect compared with ethanol was more appropriate. The release rate of the drug was decreased with longer formalization time or thicker walls. Microcapsules prepared using ethanol provided a slower release than when they were prepared with sodium sulfate, which results in a more porous coat because of the salt's ability to hinder the hardening effect of isopropanol.

Nixon and Matthews (1976) made gelatin microcapsules by preparing a 5% solution of the polymer at 40°C and adding the coacervating agent, either 20% sodium sulfate or absolute ethanol. The core was added to some of the coacervating liquid and dispersed by ultrasonic vibration. The coacervate wall was then gelled by using a 30% ethanol in water or a 7% solution of sodium sulfate in water at a temperature below the gelling temperature of the coacervate; that is, below 12°C. Partial dehydration was accomplished by using two washes of isopropanol, a final wash with ethanol and finally heating the microcapsules to less than 60°C. The product was examined using a scanning electron microscope. Microcapsules produced by using either ethanol or sodium sulfate had no cracks or fissures. The surface of microcapsules produced using ethanol were smoother than those produced using Na_2SO_4. Surface folding of the ethanol-treated microcapsules was common and is associated with the formation of vacuoles within the alcohol coacervate droplets. The authors suggest that during recovery the vacuoles collapse and the wall material folds in on itself. Crystalline deposits on the surface of sodium sulfate-produced microcapsules were that of the salt. The authors suggest that microcapsules prepared by coacervation are formed by a process that involves the combination of several smaller microcapsules.

Water in oil emulsions have been encapsulated by gelatin using the coacervation process. For example, a concentrated solution of urea in water was prepared as a w/o emulsion with corn oil and hydrogenated castor oil. A solution of gelatin and the above emulsion were heated to 40°C and

dispersed slowly in a stream into a solution of sodium sulfate at 40°C with stirring. After phase separation, the mixture was cooled, adjusted to pH 9.5 and treated with formaldehyde to harden the product (Heistand *et al.*, 1970).

The effect of ethanol, sodium sulfate and resorcinol on the induction period and some physical properties of gelatin coacervates has been studied by Zholbolsynova *et al.* (1971). Later Zholbosynova *et al.* (1988) investigated the influence of alcohol on the rheological properties of aqueous solutions of gelatin during the formation of coacervates. It was found that the viscosity of the coacervates increased with increasing concentration of the alcohol in the order methyl alcohol < ethyl alcohol < propyl alcohol. The strength of the coacervates prepared with ethanol as the coacervation agent increased with time, and was at maximum at an ethanol concentration of 13% v/v.

Nath (1973) investigated the influence of coacervation volume as altered by the temperature and the coacervating agent. It was found that as the temperature of coacervation increased in the system, gelatin, water, sodium sulfate, the volume of the coacervate increased. The volume decreased as the concentration of the coacervating agent, sodium sulfate, increased from 4.5 to 6.6%. The addition of hydrocolloid also altered the coacervation process. Dilute solutions 0.05–0.1% of carboxymethylcellulose reduced the growth of microcapsules during gelling. At higher concentrations, 0.1 to 1%, it increased the viscosity of the system. However, the capsules could not be filtered from the viscous liquid. The addition of polyvinyl pyrrolidone promotes flocculation and this interferes with coacervation.

Later, Nath and Shirwaiker (1977) studied the enhanced adsorption of atropine sulfate by kaolin in the presence of the coacervation-phase of gelatin, compared with either kaolin or the dried encapsulated form separately. The enhanced adsorption was attributed to the altered surface characteristics of the adsorbent in the gelatin–Na_2SO_4 system. Release of the drug from the coacervated kaolin product into simulated gastric or pancreatic fluid *in vitro* was considerably slower than that from the other two forms.

Simple gelatin coacervate systems have been used to enhance drug uptake by adsorption. Nath and Borkar (1979) prepared gelatin coacervates using ethanol as the coacervating agent. In three separate experiments, the amount of amphetamine bound by kaolin, gelatin coacervate and the kaolin gelatin coacervate system was studied. The authors suggest that the enhanced uptake of the drug by the coacervated kaolin results from successive layers of the coacervate phase providing new surfaces for drug deposition. Drug release in gastric and pancreatic fluid from the kaolin gelatin product follows first-order kinetics. Addition of surfactant to the

dissolution fluid, Tween 20, Tween 80 or sodium lauryl sulfate, enhances drug release, which suggests that the drug material is bound by both the core material and the coacervate coat.

Coacervation of gelatin in the presence of surface-active agents has been investigated for a number of reasons by Ohdaira and Ikeya (1973) and Ikeya *et al.* (1974a), who encapsulated lypophilic materials or water-insoluble substances using gelatin and a quarternary ammonium salt, e.g. octadecyltrimethyl ammonium bromide. The microcapsules were hardened with formaldehyde in an alkaline solution to give independent microcapsules. Subsequently, Ikeya *et al.* (1974b) used an anionic surface-active agent, e.g. sodium lauryl sulfate, in the coacervation process to aid in the encapsulation of hydrophobic materials.

Two coacervate systems of gelatin–benzalkonium chloride and acacia-gelatin were prepared and analysed for the sorption of halothane. Significant halothane gas uptake was observed in the highly structured coacervate system (Stanaszek *et al.*, 1974).

Coacervation of gelatin has been promoted by the addition of poly(vinyl alcohol). The agglomeration of gelatin was attributed, by the authors Falyazi *et al.* (1975), to be the interaction of poly(vinyl alcohol) and water, which alters the solubility of gelatin and promotes coacervation.

In order to improve its surface properties, pyrvinium pamoate was encapsulated with gelatin. Optimum results were obtained using a 10% gelatin solution at 50°C at a core to coat ratio of 2:1. Trivalent and divalent ions were effective in promoting coacervation when phase separation did not occur with NaCl. The addition of Tween 80 to the system before coacervation produced microcapsules that contained larger amounts of drug than when the surfactant was added after phase separation (Kassem *et al.*, 1975a).

An inorganic polymer has been used to induce coacervation. Hoerger (1975) induced phase separation of gelatin using Calgon (sodium hexametaphosphate) at 80°C using a lipophilic material as a core.

The stability of microencapsulated vitamin A and vitamin D concentrates in olive oil was not nearly as good as the non-encapsulated product stored under the same conditions, both in the presence of light and protected from light. It was suggested that the decreased stability was due to the porosity of the gelatin membrane which permitted light and moisture to reach the vitamins (Spiegl & Jasek, 1977).

Highly volatile liquids have been encapsulated with gelatin using sodium sulfate to effect coacervation. The microcapsules were then treated with isopropanol and formaldehyde. The product was further treated with stearic acid to prevent loss of the liquid cyclohexane. The microcapsules with a size range of 20–50 μm contain 75% of the volatile liquid (Spittler *et al.*, 1977).

Coacervates of gelatin and benzalkonium chloride have been prepared from 10% and 5% solution, respectively, by Takruri *et al.* (1977). These coacervates were compared with organic solvents with regard to the partitioning of four barbiturate salts and also the absorption of the barbiturates in the rat colon. The authors suggest that coacervation systems form a more realistic model for studying the absorption characteristics of drugs than do conventional organic solvent–water systems.

Madan (1980) studied the release behaviour of microencapsulated clofibrate, a liquid hypercholesterolaemic agent and related the data to the formation of the microcapsules. The drug fell from a capillary tube into a stirred, warm solution of gelatin type B. Then a 20% solution of sodium sulfate was added to promote the coacervation of the oil droplets. The product was poured into a 7% solution of sodium sulfate to gel the wall. Chilled isopropanol was added to dehydrate and flocculate the coacervate drops. The microcapsules were then hardened by immersion in a 10% solution of formaldehyde for up to 8 h. The process produced discrete, free-flowing particles of a uniform size (190 ± 10 μm). The dissolution of the microencapsulated drug in a 30% isopropanol solution at 37°C was studied. Several mathematical models were tested (square root, Langenbucher, cube root) but none yielded linear graphs. A close examination of the graphs showed four linear segments. The authors suggest that the matrix of the microcapsule differed from that proposed in the release of drug from solid matrices or from uniform non-disintegrating granules which tend to be homogeneous. The matrix appeared to be composed of various layers which exhibit different release characteristics.

The influence of glucose syrups and maltodextrin was studied by Marrs (1982). It was found that the inhibitory effect on gelation increases with the amount of high molecular weight oligosaccharides in the system. In addition, the properties of gelatin are modified by the composition of the starch hydrolysate.

Shchedrina *et al.* (1983) encapsulated dibunol by means of coacervation with gelatin solution. The stability of the microcapsules was investigated by determining such properties as bulk weight, friability and wearing properties after storage for 2.5 years at 20°C and 5°C. *In vivo* studies show the absorption of the oily drug was more uniform, continuous and prolonged compared with the oily liquid itself.

Nikolayev and Rao (1984) studied the effects of plasticizers on some physical properties of gelatin microcapsules prepared by coacervation. The microcapsules were prepared by treating a solution of gelatin at 50°C with a 20% solution of sodium sulfate. Oil coloured with Sudan III was added with stirring and the mixture cooled to 5°C to form the microcapsules. Microcapsules were also prepared by adding suitable amounts of plasticizer

to the warm solution of gelatin prior to the addition of sodium sulfate. The resulting microcapsules were mono dispersed with a size range of 300–400μm. The surface was smooth, the wall material was uniformly distributed and the coat on the plasticized microcapsule was thinner than on non-plasticized product. As the concentration of the plasticizer, glycerol, sorbitol, propylene glycol or polyethylene glycol 400 increased, the percentage of gelatin deposition decreased and there was also a tendency for a decrease in wall thickness. Finally, as the concentration of plasticizer glycerol or sorbitol was increased, the time for 50% release of the oil, as determined by dye concentration, decreased in a linear manner.

A matrix formulation of small particles, encapsulated with gelatin, has been prepared by decreasing the pH, causing the drug to precipitate from solution, and simultaneously effecting coacervation (Frank *et al.*, 1985). Sodium sulfadiazine was encapsulated by this method by titrating a solution of the drug in water containing ethanol, sodium sulfate and gelatin with HCl. A white suspension of microencapsulated particles was formed, which was poured into cold Na_2SO_4 solution and then stirred at the bath temperature to effect gelling of the liquid gelatin microcapsule shell.

A matrix encapsulation formulation of small particles of a water-insoluble drug, felodipine, was prepared by dissolving the drug in a little polyethylene glycol 400 and adding to the solution a 2.5% gelatin solution containing Na_2SO_4 which caused precipitation of the drug and the formation of a coacervate around the fine drug particles. A solution of Na_2SO_4 was added to complete the encapsulation; all steps were carried out at 55°C. The wall was gelled by pouring the suspension into a cold Na_2SO_4 solution and hardened with formaldehyde (Brodin *et al.*, 1986).

Gelatin coacervates have been prepared in the annulus between rotating concentric cylinders. Coacervation was induced in the water by the addition of Na_2SO_4. The coacervate droplets showed a logarithmic, normal distribution and their size depended upon the rotation rate, residence time and pH (Yagi, 1986, 1987).

Coacervation and encapsulation of fat materials such as cosmetics using gelatin was achieved at 50°C, using a small quantity of sorbitol, effecting coacervation with carrageenan, followed by treatment with glutaraldehyde to form microcapsules. This product may then be treated with other polymers such as a mixture of polydimethylsiloxane and poly(vinyl pyrrolidone) for printing on paper (Fellows *et al.*, 1987).

Rozenblat *et al.* (1989) investigated the effect of electrolytes, stirring and surfactants in the coacervation and microencapsulation process using gelatin. Lime-pretreated bovine skin gelatin with a gel strength of 60 and 225 bloom and acid-processed porcine skin gelatin with gel strength of 175 and 300 bloom were used. The first step in the procedure was the addition

of the core oleic acid and surfactant to an aqueous gelatin solution (8% w/v, pH 6.0–6.5) at 37°C, with stirring to effect emulsification. The second stage in the procedure was the encapsulation by adding a solution of 20% sodium sulfate. Finally a cool solution of sodium sulfate (7%) was added. The coacervation process was monitored by turbidity measurements. The microcapsules were observed and measured by using the microscope and a Coulter counter, or a computerized inspection system. It was found that coacervation is indifferent to the nature of the charge on the gelatin. However, an increase in bloom strength of the gelatin required smaller amounts of Na_2SO_4. These findings support the theory of Nixon *et al.* (1968). Experiments using different electrolytes could be divided into three groups. A number of fluoride salts were used to induce phase separation, for example MgF_2 and NaF. It was found that the effects of the electrolytes to induce phase separation increased with the charge density and the solubility of the electrolyte. The group was called phase separation inducers. Salts of polyvalent anions also belong in this class. A number of salts, e.g. $NaNO_3$ and NaI, require a greater amount of Na_2SO_4 to induce phase separation; these monovalent salts are known as chaotropic salts and have the ability to destabilize membranes. They decrease the energy required for solubilization and therefore increase the solubility of the gelatin. The efficiency of the chaotropic salts as inhibitors of coacervation decreases with an increase in the charge density. The inert salts do not induce phase separation and do not change the solubility of the polymer in water. Their charge density is between the previous two groups. The authors were able to encapsulate oleic acid in the presence of positively charged gelatin, non-ionic surfactants and anionic surfactants, but not in the presence of a positively charged surfactant. The inability to coat the oil drops in the presence of a positively charged surfactant was attributed to electrostatic repulsion. Encapsulation of the oil was not successful with negatively charged gelatin, but it could be encapsulated in the presence of non-ionic surfactants except Tween 20. These results disagree with those of Siddiqui and Taylor (1983). The control of stirring speed is most important during the cooling stage of the process, as it determines the microcapsule size. Prolonged stirring at stage two tends to cause an increase in aggregation.

Microcapsules of cholecalciferol were prepared by both simple and complex coacervation using gelatin A and gelatin B. Research of Sawicka (1990) shows that the properties of the microcapsules depend upon the coat to core ratio regardless of the type of gelatin or the coacervating process used. The size of the microcapsules, their dissolution in digestive juice, the coat to core ratio, the core content, and the rate of drug release were determined. With simple and complex coacervation methods, the optimum coat to core ratios were 0.25:1 and 0.5:1, respectively.

Coacervation with gelatin has been used to encapsulate drugs with an unpleasant taste. Ozer and Hincal (1990) encapsulated beclamide by simple coacervation by adding the drug to a stirred solution of gelatin at 40°C. Sodium sulfate solution was added slowly over a 35 min period. After cooling, decantation and washing with water, the microcapsules were hardened by the addition of a 75% w/v potassium aluminium sulfate solution at pH 4 and 7°C. Several other hardening agents were employed: formaldehyde, glutaraldehyde and isopropanol–aldehyde solutions. In order to improve flow properties, some of the microcapsules were dispersed in isopropanol 50% at 4°C containing Aerosil. The addition of alcohol during the preparation extracted some of the active ingredient, resulting in decreased beclamide content. Glutaraldehyde was found to be the best hardening agent. Aerosil tended to prevent the microcapsules from sticking together, in contrast to isopropanol. The mean size of the drug particle was 127.5 μm and after microencapsulation the mean size was 550 μm. The authors investigated some of the properties of the microcapsules, namely flow, consolidation, and the apparent and tapped densities. The release rates of the drug were found to be dependent on the type of gelatin and the method of hardening. Microcapsules prepared with no hardening agent had the fastest rate of release, those hardened with glutaraldehyde had intermediate rates whereas those hardened with an aldehyde and isopropanol mixture had the slowest release rate. The authors also prepared three types of tablet formulations: conventional, chewable and effervescent. Physical properties and dissolution of the drug from the tablets were also studied.

Nikolaev (1990) found that the physicochemical properties of gelatin microcapsules prepared by coacervation depended upon the polymer:core ratio and the treatment with formaldehyde. The particle size and the specific surface area of the microcapsules were influenced by the formaldehyde treatment. Properties of the final product, which contained norsulfazole as the model drug, were also dependent on the polymer density, the bulk mass and thickness of the microcapsule coatings when the number of drug particles increased.

Gelatin has been used to encapsulate natural and partially synthetic oils. The method developed by Keipert and Melegari (1992) enabled the preparation of microparticles that were approximately spherical and had a particle size of about 100–600 μm. It was shown that pH, the type of gelatin and additives to the gelatin system influence the characteristics of the microparticles, such as the mean diameter and surface, through the effects of viscosity and interfacial tension. The quality of the microparticles is also influenced by the characteristics of the core liquid, particularly the amount of unsaturated fatty acid.

Gelatin derivatives

A derivative prepared by the treatment of gelatin with succinic acid in alkaline pH was precipitated with Na_2SO_4 by Izgu and Doganay (1976). The heavier molecular weight fraction was separated and used to prepare microcapsules of sulfisoxazole. The microcapsules were hardened with alum and then with glutaraldehyde. Dehydration of the capsule wall was accomplished by using isopropanol and Aerosil. The drug release rate depended upon the degree of hardening and was found to be greater than from natural gelatin microcapsules.

Hydroxypropyl cellulose

Hydroxypropylmethyl cellulose and hydroxypropyl cellulose have been used as wall material for the preparation of encapsulated pharmaceuticals such as tocopherol acetate. The microcapsules were prepared by dissolving the wall material in water, along with dextran and effecting dehydration phase separation to give a product size of 100–300 μm diameter in the dispersion. The dispersion was then sprayed into fluidized silicone dioxide and dried to give microcapsules covered with silicone dioxide (Oowaki *et al.*, 1988).

Methylcellulose and derivatives

Methylcellulose or derivatives have been employed as a wall material to encapsulate lemon oil (Takahashi *et al.*, 1989). The oil was added to a 5% solution of methylcellulose to give an o/w emulsion, then a concentrated solution of hydrolysed starch as the coacervating agent was added to form the microcapsules, followed by dehydration with a 25% solution of NaCl and rinsing.

Polyethylene glycol

In a series of papers, Szretter and Zakrzewski (1984a,b, 1987a,b) encapsulated the vitamins riboflavin, thiamine nitrate, ascorbic acid and nicotinamide with polyethylene glycol (PEG) 6000 or 10 000 by heating, for example, a mixture of the vitamin and the polymer with paraffin oil, ligroin and Span 60. After cooling to room temperature, the product was washed with ligroin. The products showed improved stability with regard to humidity, air and light, depending upon the vitamin used.

Poly(vinyl alcohol)

Coacervates of poly(vinyl alcohol) have been prepared using colloidal silica as the core material (Iler, 1973, 1974). The coacervate was prepared from a dilute aqueous solution of the polymer and colloidal silica at pH 10. The pH was lowered to 2.6 with HCl and deaerated with a mixture of dodecyl alcohol and propyl alcohol, boiled in a vacuum and cooled to 25°C to form the coacervate. The maximum yield of coacervate was obtained when the ratio of colloidal silica to polymer in the coacervate was proportional to the particle diameter. For every nm^2 of colloidal silica surface, there were 2.5 hydroxy-ethyl chain segments. The coacervate consisted of silica particles whose surface was covered with a monomolecular layer of the polymer. The hydroxyl groups of the polymer were bonded to the SiOH group on the silica surface so that the hydrocarbon chain formed a hydrophobic coat.

Poly(vinyl methyl ether maleic anhydride)

Mortada (1981) prepared microcapsules of phenacetin using the polymer *n*-butyl half ester of poly(vinyl methyl ether maleic anhydride). The optimum conditions for coacervation were determined from a triangular phase diagram. Sodium acetate was used to dissolve the polymers in water and sodium sulfate was used to effect coacervation. The optimum conditions were polymer 0.5–3%, total salt 6.5%. During the microencapsulation of phenacetin, the coacervate drops tended to deposit on the surface of the drug suspended in the system. Gradual addition of sodium sulfate resulted in the continuous deposition of the coacervate onto the coated drug particle. As the core to coat ratio increased, the mean diameter of the microcapsules decreased slightly. However, the time required for the maximum amount of drug to be released decreased. Drug release was enhanced as the pH of the dissolution medium increased.

Poly(vinyl pyrrolidone)

Porous adsorbents such as activated carbon have been encapsulated with poly(vinyl pyrrolidone) to give improved selectivity. A dispersion of the adsorbent in a concentrated solution of the polymer was treated with a 30% solution of gum arabic, an incompatible polymer, and then coagulated with sodium sulfate and tannic acid to give a powder about 0.3 mm in diameter (Fukui, 1978).

Povidone and sulfathiazole microcapsules were prepared by suspending

the drug in 2% solution of the polymer; a 20% solution of resorcinol was then added dropwise until complete separation was obtained. The product was then filtered and air dried to give a fine free-flowing powder. The authors Badawi and El Sayed (1980) also prepared a number of interaction products of the drug and polymer by different means and compared the various products by solubility and dissolution tests. The coacervate complex had higher solubility and a slightly higher dissolution rate than sulfathiazole. It resisted the action of dilute acids and alkaline which suggested a bonding between the polymer and the drug. A model is discussed to describe the dissolution profiles of the different systems prepared.

Starch

Starch microgels have been prepared by coacervation by Ohno and Higano (1992). Separate concentrated solutions of starch and poly(ethylene oxide) were prepared at 80°C, and then were mixed to form simple coacervates of starch by means of phase separation. After immediately cooling in an ice-cold water bath, spherical starch microgels were formed with an average size of 35 μm. The diameter could be increased, for example to 180 μm, by lengthening the incubation time, for example to 10 min.

Various polymers

Meshali *et al.* (1989a) encapsulated both oxyphenbutazone, acidic, and glafenine, basic, non-steroidal anti-inflammatory drugs with various water-soluble polymers. Carboxymethylcellulose, an acid polymer, was dissolved in water and the drug was added with stirring. This dispersion was then poured in a thin stream into a concentrated solution of aluminium sulfate for the oxyphenbutazone or calcium sulfate solution for the glafenine drug with stirring. After coacervation was complete, as noted by the presence of a clear supernatant, the product was filtered and dried. In a separate preparation, hydroxypropyl methylcellulose, a neutral polymer, was dissolved in toluene by heating at 40°C, the drug was dispersed with stirring and then the mixture was cooled. After filtration, the product was dried. In another preparation, chitosan (amino cellulose), a basic polymer, was dissolved in a dilute acetic acid solution and added dropwise to glafenine which was dispersed in a sodium hydroxide solution. After stirring for 1 h the polymer precipitated on the drug particles which were then washed with water and dried. Microcapsules of the two drugs were also prepared by fluidization technique. The percentage yield in the coacervation technique ranged between 68 and 94% and the actual amount of the drug present in

the microcapsules ranged from 95.8 to 98% of the theoretical amounts. The microcapsules consisted of irregular aggregates thought to be due to polymer bridging caused by traces of polymer remaining in solution. The average diameter increased as the ratio of coating material in the microcapsule was increased. The dissolution rates were discussed in terms of the property of the drug, acidic or basic, and solubility of the drug as affected by pH and polymer concentration and the pH of the dissolution medium and the properties of the polymer. In a subsequent paper, Meshali *et al.* (1989b) found that all cellulose derivatives decreased the gastric ulcerogenic activity of the drugs.

COACERVATION-PHASE SEPARATION USING TWO WALL-FORMING POLYMERS SOLUBLE IN WATER

Acrylates

Acid and basic methacrylate polymers based on methacrylic acid and dimethylaminoethyl methacrylate were prepared and characterized by nuclear magnetic resonance spectrosocopy and dilute solution viscometry. Relations between pK_a, pK_b, pH, solubility and extent of ionization were determined by acid–base titration. Complex coacervates of these high charge density polymers were prepared and both yield and water content determined. Short-term cell viability using erythrocytes in these microcapsules was shown. The coacervates may be used for prostheses for organ transplant (Wen *et al.*, 1991a).

In a second paper, Wen *et al.* (1991b) reported on the ionizable group content, structure, molecular weight, solubility, solution behaviour and efficacy of ionic complex formation through complex coacervation for a range of sparingly soluble synthetic weak polyelectrolyte polymers with low charge content based on hydroxyalkyl methacrylate. Selected polymers containing methacrylic acid and dimethylaminoethyl methacrylate showed promise as forming pairs for the entrapment of mammalian cells. The solubility of basic polymers was enhanced through quaternization of the *N*-methyl group. The survival of guinea pig erythrocytes was indicated.

Albumin–acacia

Coacervates of serum albumin and gum arabic are unstable with respect to size. Studies of these static coacervates, that is coacervates in which no chemical reactions are occurring, showed that the turbidity increased with time to a maximum, then after a period of time, the turbidity decreased.

The turbidity was dependent upon the initial concentration of the coacervate forming system. Furthermore, based on light-scattering measurements, the coacervates were not stable during the period in which the turbidity measurements remained constant, because the coacervates coalesced into larger droplets (Gladilin, 1973).

The coacervation of albumin–acacia has been studied by Burgess *et al.* (1991a). Microelectrophoresis studies were used to determine the optimum pH condition for complex coacervation to occur. At pH 3.9 the polymers carry equal and opposite charges. The coacervate yield was maximum at an ionic strength of approximately 10 mM. The coacervate yield decreased at both lower and higher ionic strengths. High ionic strength affects the charge carried by the polymers through a screening effect of the counter ions; thus, the attraction of one polymer for the other is decreased. The decrease in coacervate yield with decreasing ionic strength is not predicted by a number of theories. This phenomenon can be explained when the configurations of the molecules are taken into account. Highly charged molecules may exist in a rod-like configuration, rather than a random coil, and thus act as specific sites in a distributive manner. The high viscosity of the coacervate phase at optimum pH values for maximum coacervation makes it difficult to disperse the coacervate which is required for the formation of small spherical microcapsules.

In a second paper Burgess *et al.* (1991b) further investigated the complex coacervation of bovine serum albumin and acacia. Maximum coacervation was predicted to occur at pH 3.9 where both polyions carry equal and opposite charges. The optimum ionic strength for maximum coacervation yield was 10 mM. At pH 3.9 the viscous coacervate phase could not be emulsified into the equilibrium phase; however, at pH 3.8 and 4.2, microcapsules could be successfully prepared. Particle size of the microcapsules decreases slightly as the stirring speed increases.

Albumin–alginic acid

The albumin–alginic acid complex coacervate process has been investigated by Singh and Burgess (1989). Maximum coacervation was obtained at pH 3.9, which is the electrical equivalence point for this pair of polymers where alginic acid and albumin carry equal and opposite charges. The optimum ionic strength for maximum coacervation is low in this system which is in agreement with the microelectrophoresis data. At low ionic strength (5–50 mM), there is a strong interaction for coacervation to occur. At high ionic strength coacervation is suppressed, while at very low ionic strength a precipitate is formed owing to the exclusion of water. Complex coacervation was observed at 0.05 and 0.5% w/v total polymer concentration.

Above 0.5% w/v only precipitation occurred. Opalescence noted in the system suggests that spontaneous aggregation takes place, and enhanced coacervation upon temperature reduction indicates a slow rearrangement of aggregates to form the coacervate phase. The albumin–alginate system fits the Veis–Aranyi (1960) theory which states that coacervation occurs in two steps spontaneously: aggregation by ion pairing followed by a rearrangement of the aggregates to form a coacervation phase. Coacervation is limited, compared with other polypeptide-polysaccharide systems such as gelatin–acacia, due to the occurrence of precipitation rather than coacervation if some of the conditions are not optimum. The albumin–alginic acid coacervation is very viscous and this makes the system unsuitable for preparation of microcapsules.

Albumin–dextran

The interaction of diethylaminoethyldextran with bovine serum albumin has been investigated by Gekko *et al.* (1978). It was investigated at the pH range above the isoelectric point by turbidity and electrophoresis. The coacervate was affected by pH, ionic strength and the weight ratio of the compounds. The interaction between the two compounds was attributed to electrostatic charges and was further strengthened by hydrophobic effects. The localized charge distribution model of protein polyion interaction is supported.

Alginate–chitosan

Capsules consisting of precipitated chitosan, a chitosan–alginate interphasic membrane and calcium alginate layers were prepared. The wall properties such as mechanical stability and thickness could be altered by buffer treatment and by partial substitution of alginate with propylene glycol alginate (Knorr and Daly, 1988).

Dextran–polyethylene glycol

A microemulsified polyethylene glycol–dextran coacervate used to dissolve haemoglobin. Ecanow *et al.* (1990) indicated that this system mimics whole blood with regard to oxygen-carrying properties and can sustain life when transfused into an animal.

Gelatin–acacia

Luzzi and Gerraughty (1964) used gelatin and acacia to encapsulate various oily liquids. After effecting coacervation, first at pH 6.5 at 50°C, then at pH 4.5, formaldehyde was added and the mixture cooled to 10°C and then the pH was adjusted to 9.0 to rigidize the coacervate droplets. The permeability, as shown by extraction studies of the gelatin acacia shell, is not affected by oils with different saponification values ranging from 2.5 to 12. However, the amount of oil extracted increases as the acid values of the oils increase. The incorporation of the oil-soluble surfactant sorbitan trioleate 85 (Arlacel 85) interferes with the encapsulation process and gave erratic results upon extraction. Water-soluble surfactants, polysorbate 80 and sodium oleate appeared to prevent proper encapsulation. It was suggested the surfactant may compete with the gelatin–acacia complex at the oil–water interface.

In a later study Luzzi and Gerraughty (1967) encapsulated a number of different solids with gelatin–acacia, for example pentobarbituric acid, and then determined the quantity extracted in gastrointestinal fluids. They found that the quantity of solid extracted did not change very much over a 2.5 h period when the pH for inducing coacervation was varied. The minimum amount of drug extracted occurred when the starting temperature for the coacervation was 37°C. It was suggested that this was related to the fluidity of the coacervate and the solubility of the drug. The retaining power of the capsules increased as the ratio of core to coat decreased. It was suggested that this may be due to multiple droplets, thickness of the wall or the attraction of empty capsules to filled capsules.

The effects of a number of variables on the gelatin–acacia system were studied by Dhruv and colleagues (1975). An acid type gelatin with an isoelectric point of approximately 8.5 to 8.7 and acacia were separately dispersed and dissolved in water. The pH of each solution was adjusted to 6.5 with a concentrated solution of sodium hydroxide. The solutions were mixed and adjusted to specific pH values. The mixture was allowed to stand for 3 h and the coacervate volume was then measured. This system yielded liquids which have a low viscosity and thus it is easy to measure the coacervation volume. At a given temperature the volume of the coacervate increased as the pH increased from 3.5 to 4.5 and the maximum volume was obtained at an equilibration temperature of 40°C. Microscopic observations showed that droplets tended to be smaller at higher temperatures. It was found that there was a linear relationship between the acacia:gelatin ratio and pH values for maximum coacervation volume and the final pH. Finally, it was found that at a given pH value the coacervation volume increases to a maximum at 4% total concentration and then decreases

abruptly; this was attributed to an increase in the number of inorganic ions present and possibly an increase in the viscosity of the system.

In a study to compare the release rates of sulfathiazole by microencapsulation by complex coacervation, Kassem and El Sayed (1973) used gelatin in combination with acacia, sodium alginate or pectin. It was found that the release follows a first-order process and the rate of release was in the order gelatin-alginate > gelatin-acacia > gelatin-pectin. Furthermore, the amount of drug release increased with a decrease in particle size in all systems.

In a subsequent paper Kassem and El Sayed (1974) investigated a number of factors that affected the release of sulfathiazole. They found that the starting pH for coacervation (6, 6.5, or 7) did not affect drug release after 2 h, but the final pH (8.5, 9.0 and 9.5) enhanced release into gastrointestinal fluids. The release was increased when the starting temperature was raised from 36 to 44°C and as the core to coat ratio increased, and when 1 or 10 ml of formaldehyde were used rather than 5 ml.

The reaction of glutaraldehyde with gelatin-gum arabic coacervate gels has been studied by Thies (1973). Both acid and alkali precursor gelatins were used to form coacervates. All gels had a consumption of 0.3 to 1.6 mmol of aldehyde per gram of gelatin. The consumption of glutaraldehyde by acid precursor gelatin acacia coacervate increases with gelation temperature 4–28°C due to changes in the gel structure. The reaction of the gels with the aldehyde causes insolubilization as a result of intermolecular cross-linking. Most treated gels were at least 85% insoluble at 55°C in phosphate buffer after 4–28 days of extraction. Gum arabic has little tendency to react with the glutaraldehyde, but is entrapped in the cross-linked structure.

Coacervate systems such as gelatin-acacia and gelatin-benzalkonium have been investigated in terms of their uptake of halothane. It was found that the coacervate took up considerably more halothane gas than did the dissolved or broken coacervate system. Stanaszek *et al.* (1974) suggested that the increased uptake indicates the presence of a highly structured, nonpolar system similar to surfactant micelles in a polar medium.

Optimal conditions for the preparation of gelatin-gum arabic films from coacervates have been investigated by Palmieri (1977). Various concentrations of gelatin and acacia were mixed at various temperatures and pH values. The pH was decreased to the 3–4.5 range and formaldehyde added. The filtered resuspended product was treated with isopropanol solutions and the product dried on a teflon coated sheet giving, on average, a film thickness of 95.61 μm.

Takenaka *et al.* (1979) related the wall thickness and amount of hardening agent to the release characteristics of sulfamethoxazole. The Higuchi

model was used to interpret the release characteristics of the drug and linear correlations were obtained up to 60–80% release when water was the dissolution medium. The release rate decreased with increasing wall thickness of the microcapsule. An increase of formalization also delayed the release rate. Diffusion coefficients through the microcapsule wall were found to range between 1.63 and 283×10^{-9} $cm^2 s^{-1}$ and decreased with the coacervate pH and with increased amounts of hardening agent used. Tortuosity increased with an increase in coacervate pH and an increase in the amount of hardening agent used.

Sulfamethoxazole microcapsules were prepared by Takenaka *et al.* (1980a) using gelatin and acacia solutions, and by adding the drug to the acacia solution. The solutions were mixed at 50°C and treated with acetic acid until the desired pH (2.5–4) was achieved. After cooling to 5°C and washing, the coacervates were hardened with formaldehyde. As the pH increased, the particle size decreased. The particle size of formalized microcapsules was larger than that of the unformalized ones because formaldehyde prevents shrinking of the microcapsules during the dehydration and drying process. Unformalized microcapsules had a smooth surface in contrast to the wrinkled appearance of the formalized product. Spray dried microcapsules had folding and invagination. The optimum pH for coacervation was 3.5 and this produced the highest core content (77.5%). Spray drying of the product changed the drug into the amorphous form, as studied by X-ray diffraction.

Takenaka *et al.* (1980b) found that the zeta potential increased and then decreased with increasing amounts of formaldehyde and this was attributed to denaturing of the gelatin and release of acacia from the microcapsule wall. The zeta potential of spray dried microcapsules showed that the wall was denatured during the process.

Further studies by Takenaka *et al.* (1981) indicated that coacervation occurred on the surface of sulfamethoxazole particles with adsorbed acacia. They also showed that the coacervate droplets were deformed to an ellipsoid in an electrical field. This phenomenon, the Buchner effect, showed that the coacervate wall was flexible. The denaturation of gelatin by formaldehyde did not occur at the coacervation stage, but during succeeding drying processes which completed the hardening of the microcapsules. Spray drying also denatured the gelatin.

Takeda *et al.* (1981) encapsulated indomethacin in soybean oil by preparing a coacervate of gelatin and acacia and hardening the microcapsules with formaldehyde at 5°C for 24 h. Sodium hydroxide was not used in the hardening process as indomethacin is degraded in its presence. After repeated washing with water, no formaldehyde could be detected. The yield of product in terms of the original amount of drug was greater than 80%.

The microcapsules dissolved more slowly than indomethacin. Both the microcapsules and the soybean oil suspension gave higher and more prolonged serum concentrations than the drug alone.

Indomethacin in the form of a paste in a water-miscible liquid, polyhydroxyalkane, was encapsulated with a coacervate of gelatin–acacia. A 40% formaldehyde solution was used to harden the walls and, after treating with isopropyl alcohol, gave a free-flowing product. The microencapsulated indomethacin reduced the gastrointestinal irritation compared with uncoated drug (Rowe and Carless, 1981).

A somewhat different method of preparing microcapsules of an oil, namely liquid paraffin containing a dye, was patented in Japan (Shionogi and Co, 1982). An emulsion was prepared using liquid paraffin and an 11% gum arabic solution. Emulsification continued until the particle diameters were 30 to 50 μm. Then a solution of acid-treated 11% gelatin was added and a 5% solution of polyethylene oxide which effected phase separation. After dilution with water the pH was adjusted to 7.7, cooled to below 10°C and treated with formaldehyde to form microcapsules.

An elaboration of the above method was described by Jizomoto (1984). Briefly, an emulsion of liquid paraffin is prepared using acacia or other anionic polymers such as carboxymethylcellulose or ethylene–maleic anhydride copolymer. The gelatin solution (11%) and the non-ionic polymer, for example, polyethylene glycol 6000, either in solution or in flake or powder form are added. The pH is adjusted with a solution of NaOH and the mixture is cooled. The mixture is subjected to a hardening treatment using diluted glutaraldehyde or formaldehyde. The product is then filtered and washed. The authors indicate that the addition of a small amount of polyethylene glycol or polyethylene oxide to the system of gelatin acacia allows microencapsulation to proceed over an expanded pH range of 2–9 and spherical microcapsules can be obtained. Other non-ionic polymers were also investigated such as dextran or poly(vinylpyrrolidone), but gave coacervate systems of higher viscosity in the cooling process which made it difficult to prepare good microcapsules. The authors attribute the spherical shape of the microcapsules to the appropriate viscosity of the mixture which was affected by both the molecular weight and the concentration of the non-ionic polymer. Jizomoto (1985) further described the value of polyethylene oxide or polyethylene glycol in an aqueous system of gelatin with or without acacia for a wide pH range of 2.5–9.5. The expanded pH range makes both processes more useful for drugs which may be water-soluble or have stability problems in certain pH regions. Further information on the effect of molecular weight on the induction of phase separation was discussed in the theory section.

Indomethacin was also encapsulated using gelatin and acacia with and

without hydroxypropyl celluose by Ku and Kim (1984). The rate of drug release and the drug content of the microcapsules decreased as the amount of wall material increased. The drug content was lower in microcapsules which contained the added polymer. The release rate of the drug from microcapsules with a 1:2 drug to matrix ratio was delayed as the formaldehyde treatment time was increased.

The release of nitrofurantoin encapsulated with gelatin–acacia coacervates was studied by Mesiha and El-Sourady (1984). The plain powder gave the fastest rate of release, followed by the directly encapsulated drug and then an encapsulated paraffin oil suspension of the drug. All samples showed a fast initial release rate followed by a slower sustained release with the encapsulated systems. As the viscosity of the oil increased, the release rate decreased.

A gelatin–acacia coacervate has been used by Noro *et al.* (1985) to prepare microcapsules of activated charcoal. The coacervates were gradually hardened with formaldehyde solution. Then the polymers were crosslinked by raising the pH above 9 using sodium hydroxide. The mixture was stirred at 50°C for varying times from 15 to 240 min. Adsorption studies of creatinine and components of higher molecular weight were carried out using coated microcapsules as the absorbent. As a result of the formaldehyde treatment, a stable semi-permeable membrane on activated charcoal was formed and the adsorption rate of creatinine was controlled by changing the cross-linking time. The substances with high molecular weight such as nutrients and enzymes had difficulty penetrating the membrane. It was suggested that administration of the encapsulated activated charcoal would be useful as a supporting technique in the treatment of patients with renal failure.

Indomethacin has been encapsulated by suspending the powder in rape oil and effecting coacervation with gelatin–acacia. The bioavailability from the microcapsule was high and showed a prolongation of action (Lu *et al.*, 1986).

The preparation of microcapsules by means of complex gelatin–acacia coacervation has been facilitated by the use of ionizing colloids, ionic surfactants or ionizing long-chain fatty acids, added prior to the dispersion of the core (Ninomiya, 1986).

In a study of the microencapsulation of oils such as paraffin, lemon and orange, Arneodo *et al.* (1986) determined various interfacial tensions. The interfacial tension between the oils and water > oil and the supernatant > oil and coacervate. The oils showed two types of interfacial behaviour with respect to the aqueous solutions. In the first type, a decrease of interfacial tension occurred up to the attainment of pseudo-equilibrium and no chemical modification occurred at the interface. In the second type, the

interfacial tension decreased to zero as a function of the temperature and the oil, and in this case a physicochemical modification occurred at the interface. Gelatin and various anionic substances were used such as Calgon 206, gum arabic and sodium alginate in the experiments.

Arneodo and colleagues (1987, 1988a,b) investigated a number of physicochemical properties of complex coacervates prepared from gelatin and anionic polymers. The solid contents and viscosities of the systems gelatin–gum arabic, gelatin–sodium polyphosphate, and gelatin–sodium alginate, were assessed. The solid content of the gelatin–gum arabic did not change much with the temperature, but the solid content of the other two systems decreased as the equilibration temperature decreased. The high viscosity of the last system was attributed to the high ionic interaction of the oppositely charged colloids. The interfacial tension of coacervates of the above three systems and four citrus oils were determined by the Wilhelmy plate method. The initial values were less than 8 mJ m^{-2} and decreased with time. At 40–50°C the interfacial tension decreased within 6 h to a value too low to measure. Further studies indicated that some of the constituents of the oil dissolved in water and were at least partly responsible for the decrease in interfacial tension.

Various types of surface active agents, anionic, cationic and non-ionic, have been shown not to have an appreciable effect on particle size of microcapsules prepared by coacervation using the gelatin–acacia system (Duquemin and Nixon, 1986). However, the amount of the core, phenobarbital, incorporated depends upon the type and concentration of the surfactant. The best conditions for encapsulating the drug were 2% w/w colloid at a stirring speed of 180 or 250 r.p.m. and the inclusion of 0.025% w/v cetrimide. High concentrations of the surfactant decreased the encapsulation of phenobarbital owing to a decrease in interfacial tension, and also steric and electrostatic effects caused by surfactant adsorption onto the coacervate drops and core.

Nixon and Wong (1989) evaluated the permeation of three compounds through polymeric membranes as a model for the release of drug from gelatin–acacia microcapsules. The membranes were prepared by mixing equal volumes of 2% gelatin and acacia solutions at 41°C with stirring and adjusting the pH to 4.0–4.2, then adding a formaldehyde solution. Three methods of casting were employed:

1. Without prior removal of the equilibrium fluid.
2. Removal of the equilibrium fluid by centrifugation at 20°C.
3. Cooling to 4°C and removal of the equilibrium fluid by filtration and then resuspension of the coacervate with water.

Each of the coacervates were then poured into steel dishes and dried to form

the film. Methods 1 and 3 produced films which had incomplete fusion of the coacervate droplets, as seen by scanning electron microscopy. In contrast, the film formed by slow phase separation, method 2, permitted good fusion of the droplets and resulted in a smooth surface. These films were similar to their corresponding microcapsules which are usually non-porous. The swelling of the films depended on the use of the cross-linking agent and indicated that swelling was complete after about 8 min for the cross-linked film, whereas with the non-crosslinked film, swelling continued to increase slowly for 60 h. The estimated permeability of the microcapsule wall was approximately 10^2–10^4 less than that of the film. This was attributed to difference in cross-linked density between the microcapsule wall and the cast film. It was found that gelatin–acacia coacervate does not slow the release of the drug core and, with N-7 theophylline acetic acid, a faster dissolution was obtained compared with the unencapsulated drug.

Burgess and Carless (1986a) studied the microelectrophoretic behaviour of gelatin–acacia complex coacervates and gelatin–gelatin complex coacervates and found that it was identical to that of equivalent mixtures of these polyions adsorbed onto a colloid carrier, namely silica with a geometric mean diameter of 2.7 μm. The charge carried by gelatin–acacia coacervates is not affected by encapsulated indomethacin particles which indicates that the drug is completely encapsulated and is likely not to be present in any significant amount in the capsule wall. This is in contrast to the properties of gelatin–gelatin microencapsulated indomethacin which suggests that the drug particles are associated with the capsule wall and thus produce a change in electrophoretic mobility.

Huttenrauch (1986) prepared gelatin–acacia microcapsules in the presence of structure breakers and structure formers. The latter, such as sorbitol, fructose and sucrose were found to promote larger microcapsules, helical structure formation and the agglomeration of gelatin particles. Structure breakers such as urea, methylacetamide and nicotinamide showed the opposite effect.

Pal and Pal (1986) investigated the complex coacervates of sulfamethoxazole with gelatin to develop a controlled release dosage form. Rigid microcapsules were obtained at pH 5.2 at 40°C with a drug polymer ratio of 1:1. It was found that a 28.7% v/v solution of glycerin and chilled propyl alcohol were necessary for the production of discrete spherical microcapsules.

Sulfamethoxazole microcapsules were prepared by coacervation with gelatin and acacia and a study of their micromeric properties was made by Pal and Pal (1987). The number of microcapsules per gram, the density of the wall material and that of the microcapsule increased with decreasing capsule size. The wall thickness decreased with decreasing capsule size and was inversely related to the square root of the number of microcapsules

present. Infra-red and X-ray analysis showed that the drug did not complex with gelatin. Microcapsules treated with formaldehyde had thicker walls and gave a more controlled release than unformalized microcapsules. A linear correlation between the wall thickness and the *in vitro* T50% release was observed.

In a subsequent paper, Pal and Pal (1988) prepared gelatin–acacia microcapsules by a standard method, but a 28% w/v solution of glycerol was used as a plasticizer. The product was treated with formaldehyde, water and isopropanol. It was noted that the wall thickness of the microcapsules decreased and that the density of the wall increased with decreasing size. This was related to the volume fraction of the pores in the wall, which decreased with decreasing capsule size. The kinetics at the early stages of release were zero order. The apparent diffusion coefficient of the drug, sulfamethoxazole, decreased with decreasing capsule size. The release of the drug from the microcapsule was faster at pH 7.2 than at pH 1.2, although the diffusion coefficient was lower. This phenomenon was explained by taking into account the solubility of the drug, its pK_a, and the volume fraction of the pores in the membrane. The decrease of the apparent diffusion coefficient of the drug through the wall at sink conditions at pH 7.2 is due to the higher concentration gradient because of the drug's higher solubility compared with the value of pH 1.2.

Sage oil was encapsulated with a gelatin–acacia coacervate to give a particle size of 50 to 500 μm with a wall thickness of about 0.5 μm and the percentage of sage oil encapsulated was 94.7%. The antimicrobial activity of the sage oil and the encapsulated product were similar; however, lower activity of the encapsulated oil against fungi was seen (Jalsenjak *et al.*, 1987).

Ion-exchange resin complexes of ester prodrugs of propranolol and the drug itself have been encapsulated with gelatin–acacia coacervates to produce microcapsules that extended the time for 50% release from 25 to 100 min. The rate of release decreased as the ratio of core to coat decreased. Using the same coacervation procedure a double coat was formed and extended the time for 50% of the drug release to 4 h or more. Despite delayed release profiles, the authors, Irwin *et al.* (1988) found that release follows particle diffusion models.

Spiegl and Viernstein (1988) investigated the effect of various ratios of gelatin and acacia gum, types of gelatins and pH on the coacervation process. The best yield of the coacervate, 92%, with a minimum degree of hydration, was obtained at a pH of 3.9 and a gelatin–acacia ratio of 1.5:1 using a Stoess type of gelatin with a bloom strength of 250–260. This system was used to encapsulate griseofulvin.

Multicore microcapsules with a diameter of 10–50 μm have been prepared by using polymer, surfactants and coacervation with gelatin and gum

arabic. An emulsion prepared from paraffin wax, 10% aqueous gelatin solution and emulsifier was added to a 10% solution of gum arabic at 60°C and mixed with Disparlon 1860 (polyaminoamide polyester salt) at 40°C, treated with formaldehyde at pH 4 and 20°C and then heated to 50°C, changing the pH to 9 to give the product (Yoshida *et al.*, 1989).

Improved vitamin A stability in a water-in-oil type emollient lotion has been prepared by Noda *et al.* (1989). The vitamin was added to a component of liquid paraffin and cetyl isooleate and this mixture was encapsulated with gelatin–acacia and hardened with glutaraldehyde and subsequently incorporated into an emollient lotion.

Microcapsules formed by the coacervation technique from gelatin and acacia, using glutaraldehyde, were prepared by Noda *et al.* (1992) for cosmetic purposes. The breaking strength of the microcapsule was controlled by mixing a liquid and solid oil component in a suitable ratio. Chemical stabilization of vitamin A palmitate, for example, was improved compared with the emulsified substance. Further improvement in stability was achieved by increasing the wall thickness or by using polylysine to modify the gelatin film.

In order to obtain a very prolonged release of a pheromone analogue, Omi *et al.* (1991) first prepared a liquid mixture of white beeswax and 2-ethylhexylacetate which was added to a dilute solution of gelatin stirred at 250 r.p.m. at 70°C. After 5 min the mixture was cooled rapidly and filtered. These wax particles were then microencapsulated by complex coacervation with gelatin–acacia and treated with formaldehyde at pH 9 for 2 h. As the release of the pheromone analogue was too fast for the intended purpose, an alternative method of encapsulation was performed. In this method, the wax particles were dispersed in a 20% aqueous gelatin solution and this suspension (s/w) was redispersed in 200 g of liquid paraffin to give a (s/w)o product. After 30 min agitation at 250 r.p.m. a w/o emulsion composed of an aqueous formaldehyde and liquid paraffin was added to the (s/w)o dispersion. Cross-linking was allowed to proceed for a few hours, then the microcapsules were filtered, washed with benzene, cold water and ethanol. The microcapsules prepared using the complex coacervate method contain only a single core and the diameters of different batches ranged from 169 to 338 μm and the thickness of the wall was about 1.5 μm. The products showed a rapid initial release and were exhausted after only 1 week. The product produced by the multiple emulsion produced microcapsules of average diameters ranging from 618 to 1366 μm and contained a number of wax particles ranging from 10 to 70. The release profile was altered considerably and although the initial release rate was still not satisfactory, 60% of the pheromone still remained after 10 days, at which time release rate became almost constant. The authors estimate that it

would take 47 days for 50% of the chemical to be released. Mass transport parameters such as capacity coefficients and diffusion coefficients were determined using a two-stage model. It was assumed that the mass transfer resistances dominate the transport process for the chemical; one was located in the wax particles and the other through the gelatin wall.

Peters *et al.* (1992) investigated the effect of bloom grade and isoelectric points of gelatin on the complex coacervate with acacia and the microencapsulation of theobromine. It was found that the electrical equivalence pH of gelatin and acacia were in the same range as the maximum coacervate volumes. The pH range in which the most coacervate formed for high bloom grade gelatin was smaller for alkali-processed gelatin than for acid-processed gelatins. A similar small pH range was observed for low bloom grade gelatin of the acid type, compared with high bloom grade of the same type. The total amount of complex coacervate increased and the relative content of theobromine decreased for gelatin with high bloom grade. Microcapsules prepared with a high bloom grade gelatin were irregularly shaped and showed poor flow characteristics; however, no difference in theobromine release profiles from various microcapsules was noted.

Gelatin–alginate

Wajnerman *et al.* (1972) investigated the coacervation between gelatin and sodium alginate using turbidity measurements at pH 3.5–4.5. The formation of electrically neutral complexes of the two polymers was postulated as the first step in coacervation with subsequent association with sodium alginate.

Cholecalciferol solution in peanut oil was microencapsulated by three methods (Sawicka, 1985): (a) simple coacervation with gelatin type B and Na_2SO_4; (b) complex coacervation with gelatin and sodium alginate; (c) complex coacervation with gelatin and cellulose acetate phthalate. The content of the microcapsules was approximately 600 000 IU g^{-1} and the dissolution half-time was 300–400 min. The products produced by methods (b) and (c) were insoluble in gastric juice and soluble in intestinal juice, while the product produced by method (a) was soluble in both.

Benzodiazepines have been encapsulated in a gelatin–alginate coacervate, then treating the product with tannic acid and with silica to produce a cake. The cake was dried in a fluidized bed system and the silica was removed (David *et al.*, 1988).

Gelatin–arabinate

Santamaria *et al.* (1975) investigated the coacervation phenomenon between gelatin and potassium arabinate. It was found that the yield of the coacervate was greatest at pH 3.5–4.1 and when potassium arabinate was in excess compared with gelatin. The coacervation decreased in the presence of potassium halide and the effect depended mainly upon the salt concentration and also on the ionic radius of the anion. Theoretical and mathematical considerations were used to interpret the phenomenon.

Gelatin–bacterial polysaccharide

Chilvers *et al.* (1988a,b,c) have described the encapsulation of sunflower, paraffin oils and aluminum particles by means of complex coacervation using gelatin and an extracellular bacterial polysaccharide. It was found that coacervation occurred only at the pH range of 3.0–4.5. The product was treated with glutaraldehyde and washed with isopropanol.

Gelatin–Carbopol

El Gindy and El Egakey (1981a,b) investigated the coacervation of gelatin A or B and Carbopol 934, 940, or 941 (source: B. F. Goodrich Chemical Co.). The two polymers were dissolved separately at 40°C, and the gelatin solution was added to the stirred Carbopol solution and various parameters were altered to investigate the system. Best results were obtained with gelatin type A at a pH of 6.8 with Carbopol 941 and the optimum ratio of Carbopol to gelatin was 1:10. An increase in total colloid concentration up to 1.1% w/v resulted in a parallel increase of sediment weight. At higher concentrations the sediment weight was less pronounced. Stirring at 300–350 r.p.m. gave almost spherical uniform coacervates with an average diameter of 59 μm.

In a subsequent paper, El Egakey and El Gindy (1983) found that glycerol in 20–33% v/v added after coacervation, produced smooth, spherical coacervates and if glycerol was added to the Carbopol solution prior to coacervation a coarser product was formed. The addition of glycerol rendered the microcapsules less coherent and reduced their adhesion to glass. The effect of increasing the concentration of formaldehyde was to increase the sediment volume of the coacervate. Formaldehyde-treated microglobules were treated with various volumes and concentrations of alcohols. The flocculation and sedimentation efficiency showed that 2-propranol at 60% concentration gave the best results. Microcapsules of sulfadiazine encapsulated

with the gelatin–Carbopol coacervate were also prepared. As the coat to core ratio increased, the percentage of drug encapsulated increased, and the average size increased from 78 to 136 μm.

Gelatin–carboxymethylcellulose

Koh and Tucker (1988a) characterized the sodium carboxymethylcellulose–gelatin complex by adding the sodium carboxymethylcellulose solution to the gelatin solution at 40°C with stirring and allowing it to stand for 10 min before evaluation. Maximum coacervation as determined from maximum deviation from additive viscosity occurred at pH 3.5 and 30% sodium carboxymethylcellulose. Around this pH, carboxymethylcellulose is negatively charged and gelatin is positively charged, resulting in strong electrostatic behaviour and hence, complex coacervation. At a pH range of 5.0–7.0 positive deviation from additive viscosity behaviour occurred, but coacervation did not occur. The change in viscosity and complex coacervation is explained in terms of ionization and the folding of the colloid. For example, at pH 5, the isoelectric point of gelatin and the anionic carboxymethylcellulose, a negatively charged soluble carboxymethylcellulose–gelatin complex forms and, as a result, electrostatic repulsion leads to unfolding of the complex and the viscosity shows a large positive deviation. The pH range for complex coacervation was found to be 2.5–4.5, as observed by turbidity measurements. The authors suggest that coacervate wet weights and volumes cannot be used to predict optimal coacervate conditions due to a change in coacervate morphology with mixing ratio.

In a second paper, Koh and Tucker (1988b) determined the chemical composition of the coacervate and equilibrium fluid phases of the sodium carboxymethylcellulose–gelatin coacervation complex. The coacervate batches were prepared at 0.75 and 2% total colloid concentration at pH values of 3.0, 3.5 and 4.0 and a range of sodium carboxymethylcellulose compositions of 10–60%. The colloid mixing ratio at which the peak coacervate yield occurred varied with the pH. Low viscosity and high viscosity grades of sodium carboxymethylcellulose gave similar results. Phase diagrams of the three components, water, gelatin and sodium carboxymethylcellulose at different pH values were prepared. Changes in the colloid composition of the complex coacervate and equilibrium fluids of isohydric mixtures as a function of the sodium carboxymethylcellulose mixing ratio were determined. The authors concluded that the sodium carboxymethylcellulose–gelatin complex coacervation is fundamentally the same as the gelatin–acacia system.

Microencapsulation of hydrophobic oils employing gelatin, carboxy-

methylcellulose and a second anionic colloid was accomplished by first preparing an emulsion at which coacervation does not occur. The mixture is then acidified to promote coacervation and formation of microcapsules. After chilling, the solid walls are treated with a cross-linking agent (North, 1989).

Gelatin–cellulose acetate phthalate

Kassem and coworkers (1975b) investigated the coacervation of gelatin and cellulose acetate phthalate and found that the optimal pH for the process was 4.6. Polymer–polymer interactions were more important in dilute solutions just below the isoelectric point of gelatin and gave stable salt bonds. Particle size increased with increasing concentration and decreasing temperature and also depended upon the rate of stirring.

Gelatin–chondroitin

Coacervates prepared from gelatin obtained from denatured tropocollagen and chondroitin sulfate were investigated by Nagura *et al.* (1988). The coacervates were formed at pH 4.5 with a weight ratio of chondroitin sulfate equal to 0.1. The helixes of the collagen molecules consisted of a small number of triple-helix crystallites. Intermolecular hydrogen bonds occurred between the amide groups of collagen and the hydroxyl groups of the chondroitin molecules in the outer surface of the coacervate.

Gelatin–gantrez

Mortada *et al.* (1987a) investigated a number of parameters affecting the complex coacervation of Type A gelatin and Gantrez-AN (G) polymers. Gantrez-AN 119 (mol. wt 250 000) and 149 (mol. wt 750 000) are polyvinylmethylether–maleic anhydride polymers and are soluble in water with hydrolysis of the anhydride groups. In order to prepare the complex coacervate, the gelatin solution at 40°C was added to a solution of Gantrez at 40°C and stirred for 20 min and then cooled with stirring. Formaldehyde was used to effect denaturation and this product was flocculated with various alcohols. The sediment volume and sediment weight of the coacervate were determined after centrifugation and drying. The maximum coacervation was achieved when the pH of the gelatin solution was 6.8, at which equivalence of oppositely charged molecules were present. Increasing the molecular weight of Gantrez decreased the combination with gelatin.

This was attributed to the coiled structure of G149, which possesses fewer available carboxylic groups for the reaction with gelatin. The optimum combination ratio for G119–gelatin is 1:4 and for G149–gelatin is 2:3 with a total concentration of 2.5% w/v for both polymers. The optimum concentration for denaturation with formaldehyde was 18% w/v at 2 h. The order of flocculation of the formaldehyde treated microcapsules was isopropanol = *n*-propanol > ethanol > methanol.

In a subsequent paper, Mortada *et al.* (1987b) described the encapsulation of nitrofurantoin in gelatin Type A and G119 or G149. The drug was added to the Gantrez solution and encapsulation was carried out in a manner similar to that described above. The encapsulation process was reproducible and about 90% of the drug was recovered in the microcapsules. The drug content decreased as the core to coat ratio decreased. The microcapsules were free flowing and tablets could be easily obtained by direct compression. The release of the drug in phosphate buffer at pH 7.4 and 37°C was decreased by encapsulation by using the Gantrez with the higher molecular weight and using a smaller core to coat ratio. The release kinetics were treated on the basis of a matrix model and yielded a linear relationship between drug concentration and $t^{1/2}$, thus following a diffusion-controlled model. Release data from capsules and tablets prepared from microcapsules were also obtained.

In a third paper, Mortada *et al.* (1988) investigated the bioavailability of nitrofurantoin microcapsules with a core to coat ratio of 1:2. The encapsulated product provided a prolonged release compared with that of the control formulation.

Gelatin–gelatin

Veis (1970b) studied the complex formation of gelatins with different isoelectric points of pH 9 and 5 as a function of initial mixing concentration. At a temperature of 20°C, which is below the conformational transition temperature of approximately 25°C, the fraction of gelatin in the coacervation phase increases with increasing mixing concentration but at 30°C the fraction decreases with increasing initial mixing conditions.

A complex coacervate of two oppositely charged gelatins has been prepared by Burgess and Carless (1985). They noted the previous work on this coacervate by Veis and coworkers from 1960 to 1967. The optimal concentration occurred when equal volumes of 1% deionized solutes of Types A and B were mixed together at 45°C, with stirring for 1 h. Subsequently, the temperature was reduced to 25°C for 4 h, then a 16% formaldehyde solution was added to harden the walls, followed by cooling to 4–5°C. After

centrifugation and decanting the product was washed with water and isopropanol. The predicted optimum pH was 5.4, the electrical equivalence point, where the two gelatins have an equal and opposite charge. At this pH the electrophoretic mobility of the gelatins was low and was probably insufficient to effect coacervation. If the ionic strength is lowered, the electrophoretic mobility increases appreciably, promoting gelatin–gelatin coacervation. However, coacervation was not evident at 40°C and it was necessary to decrease the temperature to obtain complex flocculation. By controlled slow cooling, a more ordered gelation occurred, promoting coacervates with liquid, rather than flocculated properties. Concentrations of gelatin higher than 2.5% caused self suppression of the coacervation phase separation, likely due to the neutralization of charges, to form a large stable gel network. It was found that the shape of the droplets depended upon the final temperature. Higher temperatures (30°C) produced ellipsoid droplets, while at 15°C aggregation occurred. The authors suggest that the morphology of the droplets at 25°C is a result of the viscosity of the coacervate phase. The stirring forces may or may not be balanced by stabilizing forces within the droplet. Slower stirring speeds resulted in an increase in the droplet size and the fraction of amorphous droplets. The drug naproxen was encapsulated at a drug to colloid ratio of 1:5 at temperatures ranging from 5 to 30°C. The per cent drug encapsulated was highest at 25°C and the drug content of the microcapsule was higher when the microcapsules were produced at 30°C; however, the microcapsule yield was highest at 10°C.

Gelatin–gellan

Procedures for the microencapsulation of oils and solid particles using gelatin–gellan mixtures by complex coacervation were observed by Chilvers and Morris (1987) at low total polymer concentration and were limited to the pH range of 3.5–5.0.

Gelatin–genipin

Microcapsules with a high melting point have been prepared with gelatin and genipin for use in the pharmaceutical and food industries. For example, peppermint oil was encapsulated after emulsification with gelatin acidified with acetic acid and then treated with genipin and warmed to 40°C, washed and centrifuged (Kyogoku *et al.*, 1988).

Gelatin–inorganic

Coacervates have been prepared from a suspension of bentonite in alcohol 3:10 and a 10% solution of gelatin in water in a ratio of 20:1 by adding the bentonite suspension to the gelatin solution with stirring. After filtration the coacervate was dried at 40°C. The granules were used with other ingredients to prepare tablets for the protection of gastric mucosa (Oita *et al.*, 1982). Lenk and Thies (1986) have investigated the behaviour of acid precursor gelatin with a polyphosphate in regard to pH, gelatin–phosphate ratio and bloom strength. It was shown that the system exhibits classical coacervation complex behaviour.

Gelatin–pectin

Microglobule size, morphology and recovery of pectin–gelatin coacervates were investigated by McMullen and coworkers (1982). Coacervates were prepared by combining solutions of pectin and Type A gelatin in varying ratios at 45°C with stirring and adjusting the pH with NaOH solution. After 2 min the pH was lowered with 0.5 N HCl and after stirring for 30 min, 5 ml of 37% formaldehyde solution were added. After cooling and decanting, the microcapsules were suspended in glycerin and then treated with an alcohol as the flocculating agent. The flocculated microglobules were filtered and washed with isopropyl alcohol and dried. At a coacervation pH of 3.8 the mean globule size increases from 2 to 10 μm when the pH of mixing was increased from 7 to 10. For solutions with equal pectin and gelatin concentrations, the maximum yield of the coacervate occurred at a colloid concentration of 2%. The maximum yield and microglobule diameter occurred at a pH of about 3.8 after coacervation, but depended upon the pH of mixing which ranged between 8 and 10. These changes were related to the ionization of gelatin and pectin and the viscosity of the microglobules. Increasing concentration of glycerin from 0 to 72% changed the morphology from spheres to ellipsoids. The formation of ellipsoids was attributed to dehydration of the coacervate and increasing intermolecular association as a result of decreasing dielectric constant. Isopropanol and 1-propanolol produced satisfactory microglobules, while other alcohols were not suitable.

In a subsequent paper, McMullen *et al.* (1984) encapsulated sulfamerazine with a gelatin–pectin coacervate. It was found that the drug should be added at the starting pH, that is, before coacervation takes place. The authors suggest that the drug is entrapped and the process is not a surface-active phenomenon as suggested for gelatin–acacia. Globules of various

sizes with mean diameters 5.7, 9.2 and 25.5 μm containing 37–45% drug could be produced. The spherical shape of the microcapsules was maintained at drug loadings of $\leqslant$69% and $\leqslant$45% for 25 μm and 10 μm microglobules, respectively. A small suppression of coacervate yield occurred as the drug to colloid ratio increased, which was attributed to salt suppression by the drug. Complete digestion of the microglobules was observed with gastric and intestinal juice only. No apparent morphological change in the microcapsule was observed by extraction with 0.1 M HCl or 0.1 M NaOH or water. Several other drugs such as phenobarbital, hydrocortisone acetate and cod liver oil which have low solubility in water and small particle size were successfully encapsulated.

In a further paper, Bechard and McMullen (1986) investigated the dissolution times of gelatin–pectin microglobules as a function of formaldehyde concentration and reaction times. It was found that the dissolution half-lives, in terms of the number of microglobules, can be controlled over a period from 2.7 to 751 min in a solution of sodium chloride and polyoxyethylene sorbitan monolaurate. A decrease in dissolution rate of the microcapsules was observed with aging of the product stored at ambient conditions.

The gelatin–pectin coacervate has also been used to encapsulate indomethacin. Ku and Chin (1989) found that the optimum pH and pectin : gelatin ratio for microcapsules was 3.8 and 1.2 respectively. As the concentration of colloid solution increased, the wall thickness increased. The 50% release time for indomethacin prepared from 1, 1.5 and 2% colloid solutions were 3, 5 and 6 min, respectively, while that of indomethacin powder was 50 min.

Gelatin–polyvinyl alcohol

Cho *et al.* (1982) investigated the coacervation of gelatin and poly-(vinyl alcohol). The coacervation pH phase diagram showed a coacervate region consisting of two liquid phases and a non-coacervate region consisting of a single liquid phase. The intensity of coacervation was greatest at pH 5 and increased with increasing temperature. The coacervation was attributed to hydrogen bonding between the two polymers.

Histone–acacia

Coacervation of acacia has been studied by the nephelometric technique and the coacervate drops ranged in size from 0.5 to 500 μm. The average size and the number of drops served as parameters of the coacervate behaviour (Gladilin *et al.*, 1972).

Sulfated poly(vinyl alcohol)–aminoacetalysed poly(vinyl alcohol)

Nakajima and Sato (1972) have discussed the complex coacervation of sulfated poly(vinyl alcohol) and an aminoacetalysed poly(vinyl alcohol). The three component system of the polymer salt, water and sodium bromide was investigated. The results are interpreted according to a theoretical equation for the free energy of mixing, taking into account the entropy and enthalpy contributions.

In a second paper, Sato and Nakajima (1974a) reported on the conditions for complex coacervation of the two polymers by relating the effects of charge density on phase separation. Conditions for coacervation were discussed as a function of chain length, interaction between polymer and water, the temperature, the electrostatic interaction and the number of charges on the polyelectrolyte chain. Subsequently, the authors, Sato and Nakajima (1974b,c), discussed the conditions for the formation of coacervate droplets as a function of charge density and polymer concentration. Furthermore, they indicated that the concentration of the coacervate phase at 25°C decreased and the concentration of the equilibrium liquid phase increased with increasing polymer concentration. The reduced viscosity of aqueous solutions of both polymers increased with decreasing polymer concentrations. The volume and polymer fraction of the coacervate phase containing the two polymers passed through a maximum value with increasing polymer concentration.

Okihana and Nakajima (1976) found that a 1:1 complex formed upon mixing the ratio of two polymers. The concentration of polymers in the coacervate and equilibrium liquid depended upon the initial polymer concentration. Coacervation of the 1:1 complex was suppressed by the addition of salts owing to a change in chain conformation.

COACERVATION-PHASE SEPARATION USING A SINGLE WALL-FORMING POLYMER SOLUBLE IN AN ORGANIC LIQUID

Acrylates

Hydrophobic compounds have been encapsulated with 2-diethylaminoethyl methacrylate–methacrylic acid-styrene copolymer latex by Ushiyama (1979). For example, castor oil was emulsified in water containing an anionic surfactant, Emal A, to a particle size of 30–50 μm. The pH was adjusted to about 9 and the polymer added, which has an isoelectric point of 7.2, and the pH adjusted to 9–10 with NaOH. After acidifying to a pH of 5–5.5 to form the capsules, the product was spray dried.

Donbrow *et al.* (1984) encapsulated potassium dichromate and paracetamol with poly(methyl ethyl methacrylate) (Eudragit Retard). The polymer and polyisobutylene were dissolved in chloroform and the core material was suspended in the solution. Cyclohexane containing polyisobutylene was added at a controlled rate and coacervate droplets formed which encapsulated the core material. A decrease in the rate of addition of the non-solvent caused a decrease in the rate of release of the core material; this was attributed to structural changes as the core concentration was almost constant at about 80%. At high addition rates of the non-solvent, the microcapsules had polymer spheres attached to the surface – thus the effective wall thickness was reduced and the release rate increased. As more non-solvent was added, more polymer came out of solution – thus the percentage of core material in the microcapsules decreased and the release rate decreased. It was also found that smaller particles gave faster release rates.

Chun and Shin (1988) encapsulated aspirin with Eudragit RS polymer from a solution of chloroform with polyisobutylene dissolved in cyclohexane. The polyisobutylene functioned as a coacervation-inducing agent and gave smooth microcapsules with less aggregation. By increasing the proportion of the wall material, particle size and wall thickness, and the concentration of paraffin wax in the cyclohexane as a sealant, a product with sustained release characteristics could be obtained. Release was independent of pH of the medium and the mechanism of drug release from both non-sealed and sealed microcapsules appeared to fit Higuchi matrix model kinetics. The aspirin microcapsules were more stable than free drug in a solution of $NaHCO_3$.

Eudragit L 100, a copolymer of methacrylic acid and methylmethacrylate which is insoluble in acid but soluble in alkaline solution, was used to encapsulate aspirin (Okor, 1988). The drug and polymer were dissolved in 95% ethanol and the solution was evaporated to dryness. The product was crushed and passed through a sieve and the fraction between 710 μm and 500 μm was collected. Dissolution was retarded in acidic medium, but enhanced in neutral medium. The author suggests that drug–polymer attractions are possibly stronger than drug–drug attractions, thus partly accounting for the delayed release in the acid medium. In the alkaline medium the polymer is soluble and readily liberates the aspirin.

Okor (1989) prepared colloidal solutions of ethyl acrylate (trimethyl ammonium) ethyl acrylate chloride–methyl methacrylate copolymer using ethanol as a solvent and water as the non-solvent. Stability of the dispersion to electrolytes such as NaCl and Na_2SO_4 increased considerably with an increase in the polymer cation content. The polymer dispersions were most sensitive to Na_2SO_4 and least sensitive to NaCl. In 1990 Okor encapsulated the drug salicylic acid with acrylate–methacrylate copolymers. The drug and

polymer were dissolved in ethanol and excess water, the non-solvent, was added in the presence of a flocculating agent, NaCl. The dried coacervates were compressed into tablets or placed into capsules. It was found that drug release rates decreased exponentially with increase in polymer concentration in the coacervate, but increased exponentially with an increase in polymer cation content at a constant polymer concentration of 20% w/w. The increase in release rate was associated with an increase in polymer 'swellability'. Drug release rates from tablets were retarded compared with those from capsules; this was believed to be due to poor disintegration of the tablets.

A coacervation technique using an acrylate–methylacrylate copolymer was used to form an aqueous based coating system consisting of the water-insoluble copolymer and sucrose in varying ratios to coat matrix cores by Okor *et al.* (1991). Drug release rates increased as the concentration of the sucrose increased in the film coating. Doubling the coating thickness from 75 μm introduced a lag time for release of the model drug salicylic acid from 0.5 to 2.5 h depending upon the amount of sucrose. Overall, however, the release rates were hardly affected by the coating thickness.

Aqueous dispersions prepared by coacervation of Eudragit RL 100 and RS 100 were prepared by Okor (1991). A lower viscosity and higher gel point was observed with Eudragit RL 100. This phenomenon was explained by the higher degree of mutual repulsion of the cationic charges in Eudragit RL 100 compared with Eudragit RS 100. The fluidity of aqueous dispersion of these two polymers suggests their use in film coating processes.

Eudragit RS 100 polymer dissolved in chloroform was used to coat zipeprol hydrochloride. Cyclohexane containing polyisobutylene effected coacervation. The mechanism of drug release from the microcapsules appeared to fit the Higuchi matrix kinetics. Plasma concentration time curves suggested that the microcapsules can be used as a sustained release product (Yong and Kim, 1988).

Ferrous fumarate and ferrous sulfate were encapsulated by evaporation and various other methods using different Eudragit polymers. *In vitro* dissolution studies indicate the release was linear, but there was an inflection point that separates the initial fast release from the later, slower phase. In some cases a biphasic pattern was noted for larger size microcapsules, whereas a monophasic pattern was observed with small microcapsules. Particle size was the most important factor in determining the dissolution. The nature of the polymer and integrity of coating had a minor influence on dissolution (El Shibini *et al.*, 1989).

Kim *et al.* (1989) encapsulated a complex of dextromethorphan hydrobromide and a strong cation-exchange resin with Eudragit RS by phase separation using a non-solvent. It was found that the release rate from the

coated complex could be controlled by the amount of coating material. The effect of pH and the ionic strength on the release rate of the drug was also studied.

Sprockel and Price (1990) encapsulated the complex of chlorpheniramine maleate and a carboxylic acid cation-exchange resin. The complex was suspended in an acetone solution of polymethyl methacrylate, then emulsified in liquid paraffin containing various additives. After 12 h of stirring to permit the evaporation of the solvent, the microcapsules were collected, washed with hexane and dried. Several parameters and additives were tested and it was found that: (a) larger microcapsules were obtained if the concentration of the polymer was increased; (b) fine particles of bentonite, Veegum, carbon black or emulsion stabilizers, reduced the microcapsule size at 3% concentration, but increased the size at 6% owing to incorporation into the microcapsules; (c) silicone fluid 60 000 cp was more effective in reducing the microcapsule size than silicone fluid 50 cp; (d) magnesium stearate, glyceryl monostearate and stearyl alcohol reduced the microcapsule size; (e) formulations with higher coat to core ratios resulted in slower release of the drug from the microcapsules; (f) larger microcapsules released the drug at a slower rate than did smaller microcapsules.

Alex and Bodmeier (1990) encapsulated pseudoephedrine hydrochloride by preparing a solution of the drug in water and then preparing an emulsion in a solution of poly(methyl methacrylate) in methylene chloride with the use of a sonicator. This primary w/o emulsion was added to the external phase - water containing 0.25% poly(vinyl alcohol) as stabilizer - with stirring at 1500 r.p.m. in a small container with baffles for 10 min to give a w/o/w emulsion. The microcapsules were filtered and rinsed with water. Sonication resulted in the smallest droplet size and highest drug content. As the drug was not soluble in the polymer solution, it could not diffuse to the external aqueous solution. The method had good batch-to-batch reproducibility with respect to drug loading. The yield was above 95% and the particle size ranged from 50 to 500 μm. The drug content of the microspheres increased with drug loading, increasing amounts of solvent, polymer, and polymeric stabilizer. This last factor was attributed to an increase in the thickness of the adsorbed layer of the polymeric stabilizer and an increase in viscosity close to the droplet surface, resulting in a reduction in the rate of solvent and drug diffusion across the droplet interface into the continuous phase. The drug content decreased with increasing stirring time, increasing pH of the continuous phase and increasing volume of the internal and external aqueous phases.

Theophylline was encapsulated with Eudragit RS 100 using a solution of the polymer, and polyisobutylene in chloroform (Chattaraj *et al.*, 1991). Phase separation and rigidization of the deposited polymer was effected by

using cold *n*-hexane. Polyisobutylene below 5.5% w/w did not produce uniform microcapsules, but aggregates. The drug content of the microcapsules was at maximum at 5.5% w/w of polyisobutylene at a fixed core to coat ratio. High percentages of polyisobutylene decreased the yield of the product. Dissolution at 37°C with increasing pH indicated that, as the core to coat ratio increased, the rate of dissolution also increased. As the percentage of polyisobutylene was increased in the preparation of microcapsules, the rate of release decreased. Bioavailability studies in rabbits indicated that prolonged release was obtained.

Badawi *et al.* (1991) encapsulated theophylline with Eudragit E and Eudragit L by non-solvent techniques. The best method to coacervate the drug is by using Eudragit E while the drug is dispersed in solution by the addition of a non-solvent. Eudragit E had a higher affinity for the drug and increased the surface drug by entrapment of the drug within the coat. Eudragit L formed a better barrier to the drug, but the microcapsules were less than satisfactory.

Cellulose acetate

Cellulose acetate was used as the wall material for preparing microcapsules of hydrocortisone by coacervation. The nearly spherical capsules in the range of 10–20 μm were formed and the release of the drug was sustained up to 7 days (Singh *et al.*, 1982).

Cellulose acetate butyrate

Sprockel and Prapaitrakul (1990) encapsulated paracetamol with the polymer cellulose acetate butyrate by employing three different emulsion techniques. In the emulsion solvent evaporation method (ESE) the drug was dispersed in the polymer solution using acetone as the solvent. This phase was then emulsified in a liquid paraffin solution containing 1% sorbitan monooleate and stirred at 1400 r.p.m. at room temperature until the solvent had evaporated. The microspheres were collected, washed with hexane and dried. In the modified emulsion solvent evaporation method (MESE) a limited amount of a non-solvent, hexane, was added slowly to the drug dispersion containing the polymer in acetone. This mixture was then emulsified as described above. The emulsion non-solvent addition method (ENSA) was the same as ESE, except that a limited quantity of solvent, hexane, was added to the emulsion after it had been stirred for 5 min. In the ESA method, the rate of solvent removal depends upon the rate of solvent partitioning into the mineral oil and solvent evaporation. In the MESE

method, the addition of hexane likely increased the affinity of the external phase for acetone; as a result the rate of solvent removed depends primarily on acetone evaporation and this reduced the preparation time from 12 to 8 h. In the ENSA method, the removal of the solvent, acetone, depends primarily on the rate of solvent removal into the mineral oil and hexane solution and the preparation time was considerably reduced. The drug content and the drug release from the last two methods, MESE and ENSA, were significantly higher.

Cellulose acetate phthalate

A modified method based on the work of Kitajima *et al.* (1971) to prepare enteric coated microspheres using cellulose acetate phthalate was developed by Maharaj *et al.* (1984). Several pharmaceuticals such as loperamide and trifluoperazine-isopropamide and also rabies antigen were encapsulated by suspending the active compound, diluted with sucrose containing cornstarch if necessary, in paraffin oil. Then a solution of the polymer in acetone–ethanol 95% was added. Shortly thereafter the chloroform was added to harden the microspheres which were then decanted, washed and collected. The size of the microspheres increased as the time for formation increased from 0.5 min to 10 min and the encapsulation method had no appreciable effect on the activity of the biologically active substance.

In a subsequent paper, Beyger and Nairn (1986) prepared a three-component phase diagram of the system cellulose acetate phthalate, light mineral oil and solvent, acetone and 95% ethanol, to indicate the appropriate region for preparing microcapsules and also the effect of surfactant, sorbitan monooleate, concentration on the product. Chloroform was used as the hardening liquid. It was found that aggregation of the microcapsules could be minimized at low solvent concentration. In addition, pharmaceuticals could be microencapsulated regardless of their solubility in the polymer solvent or hardening liquid. The size of the product increased as the core to coat ratio was increased to a maximum (1.5:1). In addition, the time and order of addition of the various ingredients used to prepare the microcapsules was investigated. In general, the addition of the drug to the mineral oil followed by addition of the polymer solution was preferred, although other procedures gave satisfactory results. In some cases, however, it is necessary for the drug to be present as soon as the coacervate is formed for suitable microencapsulation. Particles with a large size, 20–50 mesh, were not always suitably coated.

Dibunol has been encapsulated with cellulose acetate phthalate. A 2% polymer concentration gave the most uniform product where approximately

91% of the microcapsules had a particle size of 160–250 μm (Berseneva *et al.*, 1988).

Mortada (1989) prepared microcapsules of phenobarbital by dissolving both the drug and cellulose acetate phthalate in a 9:1 mixture of ethyl-acetate and isopropyl alcohol. Various factors affecting the coacervation such as temperature, speed of agitation, polymer concentration and drug content were studied. The release from the microcapsules was a function of both particle size and core to wall ratio.

Ku and Kim (1989) encapsulated propranolol HCl with cellulose acetate phthalate in a system containing paraffin, acetone and ethanol. The wall thickness of the microcapsules increased with increasing cellulose acetate phthalate concentration and the dissolution rate decreased. The dissolution rate in both simulated gastric and intestinal fluid was determined.

Dharamadhikari and colleagues (1991) microencapsulated salbutamol sulfate with cellulose acetate phthalate. The polymer was dissolved in acetone and the drug was mixed with light liquid paraffin. Both phases were mixed together and after evaporation of the acetone, the microcapsules were collected and washed with ether and water. Free-flowing spherical microcapsules were obtained. It was noted that the percentage of drug encapsulated increased as the amount of coating polymer increased in the coating phase. Microcapsules prepared with a coat to core ratio of 2:1 showed delayed release in an *in vitro* dissolution study during which the pH was changed.

Terbutaline sulfate and propanolol hydrochloride were also encapsulated with cellulose acetate phthalate by Manekar *et al.* (1991, 1992), in a similar manner as described immediately above. However, the dose of the drugs are small, they were diluted with mannitol. Products with low coat to core ratios were unable to prolong drug release when the pH was changed from 1.2 to 7.5; however, microcapsules with a higher coat to core ratio or with a mixture of the polymer and ethylcellulose provided release for up to 12 h. Propanolol hydrochloride in cellulose acetate phthalate followed a matrix mechanism of release in acidic media and a zero-order release in alkaline media. When coated with a mixture of the two polymers, it showed a zero-order release throughout the dissolution test as the pH was changed.

Cellulose acetate trimellitate

Sanghvi and Nairn (1991, 1992) investigated the formation of microcapsules using cellulose acetate trimellitate. Three-component phase diagrams were prepared to show the region of microcapsule formation for the system

polymer, light mineral oil and the solvent acetone–ethanol. Chloroform was used as the hardening agent. Microcapsules were only formed when the polymer concentration was in the 0.5–1.5% range and the solvent concentration in the 5–10% range. The addition of surfactants such as sorbitan trioleate or sorbitan oleate to the mineral oil altered and/or increased the region of microencapsulation. Surfactants with higher hydrophile–lipophile balance values tended to decrease the area of microcapsules on the phase diagram. Sorbitan monooleate 1% in mineral oil gave products with smoother coats and a more uniform particle size. Tartrazine-containing microcapsules were prepared and the smallest microcapsule size was obtained when sorbitan monooleate 3% was used and these microcapsules had the slowest rate of release in an acidic medium. As a result of the removal of acetone from the polymer solution by the mineral oil, a polymer-rich phase is formed and after combining with other droplets and/or the core material, the microcapsules are formed which are hardened by further loss of solvent to the dispersion medium and also by the addition of chloroform.

Ethylcellulose

It was found that the time for release of sodium phenobarbitone from ethylcellulose microcapsules increased as the core:wall ratio decreased. With a constant core:wall ratio, the small microcapsules released their contents more rapidly than the larger ones (Jalsenjak *et al.*, 1976).

In a series of papers Donbrow and Benita (1977) investigated the effect of polyisobutylene on the coacervation of ethylcellulose. Ethylcellulose and polyisobutylene were dissolved in cyclohexane and the solution was allowed to cool slowly from 80°C to 25°C with controlled agitation. After 24 h, a clear upper phase containing the polyisobutylene and a lower phase of coacervate droplets formed whose particle size decreased with phase coacervation volume increase, which was increased by polyisobutylene. The product was a free-flowing powder, in contrast to the aggregated mass in the absence of polyisobutylene. The release of salicylamide from microcapsules showed first-order kinetics and the release rate increased with polyisobutylene concentration because of the thinner coating. It was indicated that polyisobutylene acts as a protective colloid in the process and prevents the agglomeration of ethylcellulose microcapsules.

Benita and Donbrow (1980), in a second paper, indicated that using a temperature reduction method for preparing coacervation droplets, in the absence of, or a low concentration of polyisobutylene, aggregates were formed, whereas higher concentrations of polyisobutylene stabilized the droplet. Polyisobutylene is not coprecipitated and acts as a stabilizer by

adsorption. Increased concentration of polyisobutylene or higher molecular weights of polyisobutylene raised the phase coacervation volume and decreased the particle size indicating increased stabilization.

Benita and Donbrow (1982) employed polyisobutylene as a protective colloid to prepare microcapsules of salicylamide and theophylline based on the temperature differential solubility of ethylcellulose in cyclohexane. A minimum concentration of polyisobutylene was necessary to prevent aggregation and as its concentration was increased, it yielded microcapsules of higher drug content because the coating was thinner; furthermore, there was an increase in the release rate of the drug from the microcapsules. Microcapsule drug content decreased with decreasing particle size of the drug in the presence of the protective colloid. This was caused by a more complete uptake of the wall polymer on the increased surface of the core material.

A mixture of ethylcelluloses with a viscosity of 100 cp (0.1 Pa s) and a viscosity of 45 cp (0.045 Pa s) was used to encapsulate trimethoquinol using polyisobutylene as an agent to induce phase separation. The mixture was cooled from 78°C to room temperature and the microcapsules were filtered, washed and dried (Samejima and Hirata, 1979).

Samejima *et al.* (1982) prepared microcapsules of ascorbic acid with ethylcellulose using the temperature change technique. They found that polyisobutylene was better than either butyl rubber or polyethylene. The polyisobutylene changed the gel into a coacervate with the formation of smooth microcapsules with thick walls. The microcapsules did not aggregate appreciably and gave a slow release of the vitamin.

In a subsequent paper, Koida *et al.* (1983) used a similar method to encapsulate ascorbic acid with ethylcellulose using polyisobutylene. It was found that aggregation decreased with increasing molecular weight of ethylcellulose. The molecular weight of ethylcellulose which gave a minimum release rate was affected by the molecular weight of polyisobutylene. Polyisobutylene of high molecular weight gave less aggregation than polyisobutylene of low molecular weight. The relationship between the release rate and the molecular weight of ethylcellulose used depended primarily on the compactness of the wall, rather than its thickness.

In a patent, Samejima *et al.* (1984) described the encapsulation of trimebutine maleate with ethylcellulose using liquid paraffin and polyisobutylene in cyclohexane to give a solubility parameter of 7–10 $(\text{cal cm}^{-3})^{1/2}$, and then subsequent cooling. The product was free-flowing microcapsules.

Koida *et al.* (1984) investigated the effect of molecular weight of polyisobutylene on the microencapsulation of ascorbic acid using temperature reduction with a solution of ethylcellulose. After fractionating polyisobutylene, several fractions of various molecular weights were obtained. It was

found that aggregation of the microcapsules decreased with increasing $\bar{M}$ (viscosity-average molecular weight), and above a value of 6×10^5 it was almost wholly prevented. The influence of $\bar{M}$ of polyisobutylene on the coacervation process was determined by measuring the volume fraction, the ethylcellulose content and the viscosity. It was found that the wall-forming temperature was lower with higher $\bar{M}$ of polyisobutylene. With higher $\bar{M}$ of polyisobutylene, a larger coacervation volume was produced, but the concentration of ethylcellulose in the coacervation phase was less and there was a very low concentration of polyisobutylene in the coacervate phase. The viscosity of the coacervate phase was higher with the lower $\bar{M}$ of polyisobutylene; this was attributed to the higher concentration of ethylcellulose in the coacervate. It was found that the temperature of the viscosity maximum coincided with the wall-forming temperature which appeared to be the most important temperature for microencapsulation. As the temperature decreases and reaches the temperature of maximum viscosity, the size of the ethylcellulose droplets gets larger and these gel-like droplets deposit on the surface of the drug and, after fusing, they form the wall. The effect of mixing high and low $\bar{M}$ polyisobutylene showed that with an increase of low $\bar{M}$ polyisobutylene, average wall thickness and compactness increases and the wall becomes less uniform.

Several different techniques have been employed to encapsulate ion-exchange resin beads containing benzoate with ethylcellulose by temperature change and non-solvent addition (Motycka and Nairn, 1979). Different viscosity grades of ethylcellulose, either alone or in conjunction with various plasticizing agents such as castor oil, butyl stearate and the protective colloid polyethylene were used. Some of these products were then treated with paraffin. In addition, the benzoate complex was encapsulated using gelatin and acacia and also cellulose acetate butyrate. It was found that the rate of release, as described by Boyd *et al.* (1947), could be controlled by the type of encapsulating material used and the phase separation process. The slowest rate of release was achieved with the microcapsules which were subsequently treated with paraffin. It was found that tough, dense films of large molecular weight compounds delayed the release of the anion. The decrease in the diffusion of the benzoate ions corresponded with an increase of the density of the film. Additives with the greatest lipophilic characteristics, polyethylene and paraffin produced the greatest resistance to ion transfer.

In a subsequent paper, Motycka *et al.* (1985) encapsulated ion-exchange resin beads containing theophylline with ethylcellulose, inducing phase separation by temperature reduction and by evaporation. Some of the products were subsequently treated with a solution of hard paraffin. Several products encapsulated with ethylcellulose by evaporation and also

subsequently treated with a solution of hard paraffin gave a product that released the drug according to zero-order kinetics. It was found that the pattern and the rates of release could be controlled by the cross-linking of the resin and the coating procedure used.

Ethylcellulose microcapsules of ion-exchange resins containing theophylline were prepared by the evaporation method using ethylcellulose dissolved in ethyl acetate as the coating polymer, polyisobutylene dissolved in cyclohexane as a protective colloid and light liquid paraffin as the suspending medium (Moldenhauer and Nairn, 1990). Predominantly mononucleated microcapsules were formed by controlling the amount of ethylcellulose used, the particle size and the appropiate concentration of the protective colloid. The rate of release of the drug was altered by the cross-linking of the ion-exchange resin, the amount of ethylcellulose and the smoothness of the coat on the resin beads. Release rates from coated resin beads with low cross-linking followed a logarithmic plot indicating membrane controlled release, whereas coated resins with a higher degree of cross-linking followed a $t^{1/2}$ plot, indicating particle diffusion control.

In a subsequent paper, Moldenhauer and Nairn (1991) investigated the effect of the rate of evaporation on the coat structure of the microcapsules which were predominantly mononucleated. The rate of solvent evaporation influenced the surface morphology, the shape, and the porosity and the purity of the ethylcellulose coat. Microcapsules had tails and porous coats at slow evaporation rates. Faster evaporation rates resulted in the formation of microcapsules with no tails and smooth, but wrinkled coats. Coat porosity was minimal at intermediate evaporation rates. Microcapsules which showed rapid release rates of theophylline were formed when the very fast, slow and very slow evaporation rates were used to form the microcapsules. Intermediate evaporation rates formed coats with minimum porosity, leading to slow release rates of the drug.

Baichwal and Abraham (1980) encapsulated metronidazole by using ethylcellulose and polyethylene glycol 4000 in different proportions. As a result of encapsulation, the release of the drug was delayed and the percentage drug release, as a function of time, increased with increasing content of the polyethylene glycol.

Ascorbic acid has also been encapsulated using a solution of ethylcellulose in cyclohexane. The product had 2–3% wall material and a wall thickness of 6–10 μm (Shopova and Tomova, 1982).

Adriamycin was encapsulated with ethylcellulose in cyclohexane using the temperature reduction method (Kawashima *et al.*, 1984). Polyisobutylene, rather than polyethylene, was found to be an effective coacervate-inducing agent. With increasing concentration of polyisobutylene, the average diameter of the particles decreased owing to reduced agglomeration. Microcap-

sules of the drug encapsulated with ethylcellulose at 2% polyisobutylene effectively prolonged the release of the drug compared with 1% or 3% polyisobutylene. The increase in rate of release noted when 3% polyisobutylene was used was attributed to a thinner wall. Kinetics of release of microcapsules prepared with 2% polyisobutylene were linear when plotted against $t^{1/2}$ suggesting a matrix type of release.

Using a non-solvent which resulted in the formation of an emulsion, Kaeser-Liard *et al.* (1984) encapsulated phenylpropanolamine hydrochloride with ethylcellulose. The drug, 95% of the particles $<40\,\mu m$, was suspended in a solution of ethylcellulose dissolved in acetone. With stirring, a solution of equal volumes of mineral oil and petroleum ether, the non-solvent, were added over 90 min. During this period, the first emulsion of non-solvent in the polymer solution inverted to an emulsion of the polymer solution in the non-solvent at the same time phase separation took place. The microcapsules were then hardened with the addition of hexane at $-20°C$. After stirring in the cold, the microcapsules were filtered and dried. The microcapsules had a particle size in the 150–300 μm range and the yield was 90–100%. Several parameters were investigated, namely the volume of the non-solvent, the volume of the solidifying agent, rate of addition of the non-solvent, stirring rate, temperatures of the coacervation step and the hardening step and the core to wall ratio. The rate of drug release increased as the volume of the non-solvent was increased from 300 to 400 ml, as the temperature of hardening was increased from $-10°C$ to room temperature, and as the core to wall ratio was changed. The rate of addition of the non-solvent and the stirring speed did not affect the drug release from the microcapsules.

Sulfamethoxazole was encapsulated with ethylcellulose using an emulsion technique by Chowdary and Rao (1984). The drug was dispersed in a solution of ethylcellulose in acetone. This dispersion was added in a thin stream to stirred liquid paraffin which formed an emulsion. Water, the non-solvent, was then added to cause coacervation and production of the microcapsules. After centrifugation, the product was washed with petroleum ether and then dried. Batches of microcapsules were prepared using different core to coat ratios. The time for 50% of the drug to be released in an acidic and neutral medium increased as the particle size increased and as the percentage of the coat material increased.

Chowdary and Rao (1985) described the influence of Span 60 and Span 80 on the preparation of microcapsules by emulsification. It was found that the inclusion of surfactants decreased the microcapsule size, but did not alter drug release. The drug release with or without a surfactant was similar for a particular size of microcapsule.

Chowdary and Annapurna (1989) encapsulated aspirin, metronidazole,

paracetamol and tolbutamide by three different methods. Method I was coacervation-phase separation of ethylcellulose dissolved in toluene by the addition of petroleum ether. Method II was similar except that carbon tetrachloride was used as the solvent. Method III used thermal induction of the coacervate of ethylcellulose from cyclohexane. In all cases the drug was added to the polymer solution. The wall thickness was determined by the method of Luu *et al.* (1973). The apparent dissolution rate constants, K_{app}, were calculated from the initial slope of the release curve as described by Koida *et al.* (1986). The permeability constants, *Pm*, were determined from the following equation:

$$Pm = \frac{K_{app} VH}{ACs}$$

where V is the volume of the dissolution medium, H is the wall thickness of the microcapsules, A is the surface area of the microcapsules, and Cs is the solubility of the core in the dissolution medium.

The wall thickness ranged from 7.9 to 39.3 μm and the apparent dissolution rate constant ranged from 0.53 to 12.32 mg min^{-1}. It was found that for all four cores the order of permeability of the microcapsules was method III > method I > method II which suggests that the permeability depends upon the method employed.

Rak *et al.* (1984) prepared potassium chloride microcapsules using ethylcellulose by phase separation from cyclohexane by temperature change. It was noted that the addition of macrogol 300 or 4000 improved the formation of microcapsules and decreased the aggregation of the product.

Potassium chloride was encapsulated with ethylcellulose by coacervation with cyclohexane using polyethylene glycol by Chalabala (1984). The drug, with a particle size of 80 μm, had a microcapsule size of 125–187 μm with agglomerates up to 605 μm. High core to wall ratios gave smaller microcapsules.

Szretter and Zakrzewski (1984a) coated riboflavin with ethylcellulose dissolved in cyclohexane by the temperature change method. The solution also contained PEG 6000 and Tween 20. The product was stable at room temperature against oxidation, photodecomposition and humidity. The vitamin was also encapsulated with PEG 6000 by mixing at 70°C with paraffin oil, and ligroin containing PEG 6000 and Span 60 or Tegin G. The suspension was cooled to room temperature, filtered, washed and dried.

A mixture of ethylcellulose and polyethylene glycol 6000 has been used as a coating material and the process is carried out in cyclohexane to improve the stability of ascorbic acid (Szretter and Zakrzewski, 1987a).

Cisplatin was encapsulated with ethylcellulose dissolved in cyclohexane

in the presence of low density polyethylene by the temperature reduction method (Hecquet *et al.*, 1984). Two stirring methods were used during the cooling stage - mechanical and sonication; however, no difference in microcapsule characteristics could be discerned between the methods. A number of different concentrations of drug, ethylcellulose and polyethylene were used to prepare the microcapsules and several observations were made: (a) losses of microencapsulated drug content occurred on increasing the ethylcellulose concentration; (b) the average drug content did not change if the amount of polyethylene was increased, but the proportion of small-size microcapsules increased; (c) the microcapsule composition appeared to be independent of particle size; (d) the wall thickness increased with an increase of ethylcellulose concentration. The drug was not decomposed by the microencapsulation process and certain products which released 80–100% of the drug within 24 h were selected for further studies.

Encapsulation of rifampicin was effected by dissolving ethylcellulose in ethyl acetate and adding the drug mixture. After stirring for 4 h petroleum ether was added at a controlled rate until coacervation started and then the mixture was stirred for 1 h. The microcapsules were collected, washed, dried and eventually made into pellet form (Khanna *et al.*, 1984).

Dihydralazine sulfate was encapsulated with ethylcellulose by Oner *et al.* (1984). The microcapsules were separated by size. The time for half of the drug to be released increased as the core to wall ratio decreased and as the particle size increased. Release appears to take place by diffusion.

Oner *et al.* (1988) encapsulated zinc sulfate using ethylcellulose dissolved in carbontetrachloride. Warm petroleum ether, a non-solvent, was added and the product was collected and washed with the non-solvent and dried. The rate of release in distilled water was determined and evaluated kinetically by the Rosin–Rammler–Sperling–Bennet–Weibull Distribution, which gave a good fit in defining the release from the microcapsules. A comparison of the release with hard gelatin capsules was also made.

Lin *et al.* (1985) encapsulated theophylline with ethylcellulose using four types of ethylene vinyl-acetate copolymer, with different concentrations of vinyl acetate (20–40%) as a coacervation-inducing agent. When *n*-hexane was added at the last step of microencapsulation, the particles aggregated except for the polymer containing 28% vinyl acetate. Using increasing concentrations of this polymer decreases the average diameter of the microcapsules as there was less aggregation. The wall thickness, the smoothness and compactness of the microcapsules increased and the porosity decreased with increasing concentration of the coacervating-inducing polymer. Differential scanning calorimetry indicated that the coacervate-inducing polymer was absent in all microcapsules.

Lin (1985) then investigated the influence of the coacervation-inducing

agent ethylene vinyl acetate and polyisobutylene and cooling rates on the properties of microencapsulated bleomycin HCl. The particle size of microcapsules induced by ethylene vinyl acetate was smaller than that induced by polyisobutylene, and the size distribution of microcapsules using ethylene vinyl acetate depended on the cooling rate, which was different from that using polyisobutylene. The slower the cooling rate, the more prolonged was the release of the drug; this followed the Higuchi model. The time required for dissolution of 50% of the drug for both methods of microcapsule preparation decreased with an increase in the cooling rate. The rate-limiting step under certain circumstances was diffusion of the dissolution medium and the dissolved drug through ethylcellulose.

In a subsequent study, Lin and Yang (1986a) encapsulated chlorpromazine HCl with ethylcellulose using ethylene vinyl acetate copolymer as a coacervation-inducing agent. Higher concentrations of ethylene vinyl acetate decreased the microcapsule size and delayed the release of the drug because of the more compact surface and increased thickness of the wall. Microcapsules were compressed into tablets and prolonged the release considerably, which was attributed to a reduced surface area.

The release mechanism was discussed by Lin and Yang (1986b), and it was found that differential rate treatments showed that the release kinetics of theophylline from ethylene vinyl acetate copolymer-induced ethylcellulose microcapsules followed first-order kinetics.

Lin and Yang (1987) also encapsulated theophylline with ethylcellulose by temperature change using ethylene vinyl acetate copolymer as a coacervation-inducing agent. It was found that the higher the concentration of copolymer used, the more sustained was the release of the drug from the microcapsules. This was attributed to the lower porosity and thicker walls of the microcapsule. Bioavailability studies in rats indicated that microcapsules prepared with higher concentrations of ethylene vinyl acetate may act as sustained release forms.

Lin (1987) also investigated the effect of polyisobutylene of different molecular weights on the release behaviour of theophylline from microcapsules prepared with ethylcellulose. It was found that the release rate of the drug at pH values of 1.2 and 7.5 at 35°C was higher when polyisobutylenes with higher molecular weights were used. This was similar to results reported by Koida *et al.* (1984). Several equations were investigated to study the release behaviour and one of the most useful was $1/y = \mathrm{A}\ 1/x + B$ where y is the amount of drug released, x is the time, and A and B are constants that are proportional to the amount of drug released.

Cameroni *et al.* (1985) encapsulated sulfadiazine by phase separation coacervation using temperature change and ethylcellulose and polyisobutylene was used as a protective colloid. Different release rates could be

obtained by altering the wall thickness, which was controlled by the formulation. The rate of release for wall thickness $<5\,\mu m$ followed the Hixson–Crowel theory and that for greater wall thickness followed the Higuchi theory.

Encapsulation of indomethacin and indomethacin modified by dry blending with a carboxyvinyl polymer by pulverization was carried out by Nakajima *et al.* (1987), with ethylcellulose and temperature reduction using polyethylene as a coacervation-inducing agent. The microcapsules were multinucleated and released the drug very slowly in a dissolution medium of pH 7.2. The rate of dissolution decreased as the amount of polyethylene was increased in the coacervation process. Subsequently, the microcapsules were prepared in the form of suppositories and were tested for dissolution characteristics.

Singh and Robinson (1988) investigated the effects of a number of surfactants on microencapsulation. Tweens and Spans, with HLB values ranging from 4.7 to 15, were used for the preparation of microcapsules of captopril. The process was carried out by dissolving the ethylcellulose in cyclohexane containing 2% absolute alcohol at 80°C. After dispersing the drug in this solution, it was cooled to room temperature and then to about 0°C. Microcapsules retained by 500–850 μm sieves were used for further studies. Dissolution tests in 0.1 N HCl at 37°C showed that the release rate decreased with an increase in the HLB of the surfactant. Based on the work of Barnett and Zisman (1959), who indicated that many solids will not be wetted if their critical surface tension is exceeded by the surface tension of the liquid, the authors suggested that the wetting for solvation of ethylcellulose with surfactants of higher HLB values resulted in an efficient coating around the drug particles and thus caused the slowest release. It was also found that higher ethylcellulose viscosity grades were less effective in extending the release of the drug in the concentrations used. This was attributed to the high viscosity of the coacervate droplets which inhibited coalescence and thus the formation of an intact ethylcellulose wall. Different kinetic models were used to explain the release. The best fit was the first-order kinetics plot with two straight lines that had two different slopes. The initial slope has a faster release than the terminal slope.

In a second paper, Singh and Robinson (1990) investigated the encapsulation of captopril using four viscosity grades of ethylcellulose with core to wall ratios of 1:1, 1:2, 1:3 by temperature reduction in cyclohexane. Dissolution studies in acidic media showed that the release depended upon the core to wall ratio and the viscosity grade of ethylcellulose and probably on the viscosity of the coacervate. A core to coat ratio of 1:1 showed that an increase of viscosity of wall material decreases the release rates. Viscosity grade 300 cp was not satisfactory for microencapsulation. The surface, as

studied by scanning electron microscopy, showed that microcapsules prepared with 10 cp ethylcellulose were more porous and with larger pores than those prepared with 50 cp. The microcapsules did not fragment, alter shape or size or show enlargement of pores during dissolution. The *in vitro* release correlated better with biphasic first-order kinetics, rather than zero order or square root of time.

Singla and Nagrath (1988) encapsulated ascorbic acid to improve its stability in the presence of zinc sulfate. The microcapsules were prepared using ethylcellulose and the temperature change method using toluene as a solvent. The microencapsulated ascorbic acid was washed with toluene and dried in a vacuum. Several formulations including the product just described, ascorbic acid embedded in PEG 6000 or in stearic acid, were prepared in the form of tablets along with zinc sulfate. Tablets prepared from either the microcapsules or the stearic acid product had the maximum stability.

Based on a factorial design, the parameters which influence the particle size and particle size distribution of acetylsalicylic acid microcapsules coated with ethylcellulose were determined (Devay and Racz, 1988). The microcapsules were prepared by dissolving the drug and the polymer in varying ratios in diethylether in a reflux apparatus with stirring at 30°C. The solution was placed under vacuum and upon boiling, *n*-hexane was added slowly and the temperature reduced to 20°C; after filtration the microcapsules were dried. It was noted that the drug precipitated first and then became coated with the polymer. Coacervation was attributed to evaporation of the solvent, addition of a non-solvent and cooling. The parameters affecting the particle size for 50% through fall are in the order, rate of addition of hexane > drug content > ethylcellulose viscosity > speed of agitation. It was found that the standard deviation of the size increased with drug content, polymer viscosity, rate of addition of hexane and decreased with speed of addition.

Ferrous fumarate was encapsulated by phase separation using different ratios of ethylcellulose and castor oil. It was found that the drug release from the microcapsules depended upon the particle size, the thickness of the coat and the core:coat ratio (Shekerdzhiiski *et al.*, 1988).

Metoprolol tartrate was encapsulated with ethylcellulose using two different coacervation techniques by Nasa and Yadav (1989). In the non-solvent method, ethylcellulose was dissolved in a solution of carbon tetrachloride and the drug was added, then petroleum ether and talc. After decanting, the microcapsules were filtered and washed with petroleum ether. The second method involved temperature change of a solution of the polymer in cyclohexane. The product was filtered and washed with hexane and dried. It was found that the dissolution rate in distilled water of the product

prepared by the use of the non-solvent gave a slower dissolution. Furthermore, as the concentration of ethylcellulose used in preparing the microcapsules increased, the dissolution rate decreased. Stability studies of both pure drug and microencapsulated drug showed similar results.

The effect of hydroxypropyl methylcellulose as a nucleating agent was investigated using ethylcellulose and temperature change to effect microencapsulation. The core contained ascorbic acid, PEG 4000 and the nucleating agent. Optimum conditions for the formation of microcapsules, such as cooling, temperature, time, and concentration of hydroxypropyl methylcellulose, were assessed (Kaltsatos *et al.*, 1989).

Safwat and El Shanawany (1989) treated theophylline and oxyphenbutazone with a carboxyvinyl polymer, Carbopol CV 940, by dry blending to control their release. The coated drugs were encapsulated with ethylcellulose using polyethylene and temperature reduction. The release rates of the two drugs decreased as the content of polyethylene, a coacervation-inducing agent, was increased, except at a concentration of 1% with the drug oxyphenbutazone. Suppositories containing the microencapsulated carboxyvinyl polymer modified drugs showed a pseudo zero-order release profile. It was felt that this method, that is, surface treatment and microencapsulation, is a good one to prepare sustained release suppositories containing these drugs.

Vitamin C was encapsulated with ethylcellulose in cyclohexane using ethylene polymer as the coacervation-inducing agent. It was found that the dissolution rate of the microencapsulated vitamin and tablets was slower than unencapsulated samples (He and Hou, 1989).

Shin and Koh (1989) investigated the effect of polyisobutylene on the preparation of methyldopa encapsulated with ethylcellulose dissolved in cyclohexane using temperature change. When polyisobutylene was used, there was low aggregation and the surface of the product was smooth and had a few pores. The dissolution of the drug was altered by the core to wall ratio. The microcapsules were also treated with spermaceti, which reduced the rate of release of the drug; the release was also influenced by the amount of sealant used and the particle size of the product.

Chemtob *et al.* (1989) investigated the influence of polyisobutylene on the microencapsulation of metronidazole by dissolving ethylcellulose in cyclohexane at 80°C and cooling. The molecular weights of polyisobutylene used were 3.8×10^5 and 1.12×10^6. As the concentration of polyisobutylene is increased, aggregation is minimized and spherical microcapsules are obtained. At high concentrations of polyisobutylene some empty microcapsules are formed; this was also noted by Benita and Donbrow (1982). At a concentration of 3%, the higher molecular weight polyisobutylene gave less aggregation, similar to that reported by Koida *et al.* (1983). The percentage

of the sieve fraction $<315\ \mu m$ is generally increased when polyisobutylene is added during the preparation of the microcapsules. It was found that the total drug content was not generally influenced by the addition of the polyisobutylene. It was noted that the times for 50% of the drug to be released at a pH of 1.2 and 37°C decreased as the concentration of polyisobutylene with the lower molecular weight increases at a core to wall ratio of 1 to 1, but not at a ratio of 2 to 1. When polyisobutylene with a higher molecular weight was used T50% varied with polyisobutylene concentration.

Piroxicam microcapsules were prepared by coacervation using ethylcellulose. It was found that it took 240 min to release 63% of the drug from microcapsules, compared with 6.9 min for the drug in hard gelatin capsules (Bergisadi and Gurvardar, 1989).

Dubernet *et al.* (1991) prepared microcapsules of ibuprofen with ethylcellulose dissolved in methylene chloride. Methylcellulose or polyvinyl alcohol, as the emulsifying agent, was dissolved in water and then the polymer solution containing the drug was added, an emulsion formed and evaporation proceeded until all the solvent was lost. In addition to the above procedure the crystal window concept was used in which the solvent evaporation is interrupted and the supernatant removed to prevent crystallization in the aqueous phase. This tends to remove drug molecules and prevent deposition. However, crystal formation was in some cases observed in both systems. Based on altering the drug concentration in both the aqueous and non-aqueous phases and the nature of the emulsifier, a mechanism for crystal deposition is proposed which involves the formation of nuclei in the unstirred layer surrounding the emulsified droplet during solvent evaporation. Crystal growth is also controlled by the drug concentration in both phases and the viscosity of the polymer layer at the interface.

Propranolol hydrochloride microcapsules were prepared by solvent evaporation by dissolving ethylcellulose in acetone and adding the dispersion to liquid paraffin by Ku and Kang (1991). The amounts of drug dissolved at pH 1.2 in aqueous solution increased as the drug content of the microcapsules increased and the dissolution was not affected by the concentration of sorbitan tristearate in the microencapsulation process.

Bacampicillin was encapsulated with different viscosity grades of ethylcellulose dissolved in cyclohexane, employing polyisobutylene with different molecular weights (Oppanol B200, B100, B50, B3) as the coacervation-inducing agent (Kristl *et al.*, 1991). It was found that when polyisobutylene of low molecular weight was used agglomerates are formed as a result of large coacervate droplet size and low viscosity of the continuous phase. If a high molecular weight of polyisobutylene is used, much of the ethylcellulose was not used for wall formation. Further experiments were carried out with Oppanol 50, and different organic liquids were used for washing

purposes. It was found that a non-agglomerated, free-flowing product was obtained when *n*-heptane was used, in contrast to some agglomeration obtained when petroleum ether or cyclohexane were used. Different celluloses and different core to wall ratios influence the shape of the microcapsules. Usually, spherical and small microcapsules were obtained using ethylcellulose N-50 with a core to wall ratio of 1:1.5. Stability studies showed that most of the original drug was retained. A kinetic analysis of the release of the drug was carried out. It was found that a combined zero- and first-order kinetic relationship was most suitable. The drug release decreased with increasing molecular weight to a minimum when the molecular weight of ethylcellulose was approximately 13×10^4, depending upon the polyisobutylene used, then the rate of release increased with increasing molecular weight of ethylcellulose.

Chloroquine phosphate and quinine hydrochloride microcapsules have been prepared by a thermally induced coacervation method using ethylcellulose. The microencapsulation process masked the taste of the drug and dissolution studies showed a prolonged release profile. Tablets of the microencapsulated drug were also prepared and tested (Chukwu *et al.*, 1991).

Sveinsson and Kristmundsdottir (1992) encapsulated naproxen by coacervation-phase separation from a warm solution of ethylcellulose. The product after cooling was washed with cyclohexane and dried. The core to wall ratio was 1:1 or 1:2 and polyisobutylene concentrations ranged from 0 to 8%. It was found that an increase in the speed of stirring produced a greater proportion of smaller microcapsules, but dissolution characteristics and drug loading remained unaffected. Results of the sieving analysis indicated that the presence of polyisobutylene resulted in a pronounced decrease in the size of the microcapsules at both core to wall ratios. On increasing the concentration of polyisobutylene, the surface of the microcapsule became smooth and compact, but the shape remained irregular. The microcapsules were composed of aggregates of individually coated particles. The time for 50% of the drug to be released at a pH of 7.5 decreased from 140 min for 0% polyisobutylene to 20 min for 6% polyisobutylene when the core to wall ratio was 2:1.

Indomethacin was encapsulated with ethylcellulose by complex emulsification. By altering the core to coat ratio, the size range of microcapsules, or by incorporating a channelling agent such as PEG 4000 the drug release rate can be controlled (Jani *et al.*, 1992).

Puglisi *et al.* (1992) prepared microspheres of tolmetin by cooling a solution of ethylcellulose containing polyisobutylene or ethylene vinyl acetate copolymer. The presence of the coacervating agent did not appreciably influence the drug content or the wall thickness, but did increase the particle size, especially when polyisobutylene was added. Coacervation with

either agent produced a smooth surface and fewer holes were observed with ethylene vinyl acetate, by both scanning electron microscopy and fluorescent microscopy. Dissolution studies were carried out at 37°C at pH 7.4 and 4 in aqueous medium and also in the presence of Tween 20. In all cases the encapsulated drug delayed the release. Gastric lesions produced by a tolmetin preparation in rabbits were reduced when the drug was encapsulated; this was attributed to a shorter contact time with the gastric mucosa. A decrease in body temperature effected by the drug and the encapsulated drug with or without a coacervating inducing agent was similar.

Hydroxypropyl methylcellulose phthalate

Morishita *et al.* (1973) encapsulated kitasamycin tartrate by emulsification and evaporation of 10% w/v solution of hydroxypropyl methylcellulose phthalate in a solution of acetone and methanol which was emulsified in paraffin oil at 5°C. The antibiotic, with a particle size of 200–500 μm, was then added with stirring and the emulsion was slowly heated to 30°C to give, after 3–4 h of evaporation, microcapsules with an enteric coat and a size of 300–700 μm.

Encina *et al.* (1992) prepared a three-component phase diagram for the system hydroxypropyl methylcellulose phthalate, light mineral oil and acetone to show the region at which phase separation and microcapsules could be formed. The addition of small quantities of the surfactant sorbitan monooleate or sorbitan trioleate increased but sorbitan monolaurate decreased the region of the phase diagram where microcapsules were formed. Increasing the concentration of the surfactant did not affect the particle size appreciably, but an increase of polymer concentration increased the size of the microcapsules at all levels of surfactant concentration.

Poly β-hydroxybutyrate hydroxyvalerate

The preparation of reservoir type microcapsules was described by Embleton and Tighe (1992). The initial w/o emulsion was prepared by adding an aqueous gelatin solution to the polymer dissolved in dichloromethane, shaking and cooling and then transferring to a large volume of polyvinyl alcohol solution. Solvent evaporation occurred with stirring for 5 h. The microcapsules were sieved, washed with water and dried. A series of nine different poly β-hydroxybutyrate hydroxyvalerate polymers, in which both the molecular weight and hydroxyvalerate content were altered, were used. Microcapsules prepared from low molecular weight homopolymers were

non-porous but shrivelied. These features disappeared as the molecular weight increased. Decreasing the molecular weight of the copolymer produced particles that were distorted and had a macroporous surface. Increasing the temperature to 40°C after phase combination usually produced a smooth, less porous particle.

Poly(lactic acid)

The rate of release of thioridazine from polylactide microcapsules, prepared by solvent evaporation from oil in water emulsions, was enhanced by the use of a base, NaOH. The rate of drug release depended upon the amount of base added to the aqueous phase of the emulsion. Using the results from scanning electron microscopy, it was suggested that the drug release could be due to modification of the internal structure of the microspheres during their preparation (Fong *et al.*, 1987).

Bodmeier and McGinity (1987c) encapsulated quinidine and quinidine sulfate with poly(DL-lactic acid) by the solvent evaporation method. The drug and the polymer were dissolved with heat in methylene chloride and this solution was then emulsified into the aqueous phase containing polysorbate 80 and at the pH of minimum drug solubility to minimize drug loss to the aqueous phase. Stirring was continuous until the organic solvent evaporated. The product was then filtered, washed with water and dried.

In a second paper dealing with quinidine and poly(DL-lactic-acid), Bodmeier and McGinity (1987b) showed that the drug loss to the aqueous phase occurred within the first 1–2 min of the emulsification step, as the pH was changed from 7 to 12 or 12 to 7. They suggested that the ability to change the pH without influence to the actual drug content within the microcapsule may permit the preparation of microcapsules at extended pH values. An increase in the volume of the aqueous phase resulted in an increase of drug content in the microcapsules. This was attributed to faster precipitation of the polymer at the droplet interface, as a result of polymer solvent diffusing into the water. An increase of temperature from 0 to 35°C during the formation of the microcapsules caused a decrease in the quinidine content of the product. This was attributed to an increase in the solubility of the drug in the aqueous phase. The higher temperature also caused an increase in the vapour pressure of the polymer solvent, leading to an increasing flow across the interface, resulting in film fracture.

In a subsequent paper, Bodmeier and McGinity (1988) reported on solvent selection for the preparation of microspheres by the evaporation method using poly(DL-lactide). The successful encapsulation of the drug within the microsphere was associated with: (a) a fast rate of precipitation

of the polymer from the organic phase; (b) a low water solubility of the drug in the aqueous phase; and (c) a high concentration of the polymer in the organic phase. It was found that the rate of polymer precipitation was strongly influenced by the rate of diffusion of the organic solvent into the water phase. Organic solvents with low water solubility resulted in a slow polymer precipitation, permitting the drug to partition fully into the aqueous phase. Water-miscible organic solvents, when added to the organic phase, improved the drug content in the microspheres. The preparation of a solubility envelope for the polymer and an envelope for microsphere formation based on three-dimensional solubility parameters was useful for the selection of suitable solvent mixtures and the interpretation of solvent, non-solvent, polymer interactions and the formation of the microspheres.

Spores and viable cells were encapsulated with poly(lactic acid) dissolved in dichloromethane. Either spores or nutrient broth containing viable cells were added to the polymer solution. Then this suspension was added to a methylcellulose solution and the mixture stirred until the solvent evaporated. After filtration the product was washed with water and air dried. The core material was also encapsulated with gelatin and acacia using the complex coacervation method. The microcapsules produced were larger using the solvent evaporation method. Both methods permitted the encapsulated material to retain some viability. The solvent evaporation method was simple and more reproducible (Pepeljnjak, 1988).

In a series of papers Jalil and Nixon (1989) investigated the preparation and properties of microcapsules using poly(L-lactic acid) or poly(DL-lactic acid). In the first paper the phenobarbitone was microencapsulated by dissolving the polymer, poly(L-lactic acid), and drug in dichloromethane and dispersing the solution in 1% aqueous gelatin solution, to give an o/w system. With subsequent evaporation, the drug was found to be poorly encapsulated and microcapsules were small. In the other method of preparation, w/o, a solution of drug and the polymer in acetonitrile dispersed in light liquid paraffin containing Span 40 was allowed to evaporate. Drug loading in this system was high and the large microcapsules had a more porous surface.

In their next paper, Jalil and Nixon (1990b) used the poly(DL-lactic acid), acetonitrile, light liquid paraffin system for preparing phenobarbitone microcapsules. With an increase in temperature for evaporation, the surface of the microcapsules became more irregular and porous owing to deposition of phenobarbitone near the surface of the microcapsules. As the polymer concentration was increased, the surface became more irregular and non-continuous owing to rapid precipitation of the polymer, and the microcapsules became larger. The encapsulation efficiency was not appreciably affected by changes in temperature of preparation and polymer con-

centration. When the initial core loading was decreased the encapsulated efficiency decreased.

Jalil and Nixon (1990c), again using poly(DL-lactic acid), found that as polymers with lower molecular weights were used the microcapsule size decreased and the rate of swelling in an aqueous environment was greater. The gross morphology, encapsulation efficiency and density were not affected by changes in the molecular weight. In subsequent papers Jalil and Nixon (1990d,e) investigated the effect of polymer molecular weight on release kinetics and storage on microcapsule characteristics.

Gentamycin sulfate was encapsulated with poly(L-lactic acid) by adding the drug to a solution of the polymer in methylene chloride (Sampath *et al.*, 1992). Coacervation was induced by adding hexane at a controlled rate. Hardening was achieved by stirring for 2 h and the product was washed with hexane and allowed to dry. After sieving, the 125–450 μm fraction was used for further studies. A volume-based size distribution indicated a mean diameter of 343 μm, and a mean diameter of 14.8 μm was obtained based on particle number. This discrepancy was explained in terms of the breakup of aggregates. Dissolution studies at pH 7.6 showed that microcapsules with higher drug loading released their contents faster, and complete release ranged from 3 days to 3 weeks. Cylindrical implants were prepared by compressing the microcapsules in a punch and die and several dissolution studies were made on these products.

Poly(lactic-co-glycolic acid)

Lewis and Tice (1984) encapsulated several steroids, namely norethisterone, norgestimate, testosterone propionate, oestradiol benzoate, progesterone and levonorgestrel, with poly(DL-lactide-co-glycolide) using a solvent evaporation method. The quality of the microcapsules was determined by scanning electron microscopy and rate of release.

Thyrotropin-releasing hormones or analogues have been encapsulated with lactic acid-glycolic acid copolymer by means of an emulsion (Heya *et al.*, 1988). The hormone was dissolved in water and this solution was added to a solution of the polymer in dichloromethane with stirring. This emulsion was cooled to 18°C and then poured into a solution of poly(vinyl alcohol) and stirred to give a water/oil/water emulsion. The internal water/oil emulsion was solidified by evaporating the solvent and then the microcapsules were collected and freeze dried. The efficiency of encapsulating the hormone was 95.9% and the product contained 7.5% of the hormone.

Poly(DL-lactic-co-glycolic acid) copolymer 50/50 has been used to

encapsulate Triptoreline, an analogue of luteinizing hormone releasing-hormone by Ruiz *et al.* (1989). Phase diagrams were prepared by dissolving the polymer in methylene chloride and then adding successive portions of silicone oil of a specific viscosity from 20 to 12 500 cs (2×10^{-5} $m^2 s^{-1}$ to $1.25 \times 10^{-2} m^2 s^{-1}$). It was observed from the phase diagram that there were four steps involved as the amount of phase inducer was increased. First, the silicone oil produced a pseudo emulsion in the organic phase, then the beginning of phase separation occurred consisting of unstable droplets, next were a stable dispersion of poly(DL-lactic-co-glycolic acid) droplets were formed (this is called the stability window) and finally at the highest concentration the silicone oil aggregation of the droplets took place leading to precipitation. It was found that increased amounts of the silicone oil were required to reach the stability window as the concentration of lactic acid in the polymer increased. No stability window could be observed in the phase diagram when silicone oil with a viscosity of 20 cs (2×10^{-5} $m^2 s^{-1}$) was used; however, as the viscosity of the oil increased to 12 500 cs ($1.25 \times 10^{-2} m^2 s^{-1}$), the area of the stability window increased. It was found that the more hydrophobic the copolymer, the more methylene chloride is a good solvent and the more silicone oil is required to desolvate the polymer. Microcapsules of the drug were prepared by suspending it in the polymer solution and silicone oil was added to effect coacervation. A non-solvent was then added to harden the product. It was found that as the volume of the phase inducer increases, the microsphere average diameter increases and the calculated specific surface decreases and consequently the core loading increases and the initial burst effect of release lowers.

In a subsequent paper Ruiz *et al.* (1990) fractionated poly(DL-lactic acid-co-glycolic acid) copolymer 50/50 by exclusion chromatography to give five different batches and determined the size exclusion chromatographic data for the fractionated polymer such as the number average and the weight average molecular weights. It was concluded that the polymer solvent affinity is mainly modified by the variation of the average molecular weight owing to differences in solubility. The lower the average molecular weight, the better methylene chloride serves as a solvent for the polymer. For microencapsulation purposes, polymers with an intermediate molecular weight of 47 250 were more suitable in terms of core loading and release purposes.

Multiphase microspheres of water-soluble drugs such as chlorpheniramine maleate, procainamide hydrochloride, and promazine hydrochloride were prepared by Iwata and McGinity (1992). The drug was dissolved in a dilute solution of gelatin and Tween 80. This was added to a solution of aluminium monostearate in soybean oil containing Span 80 and stirred to form a coarse w/o emulsion and then micronized. The

polymer poly(DL-lactic acid) or poly(DL-lactic-co-glycolic acid) was dissolved in acetonitrile. Then the w/o emulsion was poured into the polymer solution and dispersed to give a w/o 'w' emulsion. Finally, this w/o 'w' emulsion was poured through a narrow nozzle into mineral oil containing Span 80 and the mixture stirred for 24 h to evaporate the acetonitrile. The hardened microspheres were filtered using nylon screen and washed with hexane, a Tween 80 solution, then water and dried. Drug loading efficiencies of 80–100% were obtained under specific conditions. The drug loading efficiency in the microspheres depended upon the ratio of the water/oil emulsion to polymer, and the concentration of surfactant in the mineral oil. Compared with conventional microspheres in which fine particles are homogeneously dispersed in the polymer beads, the multiphase microspheres allow a higher efficiency of encapsulation of water soluble drugs and eliminate the partitioning into the polymer acetonitrile phase.

Polystyrene

Phase diagrams for the system polystyrene-benzene-butanol were prepared by Bardet *et al.* (1969). The area of coacervation was defined and the different phases characterized in terms of their composition. The process of coacervation was related to the insolubilization of the polymer as a result of the strong interaction between the solvent and the non-solvent.

The coacervation of polystryene in a solution of cyclohexane by temperature lowering was investigated by Iso *et al.* (1985b). The polydispersity of the polymers was the important factor either to define the separation temperature for the separation of droplets or to determine the equilibrium composition of the dilute and coacervate phases. Microcapsules of glass beads had a thin film of the polymer and a thick coat of talc. The low efficiency of polymer utilization was improved by using a non-solvent for the polymer. Sodium sulfate crystals were encapsulated and the dissolution was related to the Higuchi model. It was found that the effective diffusion coefficient decreased as the encapsulation temperature was lowered.

In another paper, Iso *et al.* (1985a) investigated the three-component system polystyrene, cyclohexane and hexane and encapsulated glass beads and anhydrous sodium sulfate. The control of wall thickness was easier than when cyclohexane was used alone. The wall thickness was effectively controlled by adjusting the polymer concentration, the temperature of encapsulation and the amount of hexane added. The dissolution followed the Higuchi model.

Polystyrene was used to encapsulate frusemide or frusemide–PEG 6000 solid dispersion by El Shattawy *et al.* (1991). Coacervation was achieved by

preparing a suspension of the drug in a solution of polystyrene in cyclohexane and effecting coacervation by adding the non-solvent petroleum ether. Dissolution studies *in vitro*, LD_{50} studies and oral toxicity of the polmyer were carried out in mice. The most suitable product was frusemide, PEG 6000, polystyrene with a weight ratio of 2:2:1. The dissolution of this product was slower than that of the pure drug and faster than that of the pure drug in polystyrene microcapsules. The toxicity studies showed good agreement between the increase in LD_{50} and the decrease in dissolution rate.

Polyvinyl acetate

Microcapsules of phenylpropanolamine hydrochloride were prepared by adding a suspension of the drug in a solution of polyvinyl acetate, Rodopace, or polyvinyl acetate copolymer in acetone to petroleum ether, the non-solvent (El Shattawy *et al.*, 1992). The drug was also encapsulated using pan coating and an air suspension technique with a specified polymer solution or carnauba wax or hydrogenated castor oil solution. Several different formulations were tested. In general, microcapsules prepared by the coacervation phase separation method did not show suitable prolongation of release in dissolution studies in 0.1 N HCL compared with the other procedures. This was attributed to the porous coat leading to rapid leaching of the drug. Marked prolongation of dissolution was observed with the pan coating technique. This was attributed to the numerous thin coats that were applied and the large size of the microcapsules. It was found that the LD_{50} increased from $750\,mg\,kg^{-1}$ for pure drug, to $1200\,mg\,kg^{-1}$ for microcapsules prepared by air suspension, to $1500\,mg\,kg^{-1}$ for microcapsules prepared by pan coating. The comparison of *in vitro* to the *in vivo* studies showed close agreement between the increase in lethal dose and the decrease in dissolution rate.

Polyvinyl chloride

Polyvinyl chloride microcapsules containing sulfamethoxazole were prepared by dispersing the polymer in *n*-hexane, effecting dissolution with chloroform and then subsequent coacervation with the non-solvent *n*-hexane. After cooling for a period of time at 5°C, the microcapsules were washed with cold non-solvent and dried. A three-component phase diagram was prepared to indicate the region of coacervation. Several parameters were investigated and it was shown that as the stirring speed increased, the sieve size of the microcapsules also increased. An analysis of the dissolution

profile suggests that the drug release is controlled by diffusion, coupled with a dissolution process. Prolonged drug release was obtained over a period of 8 h (Das and Palchowdhury, 1989).

Pyridine polymers and copolymers

Several polymers, homopolymers of 4-vinyl pyridine, 2-vinyl-5-ethyl pyridine; copolymers of 4-vinyl pyridine with styrene, methyl acrylate and acrylonitrile; and 2-vinyl-5-ethyl pyridine with vinyl acetate, methyl acrylate and acrylonitrile were used to formulate chloroquinine phosphate for its taste abatement (Gupta and Agarwal, 1983). The drug was dispersed in a solution of the polymer in methanol. Then the non-solvent, ether, was added at a controlled rate. After cooling to harden the product, it was filtered and dried. Several products had satisfactory release in gastric fluid and at pH 7. Only four products, each with a different polymer, were formulated as dry suspensions. Aging tests were also carried out and dissolution characteristics were not affected by storing at 45°C for 2 months.

Rosin

Sheorey and Dorle (1990) described a method for encapsulating sulfadiazine with rosin using benzene as the solvent and this was emulsified with stirring into an aqueous bentonite suspension. After evaporation, the microcapsules were filtered, washed and dried. It was found that as the core to coat ratio increased from 1:1 to 4:1 , the drug in the microencapsulated product increased from 50 to 91% and the mean diameter decreased from 924 μm to 238 μm and the time for 50% of the drug to dissolve decreased from more than 180 min to 80 min in gastric fluid pH 1.2 and 50 min in intestinal fluid pH 7.6. It was found that bentonite, rather than ionic and non-ionic emulsifiers and other protective colloids such as gelatin or acacia, minimizes aggregration of microcapsules.

Sheorey and Dorle (1991a) again used the solvent evaporation method to encapsulate sulfadiazine with rosin. Ten different organic solvents with different rates of evaporation were used to dissolve the rosin, for example ether (fast), chloroform (medium) and petroleum ether (slow). Solvents with fast relative evaporation rates gave large microcapsules and lower drug content, and an increase in wall thickness and surfaces with many pores and fissures compared with solvents with slow relative evaporation rates. The authors suggest that quick evaporation of the polymer solvent causes rapid agglomeration of the visco-elastic polymer droplets and subsequent drying and rigidization occurs rapidly before a uniform coating of the drug

occurs; this leaves a loosely deposited wall structure. Dissolution studies showed that while ether produced thick-walled microcapsules, the rate of release was rapid because of the surface characteristics. The influence of solid dispersing agents on the formation of rosin microcapsules was also investigated by Sheorey and Dorle (1991b).

Shellac

Sheorey *et al.* (1991) encapsulated sulfadiazine with shellac, using solvent evaporation. The drug was dispersed in a solution of shellac dissolved in isobutanol which has a higher boiling point than water. This suspension was then added slowly in a thin stream into a freshly prepared aqueous bentonite solution at 70°C. Phase separation occurred and the drug was coated upon evaporation of the solvent. The microcapsules were filtered, washed with water and dried. While a dry product could be obtained without the use of bentonite, the use of this agent promoted the formation of spherical microcapsules, whereas in its absence dry flakes and needles were obtained. No coalescence or aggregation occurred during the process and only a negligible amount of bentonite was incorporated into the microcapsules. Dissolution in water at pH 1.2 showed that as the core content increased, the microcapsules decreased in size and the rate of dissolution increased. This suggests a decrease in the wall thickness. At higher bentonite concentrations smaller microcapsules with a narrower size distribution were obtained; this was attributed to an increase in viscosity of the dispersion medium which reduced the aggregation of the globules. An increase in the rate of stirring from 1000 to 4500 r.p.m. reduced the mean diameter from 265 μm to 235 μm.

Various polymers

Three polymers have been used to encapsulate a hydrophobic drug (Seiyaku, 1980). For example, polystyrene was dissolved in an organic solvent which was immiscible with water. A hydrophobic drug was then incorporated into the solution and then this core material was dissolved in an enteric high-polymer electrolyte; for example, methylacrylate. Coacervation was then carried out with a solution of gelatin at an appropriate pH and cooling. Thus the drug is surrounded by the high-polymer and a coacervate wall film of gelatin and the polymer electrolyte.

Mathiowitz *et al.* (1988) prepared polyanhydrides of the following diacids: sebacic, bis (*p*-carboxy phenoxy) propane and dodecanedioic acid. The polymers were characterized by infrared spectroscopy, X-ray diffrac-

tion, viscosity, differential scanning calorimetry and scanning electron microscopy. Microspheres were prepared by dissolving the polymer in methylene chloride, adding the core and then the mixture was dropped into silicone oil containing Span 85 and varying amounts of methylene chloride, depending on the polymer. After stirring for 1 h, petroleum ether was added, and after further stirring the microcapsules were isolated. Several modifications of the above procedure were tested. In general, the surface of the microspheres was smooth with no pores. The porosity of the microcapsules depended upon the polymer and the proportions of the polymer used to prepare the microspheres. It was proposed that the process used with low molecular weight polymers took place slowly, resulting in relatively non-porous microspheres, whereas the process used for high molecular weight polymers was rapid and resulted in spheres with significant internal porosity. Drug release was affected by polymer composition, physical properties of the microspheres and the type of drug. Microspheres loaded with insulin showed good urine and serum glucose control in diabetic rats.

Bodmeier and Chen (1989) encapsulated three anti-inflammatory agents, namely indomethacin, ibuprofen and ketoprofen, by solvent evaporation using various polymers: ethylcellulose, poly(ϵ-caprolactone), poly(methyl methacrylate), polystyrene and Eudragit RS and RL. The polymer and drug were codissolved in a water-immiscible organic solvent. This solution was then poured into the aqueous phase containing a low concentration of poly (vinyl alcohol). The resulting o/w emulsion was then agitated for 90 min at room temperature. The microspheres were filtered, washed with water and dried. The encapsulation efficiency into ethylcellulose was highest for indomethacin followed by ibuprofen and ketoprofen. This order was inversely correlated to the aqueous solubility. All drugs were encapsulated because of their low water solubility and the efficiency of encapsulation was improved by increasing the drug loading and the polymer:organic solvent ratio. The drug release in aqueous solution at pH 7.4, 37°C under sink conditions was governed by microsphere size, drug loading and polymer composition. The release of indomethacin from ethylcellulose microcapsules was too slow and could be increased by using more permeable polymers or polymers blends. The rates of polymer and drug precipitation during microsphere formation depended upon the organic solvent selected. When chloroform was used as the solvent, the drug precipitated before the polymer and indomethacin crystals were observed on the microsphere surface. With methylene chloride, the polymer precipitated before the drug and no drug crystals were seen.

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