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1. Introduction

Microparticles can be classified into microparticles in the literal sense and microcapsules. With microparticles, the active ingredient is dispersed/dissolved in the carrier matrix (matrix system), while microcapsules consist of a core-shell structure where the active substance is surrounded by a membrane (reservoir system) (Fig. 1). Microparticles range in diameter from ca. 1–1000 μm , although at the upper end of this size distribution, the classification of the particles as microparticles becomes open to question. Nanoparticles are particles in the submicron range. Most gaseous, liquid, and solid materials – whether hydrophobic or hydrophilic – can be encapsulated. The wall/carrier material and also the process of microencapsulation are selected according to the physical properties of the core and the intended application. The carrier material generally consists of natural or synthetic polymers or lipids [1–3].

Microencapsulation can modify the color, shape, volume, apparent density, reactivity, durability, pressure sensitivity, heat sensitivity, and photosensitivity of the encapsulated substance. Microparticles have many useful functions, and have been employed in many different areas, frequently connected with applications in which the contents of the microcapsule need to be kept separately from or are released into the surrounding environment [4–7, 9–21, 23].

The storage life of a volatile compound can be increased markedly by microencapsulation. Microcapsules can protect a core substance from the effects of UV rays, moisture, and oxygen. Chemical reaction between two active species can be prevented by physical separation by microencapsulation. Finely divided powders can be microencapsulated to reduce agglomeration problems.

The microcapsule is able to preserve a substance in a finely divided state, and release the substance from the enclosed capsule as required. Encapsulation of a liquid effectively converts the liquid to a fine powder solid form, whilst preserving the reactivity of the interior phase. Microencapsulation therefore improves the “ease of handling” of the liquid reactants, and allows chemical reaction to commence when the microcapsule is ruptured. The density of a substance can be increased by encapsulation, and can be decreased by including air in the capsule. A dense solid can thus be converted by encapsulation into a product which will float on water.

The techniques and practice of microencapsulation cover several scientific disciplines, including colloid and physical chemistry, polymer chemistry and physics, materials science, suspension and drying technology, and, in controlled-release applications, pharmaceutical and agricultural technology. Many of these disciplines interact with each other in practical

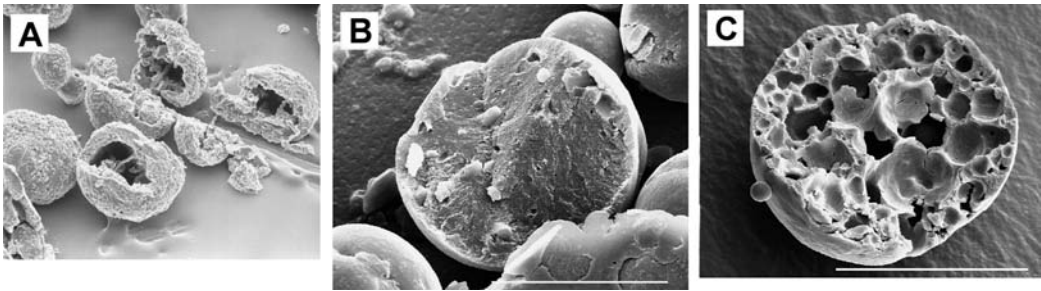


Figure 1. Internal morphology of microparticles

A) Capsule structure; B) Matrix type; C) System prepared by a multiple emulsion procedure
Reproduced in parts from [8]

applications, and in the resulting commercial implications [4–7].

Most of the possible deficiencies in microcapsules depend on the properties of the wall materials. Premature failure of the microcapsule wall in service before the required conditions for rupture are achieved can cause difficulties, which must be considered in the design of the microcapsule wall system. Many of the more recent developments in microencapsulation technology have been directed at improving the physical properties of the wall polymers in service, so that the microcapsules do not release the core contents, without rupture or leakage, until required.

The design of a microencapsulation process must take into account the total system: the active and carrier materials, the mechanism of release, and the ultimate fate of all the ingredients. Each of these parameters must be optimized if a satisfactory product is to be obtained. Many methods exist for production of microparticles which allow many variations, depending on core and wall-polymer solubility, capsule size, wall thickness and permeability, type and rate of release of core contents, and physical properties.

In choosing processes for the production of microcapsules for particular applications, several physical properties must be considered, including:

1. *Core Wettability.* The key property is the ability of the core to be wetted by the wall material. In principle, this property can be predicted, but, in practice, it is usually determined during the microencapsulation process
2. *Core Solubility.* The contents of the microcapsule core should not be soluble in the

solvent for the wall polymer, and the polymer should not dissolve significantly in the liquid core. With spray coating, a water-soluble solid can be coated with a water-soluble polymer solution, because the water evaporates rapidly during microcapsule formation

3. *Wall elasticity* is determined by the nature of the wall polymer, its thickness, and the size of the microcapsules formed
4. *Wall permeability* determines whether the microcapsule core contents can be retained indefinitely (impermeable wall) until ruptured, or may be released at a predetermined rate (permeable wall) as in controlled-release applications
5. *Wall polymer adhesive characteristics* are markedly affected by solution temperature and concentration, and depend on the physical properties of the wall polymer, notably the melting point and glass transition temperatures, degree of crystallinity, and degradation rate (under microcapsule formation conditions). Stickiness during capsule formation, and “stringiness” during spray drying can be major problems affecting microcapsule manufacture and storage behavior

2. Applications for Microencapsulation

The principal reasons for using microencapsulation are listed below.

Protection of Core Contents Against Atmospheric Effects. Vitamin A palmitate (widely

used as an animal feed additive, especially for egg-laying hens), e.g., is microencapsulated with gelatin to increase resistance to moisture and atmospheric oxygen, and therefore improve stability. Other fat-soluble vitamins or unsaturated fatty acids used as nutrition supplements are similarly treated. Microencapsulated feeds are used in industrial fish farming. These are basically high protein-fat mixtures which are microencapsulated to reduce oxidation of the product during storage, and to delay the rate of release into the aqueous environment of the fish farm. Such protection greatly increases the feeding efficiency and growth rate of the fish.

Reduction of Health Hazards. Pesticides are often encapsulated to reduce the hazard to the user. The antibiotic ampicillin has been microencapsulated to reduce the possibility of sensitization of factory staff. Encapsulation of drugs (e.g., iron(II) sulfate, acetylsalicylic acid) reduces gastrointestinal irritation by controlling the rate of release into the digestive system. Enteric polymers, for example, do not release the drug in the low pH environment of the stomach, but in the intestine. Gastric upset can therefore be avoided.

Masking of Taste and Odor. Microencapsulation can be used to disguise the unpleasant taste or odor of compounds such as pharmaceuticals. However, taste masking can also be achieved at lower cost by packaging pharmaceuticals in hard gelatin capsules, or by incorporating the unpleasant compound in sugar- or film-coated tablets.

Masking of Core Properties. The chemical properties of the microcapsule core (e.g., pH or catalytic properties) can be masked until release is required. The major application of this type is the control of the color change of leuco dyes upon pH change, which is the basis of carbonless copy paper. Besides, physicochemical properties of substances can be modified. For instance, the flow properties of mixtures of the hygroscopic B group vitamins (e.g., thiamine hydrochloride, riboflavin, and niacin) with iron phosphate are improved by microencapsulating them before they are compressed into tablets. Choice of suitable coating materials can improve the perfor-

mance (in compaction and disintegration) of tablets made from encapsulated drugs.

Separation of Incompatible Components for Functional Reasons. An example of this application is the use of microencapsulated free-radical catalysts (e.g., benzoyl peroxide) mixed with curable polyester resins, which harden in situ at the point of use.

Retention of Volatile Substances. Many flavors and fragrance compounds (e.g., methyl salicylate and peppermint oil) can be prevented from evaporating by microencapsulation.

Odor Release Control. In general, the same considerations apply as in masking. However, in addition to protection and reduction of core volatility, the principal use of microencapsulation for perfume-like materials has been in the preparation of "scratch-and-sniff" coatings which can be applied by printing techniques to advertising material. Upon rupture of the microcapsules by mechanical scratching, an odor related to the product being advertised is released.

Controlled Release. Release of the active component is controlled by the carrier material, various release profiles can be obtained. Many of the actual or potential uses of microparticles can be found within this category, usually with additional functional requirements.

Other Reasons. Other reasons for microencapsulation include the protection of the active component from physical damage and conversion of a liquid active compound into a fluidized "solid powder" form. The latter is sometimes employed with food additives, so that the active component (e.g., a flavor oil, or a bakery additive) can be evenly distributed in a dry powder mix.

In many cases overlapping applications are found. In an example taken from food industry, microencapsulation of omega-3 unsaturated fatty acids extracted from cold water fish enhances stability against oxidative degradation and allows simultaneously a significant taste masking [22].

3. Materials

Core Materials. A wide range of materials have been encapsulated. These include:

Solvents. Benzene, toluene, cyclohexane, chlorinated phenyls, paraffins, esters, ethers, alcohols, and water.

Plasticizers. Citrate-, phthalate-, adipate-, and phosphate-type, silicones, and chlorinated hydrocarbons.

Acids and Bases. Boric acid, caustic alkali, and amines.

Catalysts. Curing agents, oxidants, free radical initiators, and reducing agents.

Colorants. Pigments and dyes, especially leuco dyes for carbonless copying papers.

Adhesives. Polysulfides, cyanoacrylates, isocyanates, epoxy resins, and thermally-sensitive adhesive compositions.

Fragrances. Menthol, essences, and speciality compositions.

Foods. Oils, fats, spices, and flavors.

Pharmaceuticals. Aspirin, vitamins, antibiotics, antidepressants, and peptides/proteins.

Agricultural Chemicals. Herbicides, insecticides, and fertilizers.

Recording Materials. Reprographic toners, coupling agents, developers, silver halides, fixing agents, photochromic compounds, and liquid crystals.

Rust Inhibitors. Zinc chromate and other compounds.

Others. Detergents, bleaches, and fire retardants.

Wall Materials. Wall materials [23] may be natural, semisynthetic, or synthetic, a non-exhaustive list is given below:

Natural Materials. Gum acacia (gum arabic), agar, agarose, maltodextrins, sodium alginate, sodium pectinate, dextran, fats and fatty

acids, cetyl alcohol, milk solids, molasses, gelatin, gluten, albumin, shellac, starches, caseinates, stearins, sucrose, and waxes (e.g., beeswax, carnauba, and spermaceti).

Semisynthetic Materials. Cellulose acetate, cellulose acetate butyrate, cellulose acetate phthalate, cellulose nitrate (collodion), ethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, hydroxypropyl cellulose phthalate, methyl cellulose, sodium carboxymethyl cellulose, hydrogenated tallow, myristyl alcohol (1-tetradecanol), glyceryl mono- or dipalmitate, hydrogenated castor oil, glyceryl mono-, di-, or tristearate, and 12-hydroxystearyl alcohol.

Synthetic Materials. Acrylic polymers and copolymers (e.g., polyacrylamide, poly(alkyl cyanoacrylate), and poly(ethylene-vinyl acetate)), aluminum monostearate, carboxyvinyl polymers (Carbopol), polyamides, poly(methyl vinyl ether-maleic anhydride), poly(adipyl-L-lysine), polycarbonates, polyterephthalamide, poly(vinyl acetate phthalate), poly(terephthaloyl-L-lysine), polyarylsulfones, poly(methyl methacrylate), poly(ϵ -caprolactone), polyvinylpyrrolidone, polydimethylsiloxane, polyoxyethylenes, polyesters, polyglycolic acid, polylactic acid and copolymers, polyglutamic acid, polylysine, polystyrene, poly(styrene-acrylonitrile), polyimides, and poly(vinyl alcohol).

4. Production

Microencapsulation Methods. Many different methods have been proposed for the production of microcapsules (several hundred methods/modifications have been identified in the patent literature) with many variations in detail, depending on core and wall-polymer solubility, particle size, wall thickness and wall permeability, type and rate of release of core contents required, physical properties, and detailed and overall economics of manufacture. The choice of a particular preparation method and a suitable polymer will depend on the physicochemical properties of the goods to be entrapped, the desired application, the release characteristics of the encapsulated compound, the therapeutic goal for drug substances, the

Table 1. Microencapsulation processes

Microencapsulation process	Core material	Approximate particle size, μm
Phase separation (coacervation)	solids, liquids	2–1200
Interfacial polymerization	solids, liquids	2–2000
Spray drying and congealing	solids, liquids	6–600
Solvent evaporation	solids, liquids	1–500
Centrifugal extrusion	solids, liquids	1–5000
Air suspension	solids	35–5000

biocompatibility of the carrier material and regulatory considerations for food, cosmetics, and pharmaceutical applications. From a technological point of view, the successful selection of a preparation method will be determined by the ability to achieve high product yields, high loadings with the active substance, high encapsulation efficiencies, and the potential for easy scale-up. For example, methods with high encapsulation efficiencies but with only low active loading capacity are limited to very potent active substances.

Microencapsulation methods can be classified into the following groups (see also Table 1):

1. Phase separation (Section 4.2)
2. Interfacial and in situ polymerization (Section 4.3)
3. Spray drying, spray congealing (Section 4.4)
4. Solvent evaporation processes (Section 4.5)
5. Coating Processes (Section 4.6)
6. Spinning disk (Section 4.7)

Alternatively, encapsulation methods may be classified according to the nature of the suspending medium (liquid or vapor):

Liquid Suspending Media. If a liquid is used as a suspending medium, microencapsulation is achieved by emulsification or dispersion of two or more immiscible phases. These methods involve:

- Complex coacervation
- Polymer–polymer incompatibility
- Interfacial polymerization
- In situ polymerization
- Desolvation
- Solvent evaporation from emulsion
- Gelation

- Pressure extrusion
- Supercritical fluid technology

Vapor Suspending Media. If the vapor is the suspending medium, the microcapsules are formed by atomization of a liquid phase; methods include:

- Spray drying and congealing
- Fluidized-bed process (including Wurster process)
- Spinning disk
- Coextrusion vacuum coating
- Gelation
- Electrostatic deposition

Most microencapsulation systems employ a combination of several processes. In choosing processes for particular applications, the physical properties of the system must be considered.

Microparticle Size and Quality. Many factors affect the size and quality of microparticles. Some of these influence the performance of controlled release of drugs and active components in other applications (e.g., pesticides and aromas).

Factors affecting the size of microcapsules during production are:

- Stirring rate
- Solids content of organic phase
- Viscosity of organic phase
- Viscosity of aqueous phase
- Concentration and type of surfactant (if any)
- Configuration of vessel and stirrer
- Quantity of organic and aqueous phases
- Temperature profile during production
- Nozzle design

Factors affecting the quality of microcapsules during production are:

- Choice of solvent
- Mixtures of solvents used
- Aqueous solubility of active agent
- Rate of solvent removal
- Monomer type and concentration for polymerization
- Drying conditions
- Type and molecular mass of carrier
- Crystallinity of polymer

4.1. Phase Separation

Phase separation can be divided into aqueous or organic phase separation, depending on the solubility of the wall material. In phase separation, the core material is first suspended in a solution of the wall material. The wall polymer is induced to separate as a viscous liquid phase (not as a precipitate) by several different methods (e.g., by adding either a nonsolvent for the polymer or salts, by lowering the temperature, or by adding an incompatible polymer). This separation process is known as coacervation. Coacervation is recognized by the appearance of turbidity, droplet formation, or actual separation of liquid layers [24–26]. Coacervation may be simple or complex, or may occur as a result of a salting out effect.

Simple Coacervation. In simple coacervation, addition of a water-miscible nonsolvent (e.g., ethanol) to an aqueous polymer solution causes formation of a separate polymer-rich phase due to a partial miscibility effect. An example of the “nonionic” simple coacervation system consists of water, gelatin, and ethanol. The system is, however, difficult to control, and the core material must be insoluble in both ethanol and water.

Typical aqueous polymer solutions and the appropriate nonsolvents are:

Gelatin	ethanol, acetone
Agar	acetone
Pectin	dioxane, 2-propanol
Methyl cellulose	acetone
Poly(vinyl alcohol)	1-propanol

An example for organic phase separation is the microencapsulation of water-soluble organic compounds which can be finely dispersed in a solution of cellulose acetate butyrate [9004-36-8] (CAB) in methylene chloride. Toluene (a nonsolvent for CAB) is slowly added, causing coacervation of the polymer around the emulsified droplets of the aqueous solution of the organic compound as it separates from solution. The capsule walls can then be hardened by addition of an aliphatic hydrocarbon solvent with a low solvent power (e.g., hexane). Spherical microspheres with thin elastic walls are usually obtained.

Salt Coacervation. In salt coacervation or “ionic” coacervation, a polymer separates from an aqueous solution due to “salting out”. An electrolyte is added to the aqueous polymer solution so that phase separation occurs. This method can be used to encapsulate water-insoluble oils or dispersed solid particles. Large amounts of salt are employed, which have to be washed out of the system. Salting out has the limitation that it is difficult to control capsule size and the resulting microcapsules tend to agglomerate. The microcapsules can be stabilized by adjusting the pH or temperature. The methods can be employed with polymers such as gelatin, poly(vinyl alcohol), or anionic polymers such as sulfonated polystyrene, hydrolyzed styrene–maleic anhydride copolymer, starch, or cellulose acetate phthalates.

Complex Coacervation. Complex coacervation results from the mutual neutralization of two or more oppositely charged colloids in aqueous solution. For example, the positively charged gelatin (pH < 8) forms a complex coacervate with negatively charged gum arabic.

Complex coacervation is closely related to the precipitation of colloidal material from solution: coacervation immediately precedes precipitation. Microencapsulation by complex coacervation consists of three stages (Fig. 2):

1. Dispersion of the active component to be encapsulated into an aqueous solution of a polyelectrolyte
2. Deposition around the core material of the coacervate formed by addition of an aqueous solution of a second electrolyte of opposite charge
3. Gelation of the coacervate

This principle of phase incompatibility has also been used for production of microcapsules based on the incompatibility of different polymers. Polymer–polymer incompatibility depends on the free energy of mixing of the polymers. An example of this system is the encapsulation of coffee flavors shown in Figure 3. The components are emulsified to form microcapsules, and then stabilized by addition of a hydrocarbon oil and a dehydrating liquid.

The complex coacervation process was originally developed in the 1950s for the coating

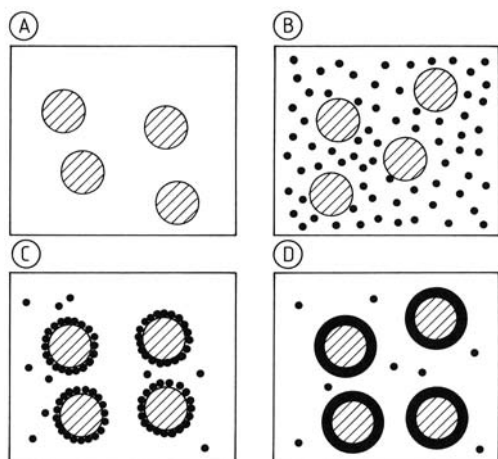


Figure 2. Microencapsulation by coacervation

A) Droplets of core material dispersed in gelatin–gum arabic solution; B) Onset of coacervation by separation of finely divided microcoacervates from the solution; C) Gradual separation of the microcoacervate on to the surface of the core material droplets; D) Coalescence of the microcoacervate into wall material of the droplets

process used in the manufacture of “no carbon required” carbonless copying paper by the NCR Company (Appleton, Wisconsin, United States) using the protein gelatin and the carbohydrate acacia gum as the electrolyte components [27].

In carbonless copying papers, the contents of the microcapsule core are released by mechanical action when the paper is struck with a typewriter key. These contents consist of a leuco dye (e.g., crystal violet lactone; → Cationic Dyes) which changes color due to the pH change occurring when it interacts with the acid clay coating of another face of the paper. In terms of volume, carbonless paper copying systems are by far the largest market for encapsulated products, although other processes, apart from gelatin microencapsulation, are now used for the production of these papers (see Section 4.3).

The dispersion of microcapsules contains an acid-sensitive leuco dye system and is coated on the underside of the top paper sheets. Impact from a writing instrument or type element ruptures the microcapsules, and releases the dye solution. The dye thus comes into contact with the acid clay coating the upper surface of the copying paper and develops its color (Fig. 4).

Coacervation is reversible, and in general, the formation of microcapsules by phase separation methods, such as coacervation, is an equilibrium

process. For gelatin–gum arabic microcapsules, the equilibrium is stabilized by cross-linking or “curing” the gelatin.

Gelatin with a high isoelectric point (pH 8, normally a pigskin-origin gelatin) and gum arabic are added to a suspension containing the active leuco dye core material at pH 4–5. The temperature is maintained above 35 °C to ensure that the coacervate is in the liquid phase. As the positively charged gelatin and the negatively charged gum arabic interact, viscous liquid microdroplets of the polymer coacervate separate. These particles are stabilized (i.e., cross-linked or cured) by reaction with formaldehyde or glutaraldehyde; reaction with CrCl_3 or CuSO_4 ; addition of alum; reaction with tannic or gallic acid or their iron salts, as activated phenolics; heat treatment or residual water extraction by solvents such as 2-propanol.

The mixture is then cooled to below 10 °C, adjusted to pH 9 and the microcapsules removed by filtration. In a variation of this process, two different gelatins, prepared by different manufacturing methods from different raw materials are used as the two polymers.

An example of a simple and reliable method for the laboratory-scale production of microcapsules by the coacervation system is outlined as follows [28]:

1. Add 10 g gelatin to 225 g water, and allow to swell for 15 min
2. Heat to 42–45 °C, and add 100 mL of internal phase (active compound in liquid form or in solution) and disperse to the desired droplet size
3. Add 10 g gum arabic in 225 g water heated to 42–45 °C
4. Adjust pH to 4.5–5.5. This will form capsules with a size of 200–700 μm . For smaller capsules (30–100 μm) add up to 700 mL water
5. Cool to 28 °C with stirring
6. Cool below 10 °C with ice
7. For hardening, add 5 mL of 25 % formaldehyde or glutaraldehyde solution. (Use of formaldehyde gives an elastic capsule wall. Use of tannic acid gives a brittle wall)
8. Wash 3–5 times to remove the free coacervate
9. Add dispersing agent (colloidal silica) and wetting agent

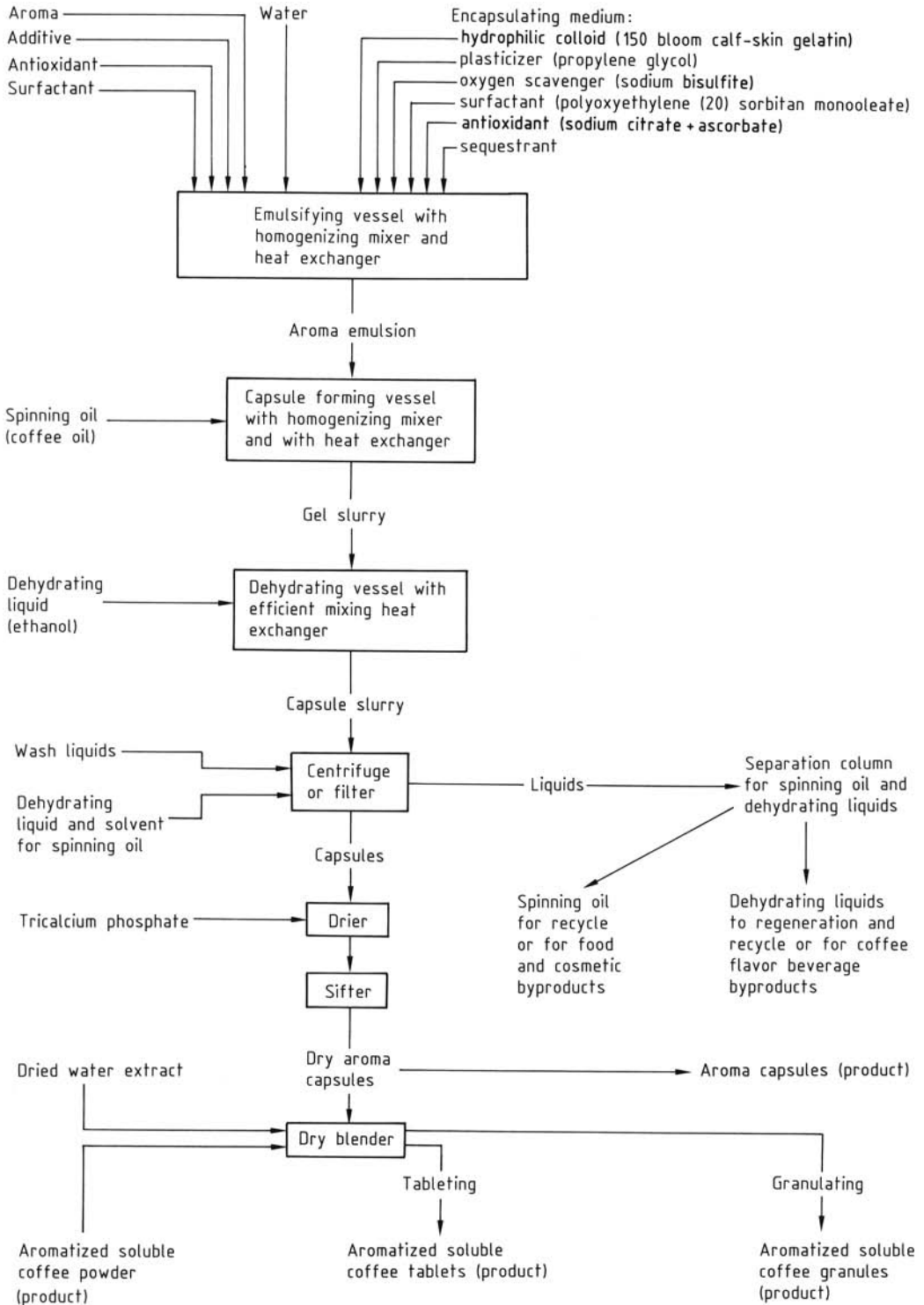


Figure 3. Flow diagram for encapsulation of coffee flavors [28]

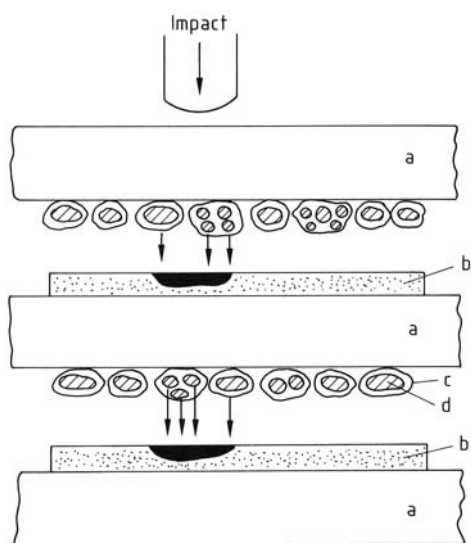


Figure 4. Three-sheet carbonless copying paper system with microcapsules

a) Paper; b) Acid clay; c) Microcapsule; d) Oil solution of leuco dye

10. Filter microcapsules

11. Dry with cool air in a fluidized bed

4.2. Interfacial and in situ Polymerization

The principal chemical reaction methods for the production of microcapsules involve *interfacial polymerization*, typically between a diacyl chloride and an amine or alcohol. The resulting polymer films may be a polyester, polyurea, polyurethane, or polycarbonate. A range of pesticides have been encapsulated by this method, in which a solution of the pesticide and a diacyl chloride is emulsified in water and an aqueous solution of amine and a polyfunctional isocyanate is added. Upon addition of a base, the microcapsules are formed at the interface between the aqueous medium and the emulsion droplets. The isocyanate acts as a cross-linking agent to reduce the permeability of the capsule walls and to increase their resistance to damage. Durable, impact-resistant microcapsules with high-tensile-strength walls have been developed for pesticide and pheromone formulations [29].

In the related process of *interfacial coacervation*, a polymer coacervate of an emulsified water-soluble natural extract is emulsified with a cold saturated solution of diethyl ether in water that contains a polyethylenesorbitan ester emulsifier (polysorbate 20); a collodion solution is then added. The capsule walls are hardened with *n*-butyl benzoate.

In a process developed by 3M, a water-insoluble core material is emulsified into an aqueous solution of a low molecular mass urea-formaldehyde (UF) resin, followed by reduction of the pH to about 1.5–3 with formic acid, causing the formation of a UF polymer shell. The microcapsules formed have a diameter of 10–50 μm , and have been used in the encapsulation of fragrances for advertising purposes [30].

Methods based on *in situ polymerization* have been employed to prepare microcapsules for carbonless copying paper systems. Condensation polymerization systems are used to form the microcapsule wall polymers that contain the color systems. The principles of carbonless copying paper are described in this Section.

The production of microcapsules for carbonless copying paper using melamine-formaldehyde (MF) and UF resins condensates as wall polymers follows [31–34]:

1. Emulsify and mix aqueous solution of MF/UF precondensates and acrylamide-acrylic acid copolymers with capsule contents (solvent + dye)
2. Add dilution water and stir for 30 min
3. Adjust pH with acetic acid to pH 4.7
4. Maintain at 55 °C for 2 h
5. Cool and stir overnight
6. Raise pH to 10.0
7. Microcapsule mixture ready for coating

The more recently developed carbonless copying paper systems using MF resins and a controlled acid developing system are described in detail in [35, 26]. The polymers used for microencapsulation of the leuco dye comprise methylated MF precondensates with acrylamide-acrylic acid copolymers in aqueous solution. Water-soluble polymers (starch or cellulose ethers) are added as viscosity controllers. The microcapsule leuco dye system is coated on the back of the top paper sheet. The acid component is coated onto the front of the lower sheet of the self-copy

system and is based on a dispersed hydrated silica coated with an aluminum salt [37].

The (acid) aluminum compound is distributed preferentially on the surface of the silica, and may be modified with other metal ions. There are further developments, especially with the introduction of improved cross-linking and encapsulating systems for the dyes.

4.3. Spray Drying, Spray Congealing

Spray drying. This manufacturing method is a very attractive and versatile microencapsulation process for a variety of reasons. Active materials with differing solubility properties can be encapsulated with various wall materials and partitioning of the active substance between two immiscible phases is avoided. In addition, when compared to other multi-step microencapsulation processes, spray drying is a continuous single step operation, which has been scaled up in other industrial applications. In the spray-drying process, a microparticle powder is formed by spraying (atomizing) a solution/dispersion of active material and the film-forming wall material as fine droplets into hot air. The water then evaporates and the dried solid is separated, usually by air separation [9] (see also → Drying of

Solid Materials, Section 2.1.5.). Several process variables can be important in achieving the desired properties, including the core: wall material ratio, and the concentration, viscosity, and temperature of the starting solution. An aqueous solution, an organic solution, or a slurry of the material to be coated may be used. This method has its limitations due to the inflammable properties of many solvents being suitable for micro-particle preparation.

The design of the spray dryer can be important (e.g., the structure of the drying drum, flow pattern and flow rate of the air current, drying temperature, and type of collector). Some examples of materials encapsulated by this technique are given in Table 2.

Similar types of spray-drying systems using different operating conditions can be used for microencapsulation of labile materials because of the brief contact time in the dryer. The method has been used to encapsulate fragrance oils, which are emulsified into a water-soluble polymer solution (e.g., with acacia gum) to make fine particles. These are used in products such as bath powders, when the formulation is controlled to release the aroma when the mixture is dissolved.

Spray Congealing. The related spray-congealing process is carried out by mixing the core

Table 2. Microencapsulation by spray drying* [7]

Core	Polymer solution	Drying temperature (inlet–outlet), °C	Microcapsule size, μm
Water-insoluble polymers			
Liquid paraffin (100)	acetyl cellulose (50) acetone (600)	130	50
Dye solution (50)	zein (40) methanol (200)	130	1–60
Carbon black (1)	polystyrene–butyl methacrylate latex (15 %) (16)	95–80	7–11
Paraformaldehyde (1)	polycarbonate (2) chloroform (100)	110 (steam)	10
Water-soluble polymers			
Liquid paraffin (100)	hydroxyethyl cellulose (150) water (300)	130	5
TiO ₂ (200) CaCO ₃ (385)	polyacrylic acid (325)	50–35	2
Choline chloride (63)	clay (11) water (37)	160–190	100
Lemon oil (37)	carboxylated dextrin (150)	85–38	10–20
Dimethyl polysiloxane (50)	methyl cellulose (5) solid milk (45)	265–120	100

*The figures in parentheses indicate parts by weight.

material with a molten wax or fat. The molten formulation is then sprayed and chilled below its melting point to form particles. The system can be used for microencapsulation of such solid materials as citric acid, vitamin C, potassium chloride, and iron(II) sulfate.

As a drying process, spray drying is relatively expensive, but appropriate variations on the basis principle can be an economic form of production of microcapsules.

4.4. Solvent Evaporation Processes

The solvent evaporation method is a technique widely used for the preparation of biodegradable and nondegradable polymeric microspheres, mainly for pharmaceutical applications [38–40]. In this method, the active material and the polymer are dispersed or dissolved in a volatile, water-immiscible organic solvent (e.g., methylene chloride, chloroform, ethyl acetate). This solution or dispersion is then emulsified in an external aqueous phase containing an emulsifying agent by using conventional emulsification equipment to form an o/w-emulsion. Microspheres with a size range generally between 5–250 μm are obtained after solvent evaporation. Depending on the solubility of the active substance, various modifications of the solvent evaporation method exist. A multiple emulsion (w/o/w-method) or an external oil phase can be used for water-soluble active compounds. This is a common technique to prepare protein loaded microspheres [65] entrapping the drug inside internal cavities (Fig. 1C) [8].

4.5. Coating Processes

Small, particulate cores can also be coated by air suspension coating (fluidized-bed coating technologies). In air suspension techniques, particles are suspended in an upward-moving air stream and are coated by spraying polymer solutions or aqueous colloidal polymer dispersions onto the particles.

Equipment for this (and other) types of coating is made by several firms [41, 42]. The most widely used device is the *Wurster coating chamber*. It is particularly suited for uniformly coating particles in a single operation. It is used for

pharmaceutical products (particularly for controlled release and taste masking), foods, and animal feeds (to improve shelf stability and reduce caking), chemicals (for controlled release and to change surface and adsorption properties), agricultural products (seed coating for easier handling and machine planting), pesticides, nutrients, and rodenticides (for taste masking and controlled release).

“Combination” sets of equipment can be modified for use with different coating systems. The equipment is automatically controlled and is designed for safe operation, taking account of the explosive hazard problems of electrostatic charges which can occur in coating systems employing flammable organic solvents with a low boiling point. For this reason, pressure-release devices are normally incorporated into production equipment. It is claimed that air control and powder coating systems provide more uniform film coatings on the active materials. This in turn gives reliable reproduction of predetermined release profiles for controlled-release microencapsulation systems. A typical small-scale fluidized-bed unit for pharmaceutical applications including granulating, drying, and film coating of solids (powders, tablets, and pellets) is shown in Figure 5.

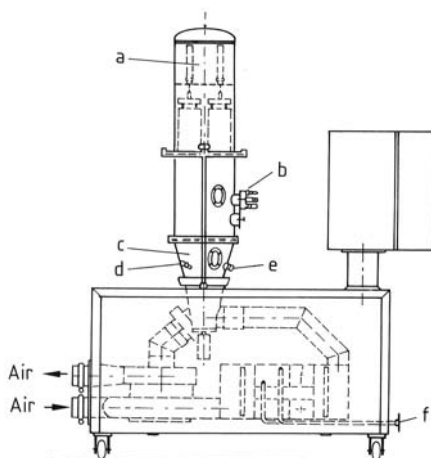


Figure 5. Small-scale general-purpose dryer/encapsulator for pharmaceutical and related products (Glatt AG)
a) Exhaust air filter; b) Spray nozzle; c) Product container; d) Temperature sensor; e) Sample port; f) Drain

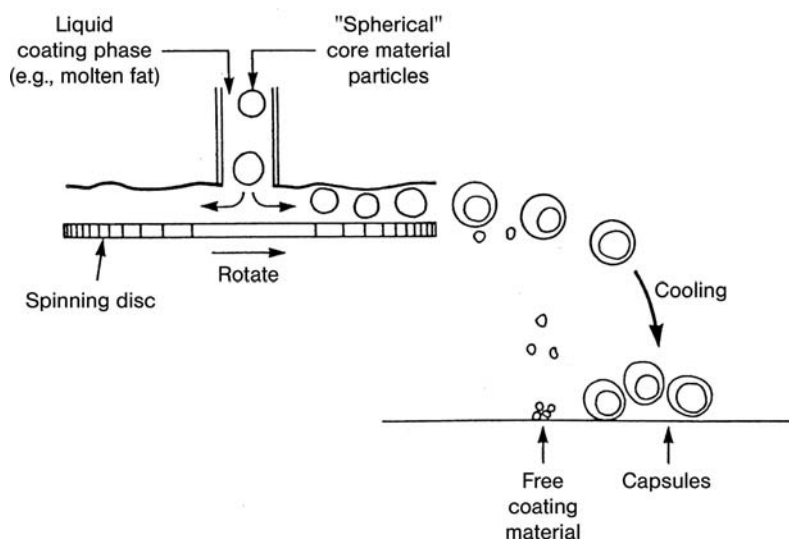


Figure 6. Spinning disk apparatus for the preparation of microcapsules

4.6. Spinning Disk

The spinning disk method is based on a rotating device which is alimented with the polymer solution containing the goods to be entrapped. Due to the high rotating velocity droplets are decanted and during flight particles are dried until a solid capsule structure is obtained. Dry particles are recovered (Fig. 6). This method is applied in the field of food industry and for the encapsulation of fragrances.

5. Other Forms of Microencapsulation

Nanoparticles are active substance-containing colloidal particles with a size $< 1 \mu\text{m}$. The active compound can be present in various physical states; it can be dissolved in the polymeric matrix, it can be encapsulated, or it can be adsorbed or attached to the surface of the colloidal carrier. The techniques used to prepare nanoparticles are generally classified into two groups. In the first group, nanoparticles are prepared by various polymerization reactions of lipophilic or hydrophilic monomers. Alternatively, nanoparticles are formed from preformed polymers.

Nanoparticles Prepared by Polymerization of Monomers. The methods used to prepare

nanoparticles by polymerization are derived from methods developed to prepare latices. The monomers, which are primarily of acrylic origin, can be either dissolved or emulsified in the continuous phase, with the resulting polymer being insoluble in either case. The preparation of nanoparticles by polymerization reactions is generally classified according to the resulting polymer or the resulting particle structure.

Nanoparticles Prepared from Preformed Polymers. Nanoparticles have been prepared from a variety of both water-soluble and water-insoluble polymers of synthetic, semi-synthetic, or natural origin. The use of preformed polymers has several advantages as compared to nanoparticles prepared by polymerization of monomers. Advantages include the established safety and approval standards, the absence of residual monomers or polymerization reagents (e.g., initiators or catalysts) and the lack of possible reactions between drugs and monomers.

Most techniques to prepare nanoparticles from *synthetic water-insoluble polymers* are derived from conventional emulsification technologies, which have been used to prepare microparticles, such as the solvent evaporation method. To prepare nanoparticles and not microspheres, the o/w-emulsion is homogenized under high shear with an appropriate homogenization

equipment (e.g., microfluidizer, sonication) prior to the precipitation of the polymer in the presence of a potent surfactant [43–46]. Drug–polymer particles in the nanometer size range are formed after solvent diffusion into the aqueous phase and evaporation at the water/air interface causing polymer and drug precipitation. Nanoparticles have been prepared with conventional laboratory homogenizers [43], by ultrasonication [44, 45, 47] or by microfluidization [46].

Hydrophilic polymers are primarily of natural origin. The nanoparticles are prepared either by an w/o-emulsification method or by aqueous phase separation techniques (e.g., coacervation). Preparation of nanoparticles of hydrophilic polymers (e.g., albumin, chitosan, gelatin, or carbohydrates) by w/o-emulsification techniques has been developed for the preparation of albumin microspheres [48–51]. Basically, an aqueous polymer solution is emulsified into an external, water-immiscible phase, such as an oil or organic solvent followed by homogenization. Upon water removal, the polymer droplets solidify. Insoluble nanoparticles can be obtained by further hardening/insolubilizing the polymer through chemical cross-linking with aldehydes or other cross-linking agents or through denaturation at elevated temperatures.

6. Characterization of Microparticles

Formulation and process parameters of the described preparation techniques will strongly affect the performance of the microparticles. A precise characterization of the physicochemical parameters is important in order to develop a product of high quality.

The parameters generally used to characterize microparticles include the particle size, morphology, and surface charge, the drug loading and encapsulation efficiency, the process yield, the drug release profile, and the physicochemical state of the drug and polymer.

7. Uses

A great diversity of products have been microencapsulated for many different purposes. Only a limited number of these can be described in addition to those already mentioned.

Food Industry. Many foods and animal feed additives have been encapsulated in gelatin and vegetable gums.

Food additives are encapsulated to improve storage life by reducing volatilization and oxidative degradation. However, small amounts of free active material may be released during storage and contaminate the encapsulated product. Spray drying may overcome this problem at the cost of loss of low-boiling volatile components. Alternatively, the mixture may be microencapsulated by extrusion under pressure into alcohol at 100–120 °C to solidify the capsules. The resulting particles are larger than those obtained by spray drying, and the process may also adversely affect heat-sensitive components.

Examples of encapsulated food additives include flavors and aromas (such as citrus oils, spices, and coffee oil, see Section 4.2). Bakery flavors (e.g., ethyl vanillin) have been encapsulated in ethyl cellulose and gum arabic. Liquid additives are dispersed as droplets in a matrix of carrier material. Fish oil extracts have been encapsulated by various techniques in order to mask the unpleasant odor as well as increase the stability of the entrapped unsaturated fatty acids [66]. Garlic oil has been encapsulated to reduce odor difficulties in handling [52–55].

In animal feeds, microencapsulation is used to protect atmosphere-sensitive additives: the largest application is the coating of synthetic vitamin A with gelatin for use as a poultry feed additive to enhance the color of egg yolk. In addition, microencapsulation is being increasingly used to produce edible microglobules for fish farming. Trout feed, for example, is obtained from gelatin microcapsules that are cross-linked with glutaraldehyde to control the rate of dissolution into water [55]. Uses of such products greatly increases the food conversion and growth rates of farmed fish and crustaceans, notably trout and prawns.

Pigments. Encapsulated pigments (e.g., in cosmetics) have been prepared using acrylic copolymers as the film-forming agents. Polyvinylpyrrolidone has been used as the wall-forming polymer for microencapsulating additives for specialty paints.

Laundry Products. Microcapsules are used in the formulation of laundry products, notably

fabric softeners [56], optical brighteners [57, 58], and chlorine donors [58, 59].

Paper. The principal application of microcapsules in the coating of paper is the production of carbonless copying paper (see Section 4.2). Microencapsulated, air-containing opacifiers have also been used to increase the whiteness of the product.

Pharmaceuticals. Microcapsules are employed in many applications in pharmaceuticals (→ Pharmaceutical Dosage Forms). For example, aspirin is coated with ethyl cellulose and other cellulose esters to reduce stomach irritation [60]. Use of cellulose acetate phthalate as part of the capsule wall results in capsules which are insoluble in the acid environment of the stomach and dissolve only at higher pH in the intestines [61].

In recent years, biodegradable microparticles based on poly(lactide–glycolide) copolymers have been developed. These microparticles are used as encapsulation for diverse peptide and protein drugs. Microparticles act in these cases as a reservoir for sustained release of protein drugs in order to avoid repetitive injections [65].

Cosmetics. Microencapsulation is used in the manufacture of beauty aids, including encapsulated perfumes (delayed release) and cosmetic aids (e.g., make-up removers).

Pest and Weed Control. There have been many applications of microcapsules in agriculture, to improve the delivery of active compounds (i.e., pesticides and herbicides) to the required target organisms. In many cases, microcapsules have been manufactured from specific products for particular uses. Capsule properties (i.e., storage life, and the time and rate of release of active component under field conditions) must be related to the identified biological behavior of the organism (such as a harmful pest or weed) which is to be controlled. Many pesticides have been microencapsulated, including methyl parathion [298-00-0], diazinon [333-41-5], thiocarbamates, and pyrethrins.

Durable microcapsules have been developed for the sustained and controlled release of biologically active materials, notably pesticides, to provide long-term effectiveness. These micro-

capsules have an outer wall of gelatin and an inner wall of a synthetic polymer, which may be polysulfone, polycarbonate, poly(methyl methacrylate), or a poly(styrene–acrylonitrile) copolymer. The active components are mixed in dichloromethane with the wall polymer, then emulsified with gelatin and nonionic surfactant at 45 °C until all the solvent has evaporated [62]. This microencapsulation system has been used not only for conventional insecticides (e.g., Naled), but also for the controlled release of pheromones.

Miscellaneous Uses. *Scented strips*, made by coating perfume-loaded microcapsules onto paper, have been widely used for advertising purposes in “scratch-and-sniff” sales promotions. Both gelatin-based and amino-resin-based capsule walls have been used.

Microencapsulated anaerobic *adhesives* are used to coat the threads of bolts and other fasteners. When a nut is screwed on to a coated thread, the microcapsules are fractured, and the adhesive seals the voids, so securing the fastening. Microencapsulated epoxy resin hardeners are also produced for control of adhesive resin setting rates.

Microencapsulation has also been used to encapsulate enzymes and cells (→ Biocatalysis, 2. Immobilized Biocatalysts, → Biocatalysis, 2. Immobilized Biocatalysts) and to make artificial cells [63].

Other microencapsulated products include dental amalgams containing encapsulated mercury; photographic materials and temperature-sensitive liquid crystals; tobacco flavors; weather modification systems (using microencapsulated hygroscopic seeding agents); microencapsulated reagents and catalysts; and flame retardants (as components of rigid and flexible foams).

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