Microencapsulation

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Motivation to Microencapsulate

Microencapsulation of a substance can change the apparent physical properties (color, shape, weight, volume, solubility, reactivity, durability, pressure sensitivity, heat sensitivity, photosensitivity).

Microencapsulation of liquids can yield an apparently solid, dry powder. Solid handling characteristics are obtained, but the internal liquid phase retains its reactivity (important for leuco-dyes used in pressure sensitive copy paper and for photochromic chemicals used for cross-linking polymers). Papers coated with such capsules, after drying, feel dry.

Handling characteristics are improved and chemical reactions are controlled (to take place at a particular time, such as when the capsule is ruptured).

Changes in weight or volume can be made. A dense compound may be converted to a form that floats by microencapsulating with entrained air.

Variations in thickness and composition of microcapsule walls yield variations in controlled release profiles. Sudden and total release may be obtained by mechanical means (crushing, deformation, melting, chemical reactions). Gradual release in pharmaceuticals and agriculture is controlled by diffusion rate and dissolution rate control.
Motivation to Microencapsulate

Most microcapsule walls are only a few microns thick, and these capsule walls are in reality semipermeable membranes. Controlled release is often diffusion controlled (through such semipermeable membranes).

Protection of a substance from the effects of moisture, oxygen, ultraviolet light, chemical reaction, etc. can be achieved by microencapsulation. A desired chemical reaction can be staged by incorporating one reactant, in a microencapsulated form, in another reactant. Disruption of the capsule wall leads to the desired chemical reaction. Examples include dispersing oxidants in microcapsules within a fuel to yield an apparently one-component propellant, a mixture of rubber with microencapsulated solvent to produce a pressure sensitive adhesive tape, and an apparently “one-part” epoxy resin wherein the catalyst is dispersed in a microencapsulated state within the monomeric resin.

Rheological advantages can be obtained by dispersing liquids in microcapsules rather than in emulsions, because microcapsules typically interact less with each other than softer emulsion droplets, and this yields lower viscosities.

Unwanted leakage can lead to many different kinds of problems.
## Applications

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<tr>
<th>Industry</th>
<th>Products</th>
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</thead>
<tbody>
<tr>
<td>Agriculture</td>
<td>Seeds, Fertilizers, Pesticides</td>
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<tr>
<td>Foods</td>
<td>Flavors, Vitamins, Minerals</td>
</tr>
<tr>
<td>Cosmetics</td>
<td>Anti-perspirants, Perfumes, Advertising materials</td>
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<tr>
<td>Pharmaceuticals</td>
<td>Detoxicants, Drugs, Minerals, Cold Remedies</td>
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<tr>
<td>Adhesives</td>
<td>Bolt and Nut Adhesives</td>
</tr>
<tr>
<td>Imaging</td>
<td>Carbonless Copy, Paper, AgX Heat Developable, Silverless Color</td>
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Morphologies

<table>
<thead>
<tr>
<th>Liquid-Core Mononuclear</th>
<th>Solid-Core Mononuclear</th>
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<tr>
<td>Liquid-Core Dual-Wall Mononuclear</td>
<td>Solid-Core Dual-Wall Polynuclear</td>
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<table>
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<tr>
<th>Liquid-Core Polynuclear</th>
<th>Dual Capsule</th>
<th>Microspunge</th>
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<tbody>
<tr>
<td>Mononuclear Core with Solid Particles in a Liquid</td>
<td>Microbead or Prill Containing Dispersion of Liquid or Solid</td>
<td>Oil-in-Water Emulsion</td>
</tr>
</tbody>
</table>
Polymeric Coating of Particles

Polymeric shells can be produced by two basic methods:

(1) Adsorption of polymers onto particle surfaces

(see coacervation and phase separation)

(2) Adsorption of monomers onto particle surfaces, followed by polymerization.

Monomer binding to particle surfaces can be enhanced by:

binding a suitable preformed polymer

binding a reactive coupling agent

coating with an inorganic particle that has a greater affinity for the monomer

Radical (addition) polymerization, condensation, and oxidative polymerization have successfully been used to coat polymeric films on particles.
Coacervation/Phase Separation

The capsule wall is formed from a water-soluble polymer. A condensed phase (coacervate) is formed when the polymer separates from the aqueous solution.

Such coacervation/phase separation can be driven four ways:

1. Oppositely charged polymers interact and form a “polymer salt”.

2. A nonelectrolyte additive, such as alcohol, decreases the polymer solubility so that it condenses at the interface in a polymer-rich phase.

3. The polymer is “salted out” by addition of salt. It condenses in a polymer-rich phase at the interface.

4. The solubility of the polymer is decreased by modifying the pH. The polymer condenses in a polymer-rich phase at the interface.
Coacervation/Phase Separation

Gelatin - desolvated with ethanol or sodium sulfate

Human serum albumin - desolvated with ammonium sulfate

Alkaline casein - desolvated with HCl or sodium sulfate

Ethylcellulose - 1% solution in carbon tetrachloride can be desolvated with cyclohexane.

Coacervation/Phase Separation

- Toluene
- 11% gelatin in H₂O at 40°C

Emulsification

- 11% gum arabic in H₂O at 40°C

Mixing

- H₂O at 40°C
- Dilute acetic acid pH ~4.4

Coacervation occurs; embryo capsules form

Cooling (5°C)

- Glutaraldehyde or formaldehyde

Cross-linked microcapsules
Coacervation/Phase Separation
Two-Sheet Carbonless Copy

Gelatin-gum arabic microencapsulated leuco dye solution coated on back face of paper. Acid (attapulgite) clay coated in starch or copolymer latex binder on front face of second sheet. Writing or impact pressure causes leakage of leuco dye solution into contacting acid clay layer, wherein leuco dye oxidizes to form image dye.

U.S. Patents 2,711,375, 2,730,456, & 2,800,457 (1954-1957)

Encapsulation by Polymer Adsorption

Polylactic Acid Encapsulation

*The preformed polymer is dissolved together with the substance (active agent) to be encapsulated in a solvent mixture such as benzyl benzoate, phospholipids, and acetone. This solution is injected through a capillary into an aqueous phase containing additional stabilizers. Particles in the 200-400 nm size range are obtained. Polymer diffuses to and adsorbs to the oil-water interface.*
Encapsulation by Heat Denaturation of Albumin

Albumin (200 - 500 mg/ml) and the active agent (drug, nanoparticle) are suspended or dissolved in water and emulsified in an oil (40-80 parts oil per part aqueous phase). This emulsion is then added rapidly, dropwise, into preheated (100-180 °C) oil and held at temperature for 10 min. This heat treatment denatures the albumin, and the albumin segregates to the oil-water interface, forming a shell. After cooling the particles are removed by centrifugation and washed with either to remove adsorbed oil. Particle sizes in the range of 400-800 nm are obtained.


Interfacial Polymerization Around Emulsions

Polyfunctional amine (Y) added to aqueous phase, diffuses to interface, reacts with (X) isocyanates or acid chlorides dissolved in oil phase.

Acid chlorides must hydrolyze slowly at solvent-water interface to allow for emulsification (sebacoyl chloride, terephthaloyl chloride, trimesoyl chloride - crosslinking).

Diisocyanates, polymeric isothiocyanates, etc..., must be soluble in solvent.

Amines such as ethylenediamine, hexamethylenediamine, triethylenetetramine added to aqueous phase; base is added to scavenge acid if acid chlorides used.
Interfacial Polymerization
(a)

Both the continuous phase and the disperse phase serve as a source of reactive species.

Polyamines (e.g., ethylenediamine, ethylene tetramine, diethylenetriamine, hexamethylenediamine, 2,4,6-triaminotoluene) in the aqueous phase combine with polybasic acid chlorides (e.g., terephthaloyl chloride, adipic acid chloride) in the oil phase to yield polyamides.

Glycol polyols (e.g., ethylene glycol) in the aqueous phase combine with polybasic acid chlorides in the oil phase to yield polyesters.

Polyamines in the aqueous phase combine with bis-haloformates (e.g., hexamethylene bis-chloroformate) in the oil phase to yield polyurethanes.

Polyamines in the aqueous phase combine with polyisocyanates (toluenediisocyanate) in the oil phase to yield polyureas.

Glycol polyols in the aqueous phase combine with polyisocyanates in the oil phase to yield polyurethanes.
Interfacial Polymerization (a)

Example: (Oil-in-water)

100 mg benzoyl leucomethylene blue and 200 mg terephthaloyl chloride (monomer X) are dissolved in 25 g chlorinated diphenyl. This solution is emulsified with 200 ml of 0.5% (w/w) aqueous sodium bicarbonate and 1 ml of Carbowax 600 (dispersing aid). The bicarbonate is used to neutralize acid produced in the interfacial polymerization.

50 ml of 10% aqueous ethylene glycol are added with stirring. A glycol polyphenol (e.g., bisphenol A) is then added to the aqueous phase, and polymerization commences to produce a polyester shell. The reaction time is only a few minutes, and the particle sizes are in the range of several \( \mu \text{m} \).
Interfacial Polymerization
(a)
Microencapsulation after Electrocapillary Emulsification

Example: (Water-in-oil)

Poly($N^\alpha,N^\varepsilon$-L-lysinediylterephthaloyl) encapsulated particles (400 nm diameter) by electrocapillary emulsification of aqueous hemolysate, L-lysine, and sodium carbonate into (at 0.042 ml/min) terephthaloyl dichloride solution in cyclohexane, chloroform, and tetraethylammonium chloride mixture. The emulsification was done using a motor driven syringe with a potential of 850 V applied between the needle (anode) and a platinum wire cathode located about 5 mm from the needle in the oil phase.

Isocyanate Polymerization

Some isocyanate groups react with water to give amines and carbon dioxide; these amines react with other isocyanates to produce polyurea; direct addition of amines not required.
Spontaneous Polymerization

*N-Alkyl cyanoacrylate emulsified in organic phase; it diffuses to emulsified interface and polymerizes spontaneously to form poly(n-alkyl cyanoacrylate).*

\[
\text{HO}^- + \text{CH}_2\text{C}^\equiv\text{CN} \rightarrow \text{HO-CH}_2\text{C}^- \rightarrow \text{HO-CH}_2\text{C-CH}_2\text{C}^- \rightarrow
\]

Polymer growth is terminated with a proton.
Cynoacrylate monomer (1 ml) and the substance to be encapsulated are dissolved in an oil (8 ml) and ethanol (100 ml). This solution is added slowly through a capillary into a well stirred aqueous solution containing 0.5% (w/w) of a nonionic dispersing aid such as a Pluronic or stabilizing phospholipids at pH 6-7. Encapsulated particles having a polycyanoacrylate wall in the 200 - 400 nm size range are formed by anionic polymerization induced by hydroxide ions in the water.

Freeze fracture TEM of polyisobutylcyanoacrylate encapsulated particles.

Urea/Formaldehyde Resins

\[ \text{H} \quad \text{H} \quad \text{H} \]
\[ \text{H} - \dot{\text{C}} = \text{O} + \text{H}_2\text{N} - \text{C} - \text{NH}_2 \rightarrow \text{HOCH}_2 - \dot{\text{N}} - \text{C} - \text{NH}_2 \]
Formaldehyde  Urea  Methylolurea

\[ \text{H} \quad \text{H} \quad \text{H} \]
\[ \text{HOCH}_2 - \dot{\text{N}} - \text{C} - \text{NH}_2 + \text{O} = \text{C} - \text{H} \rightarrow \text{HOCH}_2 - \dot{\text{N}} - \text{C} - \text{N} - \text{CH}_2\text{OH} \]

Dimethylolurea

\[ \text{H} \quad \text{H} \quad \text{H} \]
\[ \text{HOCH}_2 - \dot{\text{N}} - \text{C} - \text{N} - \text{CH}_2\text{OH} \rightarrow \text{H}_2\text{C} - \text{O} \rightarrow \text{O} \quad \text{CH}_2 \]
\[ \text{H}_2\text{C} - \text{O} \rightarrow \text{N} - \text{CH}_2 \]

\[ \text{HCHO, urea} \]

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Free Radical polymerization

Ethenic monomers and initiator dissolved in oil phase prior to emulsification; polymerization initiated by heating.
Microencapsulation Procedure

Temp. 10~20°C  15~20°C  70~80°C

Mixing → Emulsification → Microencapsulation

<table>
<thead>
<tr>
<th>Capsule wall</th>
<th>Reaction</th>
<th>Wall Property</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyurethane</td>
<td>-NH₂+Cl-C-O→N-C-O-</td>
<td>tough</td>
</tr>
<tr>
<td></td>
<td>-NCO+-OH→N-C-O-</td>
<td>strong</td>
</tr>
<tr>
<td>Polyurea</td>
<td>-NH₂+-NCO→N-C-N-</td>
<td>tough</td>
</tr>
<tr>
<td></td>
<td></td>
<td>strong</td>
</tr>
<tr>
<td>Polyester</td>
<td>-OH+COCl→-COO⁻</td>
<td>tough</td>
</tr>
<tr>
<td>Polyamide</td>
<td>-NH₂-COCl→N-C⁻</td>
<td>weak</td>
</tr>
<tr>
<td>Epoxy resin</td>
<td>-CH-CH₂-NH₂→-CH-CH₂-NH⁻</td>
<td>rigid</td>
</tr>
<tr>
<td></td>
<td>-OH⁻</td>
<td>tough</td>
</tr>
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</table>
# Wall Properties

<table>
<thead>
<tr>
<th></th>
<th>Gelatin process</th>
<th>Polyurethane process</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wall formation</td>
<td>Coacervation</td>
<td>Polyaddition,</td>
</tr>
<tr>
<td>Wall</td>
<td>Gelatin</td>
<td>Polyurethane and/or Polyurea</td>
</tr>
<tr>
<td>Wall material</td>
<td>Gelatin and Gum Arabic</td>
<td>Polyisocyanates, Polyols,</td>
</tr>
<tr>
<td>Process</td>
<td>Complicated</td>
<td>Simple</td>
</tr>
<tr>
<td>Wall property</td>
<td>Flexible</td>
<td>Generally rigid</td>
</tr>
<tr>
<td>Moisture resistant</td>
<td>Swelled by high humidity or water</td>
<td>Highly resistant</td>
</tr>
<tr>
<td>Pot-life</td>
<td>Antiseptic is needed</td>
<td>Wall is not affected</td>
</tr>
</tbody>
</table>

\[
\delta = \frac{D}{2} \left(1 - \frac{\varphi^3}{m}\right)
\]

**Diagram:**

- Left: Rupture efficiency vs. pressure for different wall thicknesses (3 μm, 6 μm, 9 μm, 12 μm), wall thickness 70 μm.
- Right: Rupture efficiency vs. pressure for different capsule sizes (8 μm, 42 μm, 83 μm, 137 μm, 154 μm), capsule size 8 μm.
Capsules for Carbonless Copy Paper

Crystal violet lactone (7.2 g) was dissolved in 262 g monoisopropylbiphenyl at 80°C and mixed with 77.3 g of a 2.9% solution of Michler’s ketone and benzophenone (1:1 ratio) in trimethylolpropane-triacrylate.

After reaching room temperature, 0.5 g of a polyisocyanate prepolymer prepared from toluene diisocyanate and trimethylolpropane (Niax SF-50, Union Carbide) was added, and this mixture was emulsified in a Waring blender with an aqueous mixture containing 93.7 g of a 21% solution of isobutylene maleic anhydride copolymer (Isobam), 187.5 g of a 10% gum arabic solution, 37.5 g of hydroxyethyl-methacrylate, and 200 g of water.

This emulsion was diluted with 550 g water and placed in a 3-liter roundbottomed flask and irradiated for 2 h with a 150 watt UV lamp.

The mononuclear capsules obtained had an average size of 12.5 μm.

D. R. Shackle et al., U.S. Patent 4,532,183 (1985)
Polyaniline Coating of Copper Oxide Particles

Copper basic carbonate particles were obtained by aging 0.01 M cupric nitrate solution also 0.4 M in urea for 1 h at 85°C. Spherical 1.6 μm diameter CuO particles were prepared by calcining copper basic carbonate particles at 400°C for 1 h.

About 10 mg of dry CuO dispersed in 2 ml ethanol and 4 ml water, to which 0.4 ml aniline is added. This dispersion is agitated in an ultrasonic bath and then stabilized by adding 2 ml of aqueous (0.8%) PVA solution. This dispersion is then diluted to 10 ml with water, sealed, and heated at 100°C for 48 h with agitation.

The form of polyaniline obtained corresponds to that of polyleucoemeraldine.

Polymer shells corresponding to about 10% by weight are obtained.

The polymerization is driven, initially, by the CuO mediated oxidation of aniline.

Huang, Partch, & Matijević, *J. Colloid Interface Sci.* 170, 275-283 (1995)