MICROENCAPSULATION: FUNDAMENTALS, METHODS AND APPLICATIONS

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Abstract. Microencapsulation is widely use in industry but remains relatively unknown from the public. The reason is that microcapsules are not an end-product, but generally a technique to overcome process limitations. Micro-encapsulation allows immobilization, protection, release and functionalisation of active ingredients. Despite the high diversity of methods, this paper proposes a classification and description of the main technologies to produce microcapsules.

Keywords: microencapsulation, immobilization, controle release

1. Introduction

In the last few years, one could see the development of commercial products based on microcapsules. However, microencapsulation has been widely used in industry for several decades. The principle of encapsulation is very old. If biochemistry is a principle of life, nothing would have been possible without its integration in membrane bound structures (cells, mitochondria...). Without immobilization and spatial organization of biochemical reactions in an internal volume and through the membrane would not be possible. The high efficiency of, for example ATP production, would not be possible.

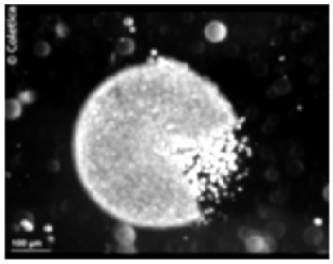

Figure 1. Multi-core microcapsules mimic biological cells and are sometimes called artificial cells. (Coletica®)

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By developing encapsulation methods, scientists and engineers mimic nature to obtain innovative structures to isolate, protect, release and functionalize active ingredients.[1] However nature is not so easy to mimic, and what humans have developed are still inferior to what biological cells offer.

Encapsulation is used in many industrial and scientific domains. It is not surprising to find then diverse definitions and terminology, often directed to a specific field. However, a generic and functional definition could be

"Entrapment of a compound or a system inside a dispersed material for its immobilization, protection, controlled release, structuration and functionalization."

This definition is more oriented to objectives than on the structure of the microcapsules. It includes a very large number of systems starting from hollow molecules such as cyclodextrin, to large solid microsphers of 2 to 3 mm. It proposes a product-oriented approach, a solution that limits debate around terminologies.

If we look a little more deeply into this definition, the first question is which type of system could we encapsulate? This could range from small molecules (some try to encapsule water) to quite complex ones (peptides, drug, DNA). It could be a mix of these molecules, or complex structures like viruses, protoplasts or even complete biological cells. Inside the capsules, the active system could be in the form of a solution, a suspension or an emulsion.

Which type of structures could represent microcapsules? The "true" microcapsule is a liquid core surrounded by a membrane. However, many different structures are included under the term "microcapsules" or "nanocapsules" (Figure 2). At the smallest scale, one could use hollow molecules inside of which the active ingredient could be fixed. At a larger scale, more or less complex molecular assemblies could form nanocapsules, or nanospheres, or lipidic structures like liposomes. For sizes less than a few micrometers, one talks of nanoencapsulation. For larger sizes, one finds hydrogel beads, solid microspheres, and microcapsules. For sizes greater than 1 mm, some talk about macroencapsulation. Encapsulation could also include agglomeration of fine particles or the coating of solid particles. Finally, some include emulsions if they are stable enough to fit the above definition.

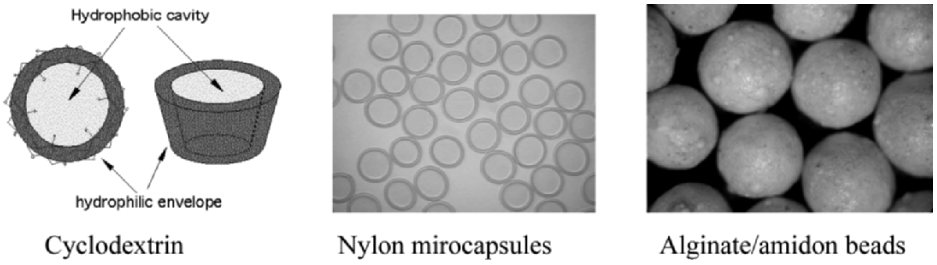

Figure 2. Examples of microcapsule structures.

Parallel to the structural complexity, a large number of technologies exist to produce microcapsules, which is a field unto itself.

2. Why Encapsulation?

Since encapsulation is costly, the requirement must first be justified. We can classify five categories for the objectives of encapsulation.

- **Immobilization or entrapment.** To limit contact between certain parts of a system. If some ingredient must be separated, encapsulation of this ingredient and release only upon rupture of the microcapsules fills this objective. The entrapment of a flavor could create a sustained aromatic effect, or to control the release at a specific time (such as during cooking). Immobilization of batteries or enzymes allows continuous processing while avoiding washout.
- **Protection.** If some ingredients are fragile and need to be protected from their environment. For example, vitamins or polyunsaturated fatty acids are denaturized by oxygen. Many biological cells are sensitive to shear. Some drugs and probiotics are destroyed during gastric transit. When incorporated in microcapsules, all these systems will be protected to some extent against the chemical, physicochemical and mechanical environmental conditions. However, the problem may be reversed. Incorporation of iron in food promotes oxidation of fatty acids. A number of industrial additives may reduce the performance of the material itself. In this case, it is more efficient to encapsulate the minor ingredients (iron, additives). Encapsulation could then be used to protect the environment from the use of some products. Most industrial enzymes are sold in an encapsulated form to avoid allergic and professional health problems.
- **Controlled release.** For practical use the active ingredient must be released. A drug must be delivered with well defined kinetics. Sometimes it is not the encapsulated ingredient that is released but a by-product. This is the case when the encapsulated product is an enzyme or a catalyst. Encapsulation may have the objective to limit release, but in some cases to make it more rapidly available. A typical example is an instant powder consisting of aggregates made of fine particles that are insoluble, in a very soluble matrix.
- **Structuration.** Homogeneous mixing of a small liquid volume with a high volume of powder constitutes a real challenge. Microencapsulation allows converting this liquid in powder and facilitating this operation. dosage forms for pharmacy applications are readily obtained by microencapsulation. By

coating brown sugar, a quite aggregative powder, with crystalline sugar, one gets a flowing powder.

- **Functionalisation.** Finally, microencapsulation may be used to develop new functions such as regulating biocatalyst activity by controlling the membrane permeability through pH changes. Microcapsules may also offer a marketing function such as giving specific "metallic" aspects to functional food to differentiate them from food and medication.

The diversity of applications is very broad and even microencapsulation is already largely used in industry, one could expect a strong development in the next decade.

3. How to Make Capsules

Many applications from a variety of fields for diverse objectives have led to many methods of encapsulation. Moreover, terminology varies from domain to domain. The same technology may have different names in different fields. Figure 3 tries to offer an approach where most technologies fit in an unambiguous way.

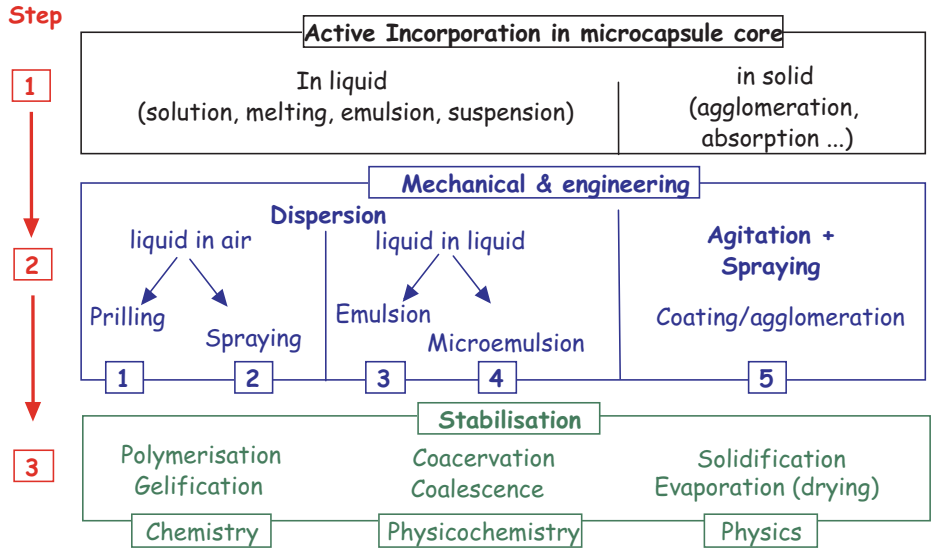

Figure 3. Technologies of encapsulation.

An encapsulation process may be generally divided into three steps.

1. The first step consists of incorporating the active ingredients in the matrix or microcapsule core. This may be in the form of a solution, emulsion or suspension, resulting in a liquid or a dispersed solid system. This could involve mixing or dispersing processes, drying, grinding and/or sieving.
2. The second stage is a mechanical operation.
   - For a liquid matrix, making a liquid–in-air (dropping or spraying) or liquid dispersion (emulsification or micro-emulsification).
   - For a solid matrix, spraying a solution on particles under agitation (fluid bed or pan coating or agglomeration).
3. The last step, is to stabilize/solidify droplets or the coating solution by a chemical process (polymerization), physicochemical process (gelation, coacervation) or physical process (drying, solidification).

These three steps may be repeated to reach the final structure. For example, microcapsules obtained by spray drying of polymer/active solution may be coated by a melted solution. The first encapsulation insures immobilization and stabilization of the active ingredient, while coating allows control of the level of protection and release.

4. Methods of Dispersion to Form Microcapsules

For incorporation of the active ingredient inside a liquid matrix (as a solution, emulsion, or suspension), the first step of encapsulation is the dispersion of this liquid as droplets, which can be classified into four categories.

4.1. PRILLING

This is simply improved methods to form droplets from a needle. The goal is to produce small droplets/microcapsules with low size dispersion (less than 10%) with a good level of production. To avoid broad size dispersion, the liquid flow must be in the laminar regime (avoiding turbulence), thus a relatively low flow rate is required compared to spraying (see below). In most cases, energy is required to reduce the droplet size (from a few millimeters with simple needle). This has led to the following systems.

- **Electrostatic generators**.[2] By application of an electrostatic potential on a pending droplet (Figure 4a), charges accumulate on its surface creating a repulsion which opposes the surface tension. The resulting droplets will

then have small sizes down to 20 micrometers for high voltage (10 kV). However, the flow rate is limited to only a few milliliters per hour and the system only useful for laboratory scale or some medical applications (artificial organs).

- **Nozzle resonances technology.**[3] While forming a jet from a nozzle, this jet has a spontaneous tendency to break into droplets. By applying a vibration at a specific frequency (Figure 4b), uniform droplets are formed with a size approximately double the jet diameter. Several liters per hours can be reached for larger size droplets of 1 mm, but decreases proportionally to the droplet diameter. On the other hand, resonance is damped if the solution viscosity is too high.
- **Jet cutter.**[4] The liquid jet can also be cut by a series of wires fixed on a turntable while turning at high speed (Figure 4c). This method provides high flow rates but is mainly useful for adequate for high viscosity solutions.
- **Spinning disks.**[5] Liquid may be flowed onto a spinning disk. Jets are formed and break into droplets (Figure 4d). The flow rate can be quite high, but literature on this subject is still limited. Further research is needed to evaluate the real performance of such systems.

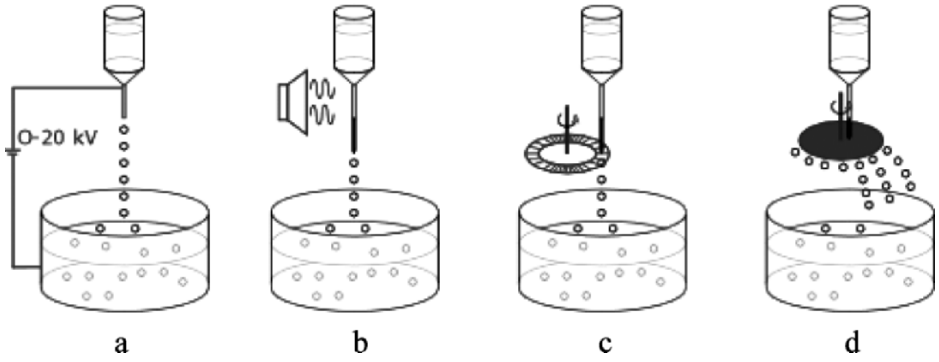

Figure 4. Scheme of different prilling methods.

4.2. SPRAY TECHNOLOGIES[6]

By flowing either through an air/liquid nozzle (Figure 5a) or on a fast rotating device (Figure 5b), a liquid can explode into fine droplets. Productivity is far superior to prilling technology, but turbulence leads to a large size dispersion (often higher than 30%).

Reactors used for spray technologies are quite similar to powder dryers, the technology of which is widely available and well understood. This technology is largely used in the food industry.

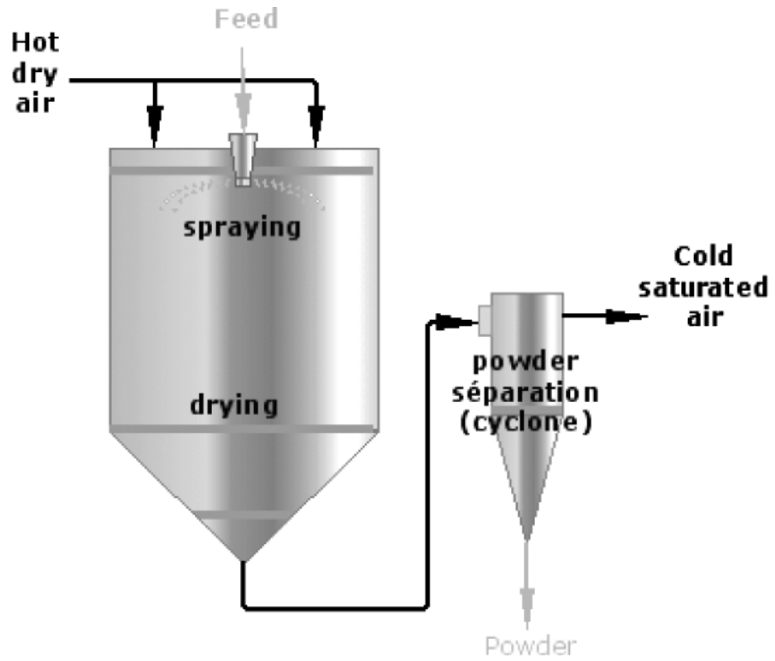

Figure 5. Spray systems.

4.3. EMULSIFICATION[7]

Liquid containing the ingredient to be encapsulated can be dispersed in an immiscible liquid to form an emulsion. For microencapsulation, one favors systems allowing dispersion at low shear to avoid denaturation of the active ingredients (for example biological cells). The simplest method is a reactor equipped with a turbine (Figure 6a). However, there is an increased interest for continuous systems, especially static mixers. This consists of a pipe where elements are inserted to promote fine division of the liquids in the static mixer (Figure 6b). Such systems allow emulsion production in a fraction of second at high flow rate (a few liters per square centimeter of section). In the majority of cases, dispersion takes place in a turbulent regime and the resulting droplet size dispersion is large (greater than 30% standard deviation).

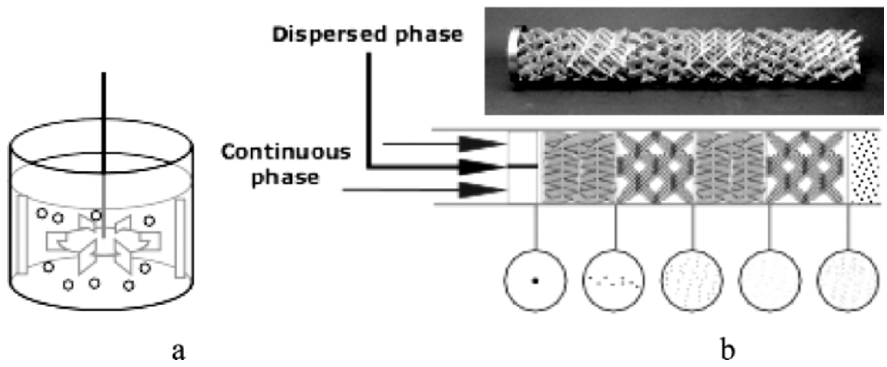

Figure 6. Liquid/liquid emulsification systems: (a) mechanical dispersion with a turbine; (b) a static mixer.

4.4. MICROEMULSIFICATION

By careful selection of the composition of a two immiscible liquid system, one can reduce the surface tension to near zero. In such conditions, with gentle agitation, a very fine dispersion (under micrometer size droplets) may be formed. This is a very stable system for an emulsion. In some conditions the size dispersion may be limited.

5. From a Liquid Dispersion to Microcapsules

All the above dispersions lead to droplets. These droplets must be transformed into solid like particles by a stabilization process. Table 1 provides the most usual encapsulation technologies by crossing dispersion methods and stabilization methods. Table 1 is not an exhaustive list.

Table 1. Usual terminology in microencapsulation technology.

	Prilling	Spraying	Emulsification	Micro-Emulsification
Solidification	Hot-melt prilling	Spray cooling		
Evaporation		Spray-drying	Solvent evaporation	Solvent evaporation
Gelation	Gelation	Spray chilling	Thermal gelation	
Polymerisation			Interfacial Polymerisation	In situ polymerisation
Coacervation	Interfacial Coacervation		Coacervation	
Micellar formation				Liposomes

- **Solidification.** The liquid forming the droplet can be melted and a reduction of temperature will result in droplet solidification. In practice, solidification is usually combined with prilling and spraying (but is easily combined with emulsification)
- **Evaporation.** As a liquid droplet is formed of a volatile solvent and a polymer, evaporation of the solvent will lead to polymer beads entrapping the active ingredients. Spray drying consists of spraying a (aqueous) polymer solution and droplet drying. Emulsification of polymer volatile organic solvent in water followed by solvent removal is called the "solvent evaporation" method.
- **Gelation.** By dropping droplet of gel forming solution in a gelation bath, hydrogel beads are formed. The gelation may be due to ionic bonding between polymer chains (such as an alginate solution dropped in calcium ions bath) or by cooling (such as an agarose solution). Gelation may also be used by spraying a thermogel (spray chilling) or through emulsification followed by cooling or pH change.
- **Polymerisation.** Emulsified droplets containing a monomer can react with a second monomer soluble in the continuous phase to form a membrane at the interface (i.e. diamine reacting with a acid dichloride). This is called interfacial polymerization. Many derivative methods can be set-up from this method, using pre-polymers in place of monomers, inversing the continuous and dispersed phases, developing a radical reaction. Covering all possible methods is not possible here.
- **Coacervation.** If an oil phase is emulsified in a polymer water solution, and the polymer is precipitated (for example) by changing the pH, the polymer precipitate (coacervate) has a tendency to accumulate at the interface. This is the coacervation process; called simple if one polymer is involved and complex if two polymers are involved. If the coacervation is obtained by dropping one polymer solution into a polymer solution of opposite charge, this is termed interfacial coacervation, or "polyelectrolyte complex formation".
- **Micellar.** By dispersing a surfactant and often a polymer, one may obtain a small assembly with diverse structures. The most well known is a liposome, generally represented by a bi-layer cell like structure. However, the structure can range from a stable emulsion to complex multi-layer vesicles.

All these capsules may need to be separated, washed and sometimes dried. They may be solid microspheres, liquid core capsules, or hydrogels beads. They may be further treated or coated to obtain the final desired properties.

6. Methods of Encapsulation by Coating, Agglomeration and Layering[8]

Coating of solid particles requires agitating the particles (to avoid agglomeration) and spraying coating solution on them. The coating must be stabilized or solidified for example by cooling or drying. The process can be repeated until a good and uniform coating is formed.

Spraying too fast, in the solidification process, results in agglomeration. However, if well controlled, the agglomeration may allow the formation of large particles from fine powders. One may also start from small particles, and spray the active ingredient to form layers of active materials. This is called layering.

Coating, agglomeration and layering can be combined to get diverse structures for the properties required by various applications.

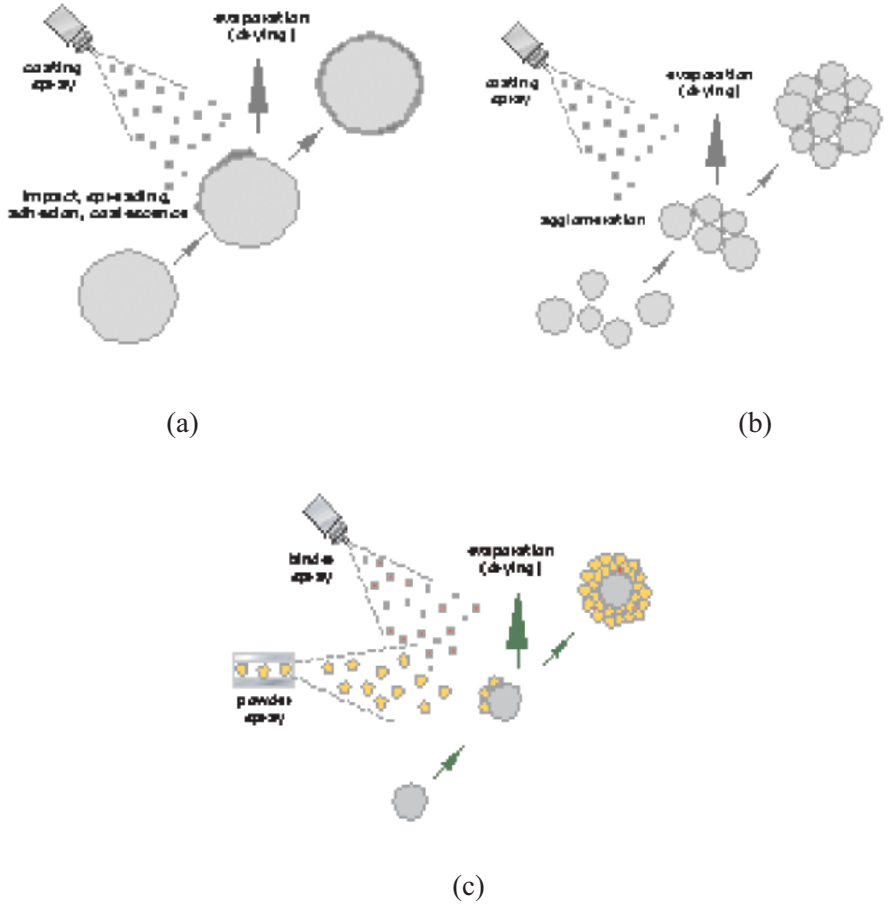

Figure 7. Technologies of coating (a), agglomeration (b), and layering (c). (Glatt international®)

Three actions are necessary to establish a coating:

- **Agitation.** Agitation has three main objectives: 1) to avoid unwanted agglomeration; 2) to create a spinning movement to particles for uniform coating; and 3) to circulate the particles to insure a homogenous coating over the batch. Agitation can be insured by an upper air stream leading to a suspended particle bed, having a similar behavior as a liquid and called a fluid bed (Figure 7a and b), or by a mechanical process such as rotation of a pan containing the particles (Figure 7c).
- **Spraying.** The coating or aggregative solution can be sprayed from the top (top spray, Figure 8a) or bottom (bottom spray or Wurster when a tube is inserted in the reactor, Figure 8b) or in the particle bed itself.
- **Solidification.** The most common for stabilizing the coating is to evaporate a solvent (drying in case of water) by injecting hot air (fluid bed) or heating the reactor (pan coating). However, there is an increased interest for hot melt coating, where a melted solution is sprayed on the particles. This reduces the time of processing and energy costs. The new powder dry technology consists of spraying simultaneously a very fine powder and a plastifiant. The powder will coalesce at the surface of the particles mainly at room temperature.

7. Microencapsulation and Chemistry

Microencapsulation covers a broad range of methods. A great number of variants exist around the above-described methods. The methods may also be combined. Engineers and scientists must refer to much scientific and technological knowledge, especially in chemistry. This includes:

- polymer chemistry for the synthesis and characterisation of polymers used during encapsulation;
- purification technology for extracting natural polymers, often used for hydrogel beads or coating;
- synthesis for controlling polymerization or cross-linking in diverse processes;
- physical and colloid chemistry to understand gelation and coacervation;
- and obviously formulation to get adequate support for the active ingredient and reach the optimum membrane structure.

Much progess has been made, but many challenges and opportunities remain in this field.

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