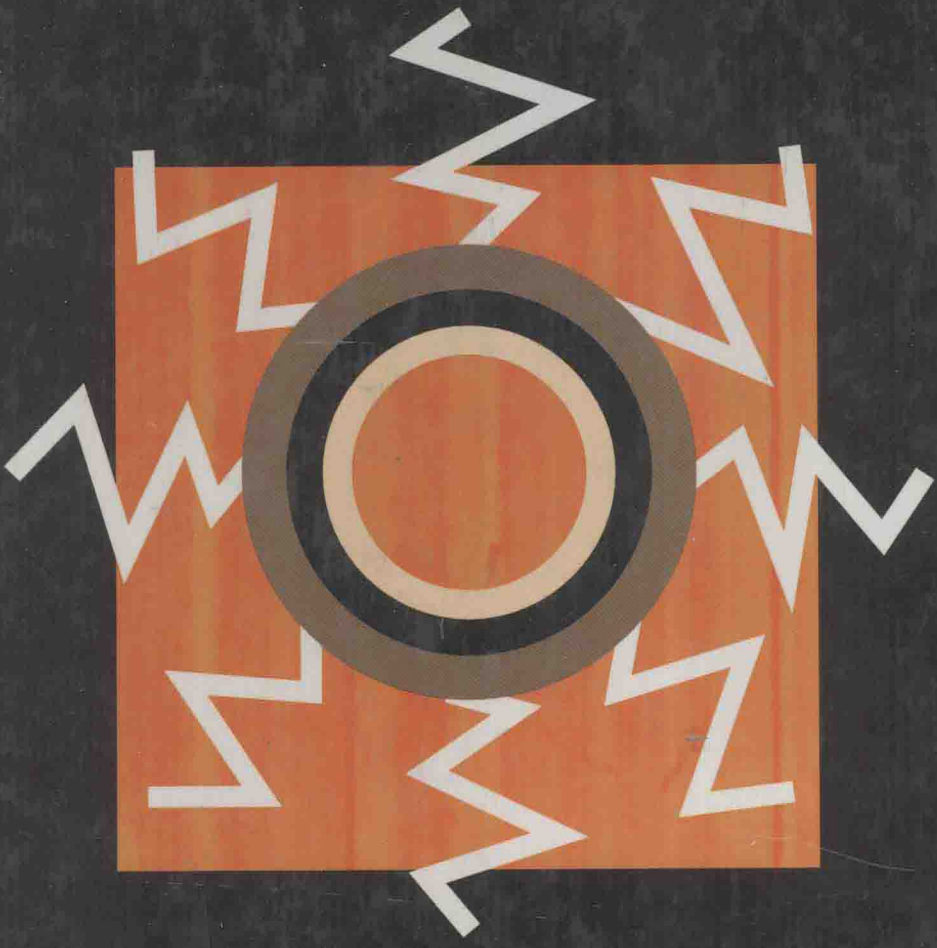
ENCAPSULATION AND CONTROLLED RELEASE



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Encapsulation and Controlled Release

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Introduction

This symposium, jointly organised by the Royal Society of Chemistry's N.W. Industrial Division and the Water Soluble Polymers Sector Group of BACS, attempts to focus on the rapidly developing field of encapsulation and controlled release and to present the reader with a snapshot of some of the more recent technological breakthroughs. This fascinating subject requires a multi-disciplinary approach in order to marry the physico-chemical nature of the encapsulating medium with the end-use and desired properties of the materials to be 'released'. Hence it is a topic which is of particular interest to those working in the field of water-soluble or dispersible polymers, as well as application chemists and biochemists in the various areas of use.

Undoubtedly, the area of encapsulation and controlled release is most developed in the area of drug delivery systems and this is reflected in many of the papers presented which relate to several aspects of this application. However, many other uses exist in the industrial sector and papers covering such diverse end-uses as enzyme encapsulation, controlled release of flavours and fragrances, and the use of these techniques in agrochemical applications are included.

There is much proprietary information in this rapidly developing field and it has proved difficult to find speakers willing to present papers in some of the more commercially sensitive areas. For example, the topic of solvent encapsulation in carbonless copy paper is one where the technology is vested in a limited number of producers who are reluctant to present their latest findings publicly. Readers are directed to the patent literature in such cases. Nevertheless, the editors hope that they have managed to provide a reasonably balanced insight into this complex and chemically challenging area of technology.

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Industrial Microencapsulation: Polymers for Microcapsule Walls

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INTRODUCTION

This is an introduction to the production and use of microcapsules intended for industrial (non-pharmaceutical, non-food) applications. It offers guidance to investigators faced with a particular chemical system and the need to obtain improved control of manufacture, bulk properties, and possible applications.

Microcapsule walls can be made from both natural and synthetic polymers, in a wide range of diameters. They are, in effect, the walls of minute containers, normally spherical if containing a liquid, and roughly the shape of the particle if containing a solid. They can have a wide range of sizes and wall thicknesses. A major proportion of the published scientific and technical literature on microencapsulation relates to pharmaceutical and food applications but is often relevant to the design of other microencapsulation processes[1]. The successful employment of these processes requires some familiarity with several scientific disciplines, including physical and colloid chemistry, polymer chemistry and physics, suspension, coating and drying technology, and, often, aspects of pharmaceutical and paper-coating technology. Not least, the application of some commonsense and an element of luck can be helpful.

Proper conceptual analysis of such systems requires examination of the constraints of the system. Consideration of these constraints, collectively, presents a form of 'decision tree', by which many impossible, unlikely (or uneconomic) approaches can be rejected, and more promising directions of investigation can be indicated. Such an analysis depends, to an extent, on proposing simple (but

sometimes searching) questions, and assessing the value of the response in relation to the known information of more-or-less related systems, sometimes from apparently distant technologies. A partial description of this approach has already been published[1], and this account extends the basic principles to a wider range of circumstances.

REASONS FOR MICROENCAPSULATION

The basic questions to be considered are:

- Why microencapsulate the product ?
- Is microencapsulation possible for the product ?
- Is the technique suitable for the product ?
- What solvent(s) are necessary components of the core (for liquid cores only) ?
- In what solvent environment is the capsule to be stored or is intended to operate ?

On this basis:

- What capsule wall should be considered ?
- What microencapsulation process should be tried ?
- What should be looked for in assessing the economics of microencapsulation ?

In assessing the answers to these questions, the major reasons for the use of microencapsulation should be noted: these include:

- Production of a novel product - the novelty may be actual, or perceived (in the latter case, the development may be market-driven);
- Protection of the product from the surrounding environment, so improving the storage life and the stability of the system;
- Protection of the environment from the product (where the active core material is hazardous or toxic);
- Control of the rate of release of the core material - either by 'catastrophic failure' by rupture of the polymer wall (e.g., by impact) for timed release, or by long-acting ('sustained') release (e.g., by solution or diffusion);
- Masking of the undesired properties of the active component - e.g., 'odour or taste masking', or masking the chemical properties (e.g. pH or catalytic activity);
- Separation of components - allowing control of the incompatibility of components;

- Formation of solid systems - conversion of liquid components to free-flowing powders;
- Targeting of the site of release of active material (notably for pharmaceutically active materials).

Most, if not all, of the actual or perceived applications of microcapsules can be classified within these categories: apart from pharmaceutical and food applications, these include (in no particular order of importance):

- Coating of carbonless copying paper, adhesives, fire retardants, speciality fertilizers, animal feedstuffs, pesticides, and liquid crystals;
- Washing powders, perfumes and fragrances, cosmetics.

PRODUCTION OF MICROCAPSULES

Many different techniques have been proposed for the production of microcapsules[3,4,5,6,7]: one source suggests that more than 200 methods can be identified in the patent literature. In general, these methods can be classified (several methods appear in more than one category):

From liquid suspending media:

- Separation from aqueous solution (including coacervation);
- Formation by polymer-polymer incompatibility;
- Interfacial polymerization;
- Polymerization *in situ*;
- Drying from the liquid state;
- Solvent evaporation from emulsion;
- Gelation in the liquid state, by cooling;
- Desolvation;

From vapour suspending media:

- Spray drying and congealing;
- Fluidised bed processes (including Würster process);
- Vacuum coating;
- Electrostatic deposition;

From monomeric starting materials:

- Addition polymerization, by
  - suspension;
  - emulsion;
  - dispersion.
- Condensation polymerization, by
  - suspension;
  - dispersion;
  - interfacial precipitation.

From polymeric starting materials:

- Solidification from the liquid state, by cooling;
- Drying from the liquid state;
- Coacervation with phase separation;
- Polymer precipitation;
- Polymer gelation;
- Polymer melt solidification;

The properties of the microcapsules formed are governed by:

- The nature of the wall polymer
- The method of formation;
- The microcapsule wall thickness;
- The microcapsule shape;
- The average size, and the dispersity;
- The 'integrity' of the microcapsules (the 'integrity' is the degree of perfection of the microcapsules - notably, the freedom from faulty microcapsules, in shape, 'pinholes' and other wall defects, and other failures to enclose the active core components).

Phase separation

In phase separation, the core contents, in solvent, are first suspended in a solution of the wall material[2]. The wall polymer is induced to separate as a viscous liquid phase by adding a non-solvent, by lowering the temperature, or by adding a second polymer (or by a combination of these methods). This process is known as coacervation. It is recognized by the appearance of turbidity, droplet formation, or separation of liquid layers. Coacervation may be simple or complex, or may take place as a result of 'salting out'.

Simple coacervation occurs when a water-miscible non-solvent (e.g. ethanol) is added to an aqueous polymer solution, causing formation of a separate polymer-rich phase. A typical example of a simple coacervation system is water, gelatin, and water: this, however, is difficult to control, so is little used in practice.

Complex coacervation occurs with the mutual neutralization of two oppositely charged colloids in aqueous solution. One of the most widely used methods of microencapsulation by this process is the use of a solution of positively charged gelatin (pH < 8), which forms a complex coacervate with negatively charged gum arabic. Other polymer systems may be employed, and other electrolytes may be used with gelatin[3]. Complex coacervation is closely related to the precipitation of colloidal material from solution: it immediately precedes precipitation. The process was originally developed in the 1950's for the coating used in the manufacture of 'no carbon required' carbonless copying paper, using the protein gelatin and the carbohydrate gum arabic as the two colloids.

In salt coacervation a polymer is separated from an aqueous solution, due to 'salting out', typically by adding an electrolyte to an aqueous polymer solution. The method may be used to encapsulate water-insoluble oils or dispersed solid particles, but it is difficult to control the microcapsule size, and the agglomeration of particles. The system may be stabilized by altering the pH or temperature.

Interfacial and in situ polymerization

These methods depend on the polymerization of two different monomers by condensation polymerization or the reaction of two different polymer pre-condensates under conditions of controlled turbulence.

Interfacial polymerization for the production of microcapsules involves chemical reaction, typically between a diacyl chloride and an amine or an alcohol. The resulting polymer film may be a polyester, polyurea, polyurethane, or polycarbonate. The method is useful for the microencapsulation of pesticides and pheromones.

In situ polymerization is used to prepare capsules for carbonless copying paper, mainly by reaction of urea-formaldehyde or melamine-formaldehyde resin condensates with acrylamide-acrylic acid copolymers.

Spray drying

There are many mechanical variations in spray drying arrangements: most of these have been developed for the production of pharmaceutical and food products.

In spray drying processes, an aqueous solution of the core material and solution of the film-forming wall material is atomized into hot air. The water then evaporates, and the dried solid is separated, usually by air separation. Several process variables are important in obtaining satisfactory microcapsules: these include the core:wall material ratio, and the concentration, viscosity and temperature of the starting solution. Many variations on the spray drying process (including spray chilling) have been employed, to encapsulate flavours, fragrance oils, citric acid, potassium chloride, iron (Fe^{++}) sulphate, and vitamin C.

Other processes

Most other processes involve mechanical extrusion of particle mixtures into a vapour stream, as in centrifugal extrusion, or air suspension in a controlled air stream, as in the Würster process. The latter method is relatively large scale, and is most economically used for larger runs of relatively low value products. Pan coating, in which particles are tumbled in a rotating pan, and a suitable coating material is added slowly with a controlled temperature profile, is principally employed for the coating of pharmaceutical products. The process is relatively expensive, but is flexible within suitable limits. It is not suitable for liquid cores.

CAPSULE WALL POLYMERS

Most applications for microencapsulated active compounds require an indefinite storage life, followed by release of the core under specified conditions. The performance of microcapsules, in both storage life and in rate of core release, depends significantly on the permeability of the polymer used in the capsule wall.

Natural, semi-synthetic, and synthetic polymers with film-forming properties are all used as wall polymers for microcapsules. In many cases, polymer mixtures are used. Those employed for pharmaceutical and food applications are chosen from polymers accepted for edible uses. Those employed in certain pharmaceutical applications may also be selected from polymers with physiologically-acceptable biodegradability - examples are polymers and co-polymers based on polylactic acid, which degrade to lactic acid, which is a normal component of body fluids.

Detailed accounts of suitable polymers for microcapsule walls, with discussion of their relevant properties have been published elsewhere [2 - 5,7]. A summary of the many polymer types suggested includes:

- Natural polymers:

  Proteins:
  Gelatin, Albumin, Casein
  Carbohydrates:
  Gum arabic (gum acacia), Agar, Alginates, Carrageenan, Starches, Xanthan and other microbial gums
  Waxes:
  Beeswax, shellac

- Semi-synthetic polymers:

  Cellulose esters and ethers:
  Methyl cellulose, Ethyl cellulose, Cellulose acetate, Cellulose acetate butyrate, Sodium carboxymethyl cellulose Cellulose nitrate
  Fatty acid derivatives
  Glyceryl mono-, di-, or tri-stearate, Stearic acid, Aluminium monostearate, Glyceryl mono-, and di-palmitate
  Fatty alcohol derivatives
  Hydrogenated tallow, 12-Hydroxystearyl alcohol, Hydrogenated castor oil, Cetyl alcohol, Myristyl alcohol (1-tetradecanol)

- Synthetic polymers:

  Vinyl polymers and copolymers
  : Polyvinyl alcohol, Polyacrylamide and copolymers, Ethylene-vinyl acetate copolymers, Polymethyl methacrylate Polyvinyl pyrrolidone, Polystyrene, Styrene-acrylonitrile copolymers, Polyvinylidiene chloride, Vinyl ether copolymers, Carboxyvinyl polymers ('Carbopol')

  Polyamides and polyesters
  : Nylon 6 - 10, Polylysine and copolymers, Polyglutamic acid and copolymers, Polylactic acid and copolymers, 'Hydrogel' polymers (polyhydroxyethyl methacrylate and copolymers), Polyglycolic acid

  Polymers prepared by interfacial polymerization
  : Polyurethanes
  : Polyureas

  Others
  : Amino-resins (urea-formaldehyde, melamine--formaldehyde, other amino-plasts), Alkyd resins, Epoxy-resins, 'Polyester' resins, Polydimethylsiloxane, Polycarbonates

  Waxes and resins
  : Paraffin wax, Hydrocarbon wax

The permeability of the capsule wall is affected by the nature of the polymer from which it is produced. Many different polymer types are employed. The principal factors are:

Polymer parameter	Effect on permeability
Density increase	Reduces
Crystallinity increase	Reduces
Orientation increase	Reduces
Increased degree of cross-linking	Reduces
Increased plasticizer level	Increases
Increased filler level	Possible increase
Use of 'good' solvents	Decreases

The permeability of the capsule wall is also affected significantly by the 'geometry' of the system. The principal factors are:

Capsule parameter	Effect on permeability
Larger size	Reduces
Wall thickness increase	Reduces
Spherical shape - higher proportion	Reduces
Post treatment (hardening, spray coating, etc.)	Reduces
Multiple wall formation	Reduces
Size dispersion variation	Varies with microcapsule

PRODUCTION FACTORS AFFECTING MICROCAPSULE SIZE

The successful production of microcapsules is greatly affected by the method of production. It is difficult to generalise on the relative importance of individual aspects, but the following factors have been shown to be significant:

- Configuration of the manufacturing vessel and stirrer;
- Rate of stirring;
- Tip-speed of stirrer;
- Solids content of organic phase;
- Viscosity of organic phase;
- Viscosity of aqueous phase (if any);
- Surfactant type and concentration (if any);
- Quantity of organic phase;
- Quantity of aqueous phase (if any);
- Organic/aqueous phase ratio;
- Temperature profile during production;
- Profile of pH during production (with some processes).

PRODUCTION FACTORS AFFECTING CAPSULE 'QUALITY'

The meaning of the term 'quality' of microcapsules is subjective, since the aim of a microencapsulation system is to cause the release of an active component under conditions specified for a particular requirement. These conditions can vary widely, so no universal definition of performance is possible. Each or all of the following factors may affect such performance:

- Choice of solvent;
- Choice of solvent mixture;
- Aqueous solubility of active component;
- Rate of solvent removal;
- Type of wall polymer;
- Molecular mass of wall polymer;
- Crystallinity of wall polymer;
- Post-treatment of wall polymer (cross-linking, etc.);
- Plasticizer level of wall polymer.

MICROCAPSULE SIZE IN RELATION TO PRODUCTION METHOD

There is no general relationship between the size of microcapsules and their method of production. However, a very approximate indication of the particle size range by different methods can be indicated:

Production method	Particle size range (μm)
1. For solid or liquid cores	
Coacervation (phase separation)	2 - 1,200
Interfacial polycondensation	2 - 2,000
Spray drying and congealing	6 - 600
Centrifugal extrusion	1 - 1,500
Electrostatic deposition	1 - 50
2. For solid cores	
Pan coating	500 - 5,000
Air suspension	50 - 1,500

ECONOMIC CONSIDERATIONS

The principal factors involved in the economics of microencapsulation processes, apart from the cost of the active component(s), are:

- Cost of wall polymer materials;
- The size of the microcapsule 'payload';
- The length of the production run.
- The solvent loss during manufacture, in relation to the cost of solvent.

The production cost of microcapsules is sensitive to each of these factors: of them, the cost of the wall polymer is, in most cases, relatively small compared with the cost of the core materials (this is especially true for high value active components, such as pharmaceuticals and pesticides). Since microencapsulation is relatively labour intensive, short production runs may be disproportionately costly: this can make 'pilot scale' trial costs atypical of the manufacturing costs of a long production run.

The size of the 'capsule payload' is significant. This depends on the core/wall ratio, which may be measured by weight or volume, and, hence, by value. Typically, a 90 % 'payload' has a production cost only about 60 % of that of a 70 % 'payload', so core active component/solvent ratios should be calculated. However, such calculations must also take account of the amount of active material actually delivered to the point of use. Details of all these factors should be established as far as possible when designing a particular microencapsulation system.

In general technical and economic terms, a microcapsule wall polymer should have:

- Good mechanical strength, to allow
- Minimum wall thickness, and, hence,
- Maximum capsule size, and, therefore,
- Maximum payload

The greater the payload, the lower will be the relative production cost, for equal amounts of active component. For the most economic solution, it is desirable to produce the largest microcapsule consistent with the performance required from the system.