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Review Article

Encapsulation Methods and Releasing Mechanisms of Encapsulated Active Drug

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Abstract

Substances of plant origin are chemically unstable and easily oxidized by external conditions. However, they have to remain in their bioactive form when they are used in food, pharmaceutical, nutraceutical and cosmetic industries. Encapsulation method is an effective technique that should protect them preventing the degradation of these active substances and thus prevent them from losing their activities.

In this review, the strategies for encapsulating plant substances and their preparation methods including emulsification, atomization, coaxial electrospray system, lyophilization, coacervation, in situ polymerization, melt extrusion, supercritical fluid technology, fluidized bed coating etc. were discussed. The release mechanisms of plant active substances were also presented.

The choice of an appropriate encapsulation technique and wall material depends on the final use of the product and the processing conditions involved. The use of liposomes, ethosomes, phytosomes, emulsions, microspheres, microcapsules, solid lipid nanoparticles including formulations based on plant substances has enhanced their therapeutic effects. With the use of all these encapsulation systems, the formulation is delivered in a targeted manner, giving it an on-site effect, and the bioavailability of the formulation is also improved. With these new drug delivery systems, actives and extracts used in herbal formulations exhibit improved stability, sustained release from the formulation, protection against toxicity, and improved therapeutic efficacy.

Keywords : nanoparticles, bioactive substance, formulation

1 Introduction

Most plant substances remain chemically unstable and are liable to deteriorate through oxidation, particularly when exposed to oxygen, light, humidity and heat. These changes have a negative effect on the shelf life, sensory properties and overall acceptability of products (1,2).

To develop safe natural health products, the encapsulation technique could be a viable option to maintain their biological and functional characteristics. It has been successfully used to encapsulate not only oils but also herbal actives to prevent oxidation, improve stability and bioavailability (1,3–8).

Encapsulation is a method in which particles or droplets are surrounded by a coating, or are incorporated into a homogeneous or heterogeneous matrix (1,9,10). The compound diffuses progressively through the structure, offering controlled release properties under the specific conditions (1,11). Consequently, this technique can be used to protect, release and enhance the properties of bioactive compounds.

Inside these structures, the encapsulated substance is introduced in the form of a solution, suspension or emulsion. The structures can be of various configurations. A micro- or nanocapsule has a core where the active substance is trapped, surrounded by a membrane. It acts as a reservoir system. In the other possible configuration (matrix system, micro or nano sphere), the active substance is dispersed in a continuous network of encapsulating material. Also, an active substance can be inside a macromolecule such as cyclodextrin. We can also associate stable micro(nano)emulsions and micro(nano)particles with this concept of encapsulation, not forgetting vesicular systems (liposomes)... Structures vary in size (from millimetre to nanometre), composition and production method. The parameters governing their physicochemical properties are just as numerous. To prepare them, you need to choose the right materials and the right method. Normally, they cannot be selected independently, as there are interdependent relationships between the materials, the process and the physico-functional characteristics of the manufactured structure, and these must be considered as a whole.

There are several ways of classifying encapsulation processes

according to different criteria (12) ; the use or non-use of organic solvents; the nature of the dispersing medium (liquid, gaseous or supercritical); the use of preformed polymers, lipids or monomers; the nature of the processes associating the molecule to be encapsulated with the encapsulating material. This last criterion enables us to classify processes into different categories:

- **Mechanical** processes *involving* spraying, droplet formation and extrusion.

- **Physico-chemical** processes, based on the control of parameters such as polymer solubility and precipitation as a function of the addition of a non-solvent, pH or temperature, as well as the control of polymer changes of state (melting, solidification, gelling).

- **Chemical** processes *are* based on in situ formation of the encapsulating material by polycondensation, radical polymerization or anionic polymerization of monomer units. As such, chemical processes are distinct from physico-chemical and mechanical methods which stabilize pre-formed encapsulating materials (polymers, lipids).

Poncelet et *al.,*) have proposed three main stages in the encapsulation process (Figure 1): *(i) Incorporation of the active ingredient into the matrix or capsule core*: This stage takes into account the physicochemical characteristics of the active substance. If the core is liquid, incorporation consists in dissolving or dispersing the active ingredient in the matrix. If the matrix is solid (powder), the active ingredient can be incorporated by absorption on the powder or agglomeration with the powder. A solid active ingredient can also itself form the core of the microcapsules; *(ii) Dispersion*: The liquid formulation is dispersed in the air (atomization, prilling) or in another liquid (emulsification) to generate droplets. A solid-state formulation will be brought into contact with the encapsulating material under agitation (fluidized bed, granulator, rotary drum, etc.); *(iii) Stabilization/solidification:* Droplets generated in (2) by solidification of the coating material dispersed in (2) on the solid form by drying/solidification.

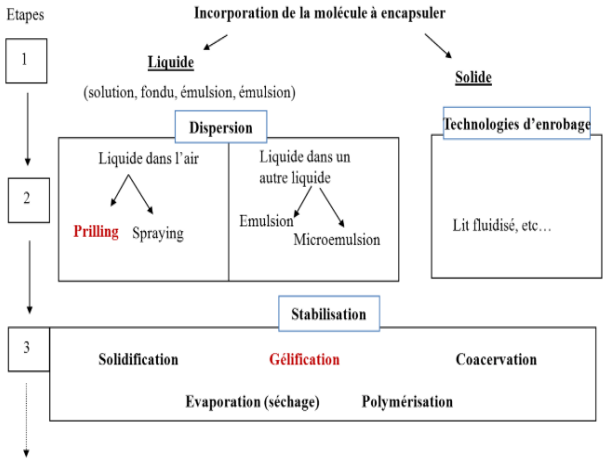

Figure 1 : ***Simplified representation of the steps involved in an encapsulation process (13)***

This work is a literature review of the various encapsulation systems for plant active substances and fats, in particular oils, with an emphasis on microparticles, the strategy adopted for this study as they present certain interesting criteria and advantages(14). Microparticles can be tailored to desired release profiles and used to deliver active substances. to specific sites. In some cases, they can even enable targeted organ release. Also, the active substance. can be easily released from the formulation. Microparticles can protect the specific function of an active substance. and release the active substance. in an external phase after a long period. Next, the various encapsulation techniques were presented, in particular ionic gelation, the technique used to formulate microparticles. Finally, the various release mechanisms for encapsulated substances were studied.

1 Encapsulation systems for plant active substances

Systems for encapsulating active plant ingredients must ideally meet two prerequisites. Firstly, it must release the active substance. at a rate adapted to the needs of the organism, for the duration of the treatment. Secondly, it must carry the active substance to the site of action. Conventional forms, including sustained-release dosage forms, can meet neither of these conditions.

In phyto-formulation research, the development of particulate systems offers a number of advantages for the active substance, including improved solubility, bioavailability, pharmacological activity and stability, protection against toxicity, prolonged release and protection against physical and chemical degradation, etc.

Thus, new encapsulation systems for plant active substances have a potential future for improving activity and overcoming the problems associated with herbal medicines (3).

These different systems, which have been used for plant active substances (3,4,14–17) and phytochemicals can be classified into the following groups (16) : (*i*) **Vesicular systems**, which include liposomes, ethosomes, phytosomes, transferosomes, etc.; *(ii)* **Biphasic systems**, such as micro/nano emulsions; *(iii)* **Particulate systems**, which include microparticles, nanoparticles and micropellets. The latter systems, in particular microparticles, will be reviewed as they constitute the encapsulation system chosen for our study.

Microparticles are small spherical particles, with diameters in the micrometer range, typically from 1 µm to 1000 µm (1 mm) (14,16), in which an active substance is uniformly dispersed in the polymer matrix and then released (16).

Microparticles can be made from a variety of natural and synthetic materials, both biodegradable and non-biodegradable. These materials include: albumin, modified starch, gelatin, polypropylene, dextran, polylactic acid etc. (14,16). Microspheres and microcapsules have high surface-to-volume ratios and widely varying densities, so they are used for a variety of applications. The interfacial surface properties of microparticles often determine their activity. The main techniques used to prepare microparticles are emulsion, solvent evaporation, spray drying and ionic gelation (16). Various studies have been reported on microparticles of different plant active substances (Table 1)

Table 1: Microparticles based on plant active substances and their applications *(3,14,18–21)*

Active plant substances	Polymers	Goal	Activities	References
Rutin	Alginate Chitosan	Site-specific release for cardiovascular and Cerebrovascular	Cardiovascular and Cerebrovascular	(Xiao et al., 1994)
Camptothecin	PEG	Dose reduction, improved Cytotoxicity	Cytotoxic, anticancer agent	(Chao et al., 2010)
Sylimarine	Cellulose Eudragit	Prolonged release, enhanced activity	Hepatoprotective activity	(Garg and Gupta, 2010)
Quercetin	Polycaprolactone	Significantly reduces the dose	Anticancer agents	(Natarajan et al., 2011)
Cynara scolymus extract	Lactose HPMC	Controlled release of neutraceuticals	Food supplements	(Gavini et al., 2005)

2 Encapsulation systems for oils

The physical encapsulation of oils can protect against photosensitivity, heat, humidity, oxygen, enzymatic degradation and chemical reactions between active substances.

It could also prevent transformation of the physical structure, mask taste, and modify the color and odor of the oils. Moreover, encapsulation could reduce their toxicity, increase their stability and their controlled release (Figure 2)(5,9,10).

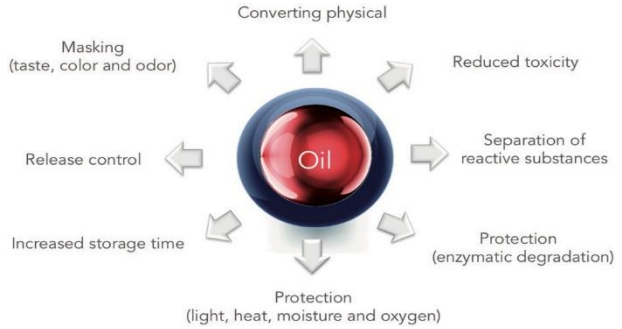

Figure 2 : ***Advantages of oil encapsulation*** *(5)*

This technique can be defined as a process of building a functional barrier between the core (containing the oil) and the membrane in order to avoid chemical and physical reactions and then maintain the biological, functional and physicochemical properties of the core materials (Figure 3). Because of these advantages, encapsulation techniques have been widely used in various pharmaceutical, food, cosmetics and fragrance industries.

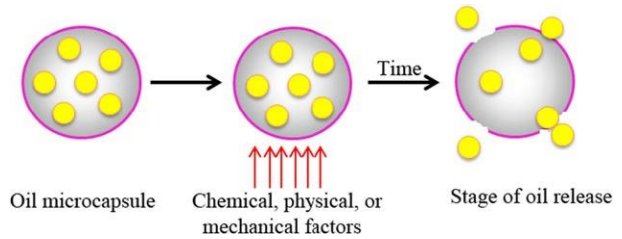

Figure 3 : ***Schematic diagram of controlled oil protection and release.*** *(1)*

Vegetable oils have been encapsulated in a variety of ways. Figure 4 illustrates the different strategies adopted to encapsulate vegetable oils.

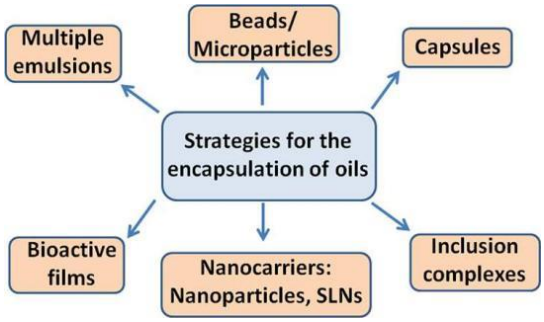

Figure 4 : ***Schematic illustration of encapsulation strategies for vegetable oils.*** *(7)*

2.1 Multiple emulsions

Since 1965, multiple emulsions have been developed for pharmaceutical, cosmetic and food applications (Engel et al., 1968). Multiple emulsions are three-phase systems, which can be W/O/W or O/W/O emulsions (W: water; O: oil) (Figure 5).

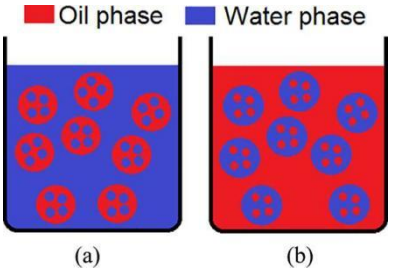

Figure 5 : Schematic representations of multiple emulsions (a) water-in-oil-in-water and (b) oil- in-water-in-oil (26)

Compared to O/W/O emulsions, W/O/W emulsions have been used for active substance administration (27). In general, W/O/W emulsions were prepared by the phase inversion method, either by one-step or two-step emulsification (28). Cournarie et *al.,* (29) reported that the two-step emulsification method offers higher encapsulation efficiencies than the one-step emulsification method (30). The advantages and problems associated with multiple emulsions are presented in Table 2 Multiple emulsions have also been synthesized using different vegetable oils (31,32).

Table 2: Advantages and problems associated with multiple emulsions *(7)*

Benefits	Problems and solutions
Ability to transport active substances. hydrophilic and hydrophobic. Sustained-release drug delivery systems Protects the bioactive ingredient from difficult gastrointestinal conditions (pH, enzymatic degradation) Masks taste/odour	Inherent thermodynamic stability is the main obstacle to multiple emulsions. Emulsion stability can be improved by adding complex- forming agents or internal phase gelling agents.

Vegetable oils must be tested for purity before being used in the preparation of multiple emulsions.

2.2 Beads and microparticles

Beads and microparticles have been synthesized to prepare food, pharmaceutical, nutraceutical and cosmetic products with a high oil content in a reduced product volume. Their advantages and disadvantages are listed in Table 3.

Table 3: Advantages and problems associated with beads and microparticles (7)

Benefits	Problems and solutions
Easy handling Transport or incorporation in other components Masks taste/odour Protection against evaporation or oxidation of essential oils Controlled-release applications	Involvement of multiple steps in the preparation method. This can sometimes lead to a reduction in encapsulation efficiency.

Although beads and microparticles can carry large quantities of oil (Figure 6), they suffer from oxidation, and unsaturated or polyunsaturated fatty acids are sensitive to oxidation. Lipid oxidation causes rancidity and affects the nutritional properties of oils. Lipid oxidation is governed by oxygen, heat or light.

However, beads and microparticles have been shown to prevent lipid oxidation and improve lipid release parameters (33–35). In addition to protection against lipid oxidation, the microparticles developed showed high encapsulation efficiencies. Release of encapsulated oils is another major concern associated with beads and microparticles. In general, leaching is due to the porous nature of the formulations. Oil loading capacity can be improved by coating the microparticles with another polymer, by increasing polymer concentration, polymerization time, etc

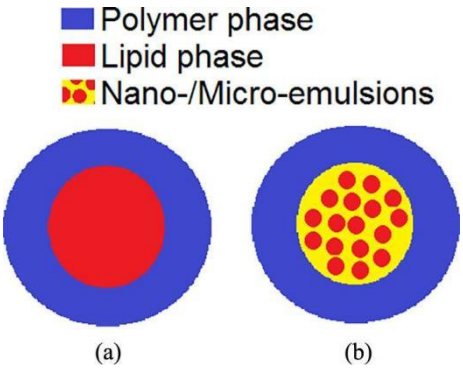

Figure 6 : ***Schematic representation of microcapsules encapsulating (a) an oil phase.*** *(36)* ***and (b) nano-/microemulsions*** *(37)*

Oil may be the main encapsulated active substance, or serve as a vehicle for hydrophobic compounds (38) (Figure 7). On the other hand, the membrane material may be water-soluble, which may favor the presence of hydrophilic substances such as proteins, hydrophilic pigments and plant extracts... in the membrane (39) (Figure 7). These oil reservoirs can be classified according to their morphology (irregular or spherical shape), number of cores (single or multi-core) and size (micro, milli). Several categories of capsules are described in the literature; in general, their structure depends on the encapsulation technique and/or the crosslinking mechanism of the membrane materials (10). Irregularly shaped capsules are structures with an ill-defined shape, generally composed of several small oil cores trapped in the membrane (Figure 7).

Polynuclear capsules have a structural organization similar to that of irregularly shaped capsules; however, the membrane has a well-defined spherical shape (Figure 7).

The main disadvantage associated with polynuclear capsules is their low oil load (<30% v/v). In addition, the oil cores may be located on the capsule surface, facilitating oil degradation and loss during storage or drying.

Oil-core capsules are spherical structures consisting of a single oil core covered by a membrane (Figure 7). These structures are useful when no active material is desired on the particle surface, or when a high oil loading (>90% v/v) is required (Figure 7). Emulsion capsules also contain a single core covered by a shell; however, in this case, the core is filled with an emulsion (40,41). This feature enables the simultaneous encapsulation of hydrophilic and hydrophobic compounds in the core, which may be of interest for the encapsulation of proteins and oily compounds in cosmetic applications (39).

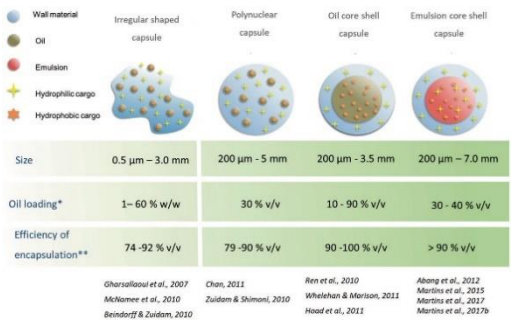

Figure 7 : ***Morphology of oil capsules. *Oil in core (volume or weight) / capsule (volume or weight); volume of encapsulated oil / volume of total oil. (5)***

In addition, soft capsules have been identified as a means of transporting active substances. liquids such as oils in soft envelopes (Figure 8).

Figure 8 : ***Soft gelatin capsules*** *(7)*

They are unit dosage forms made from gelatin, the polymer most frequently used to synthesize capsules. Glycerine is used as a plasticizer in the preparation of soft capsules.

Its presence increases oxygen and relative humidity permeability in soft capsules (42). Replacing the gelatin polymer with any other suitable polymer can solve this problem (43).

A precise range of sizes has been established to classify the capsules (Table 4).

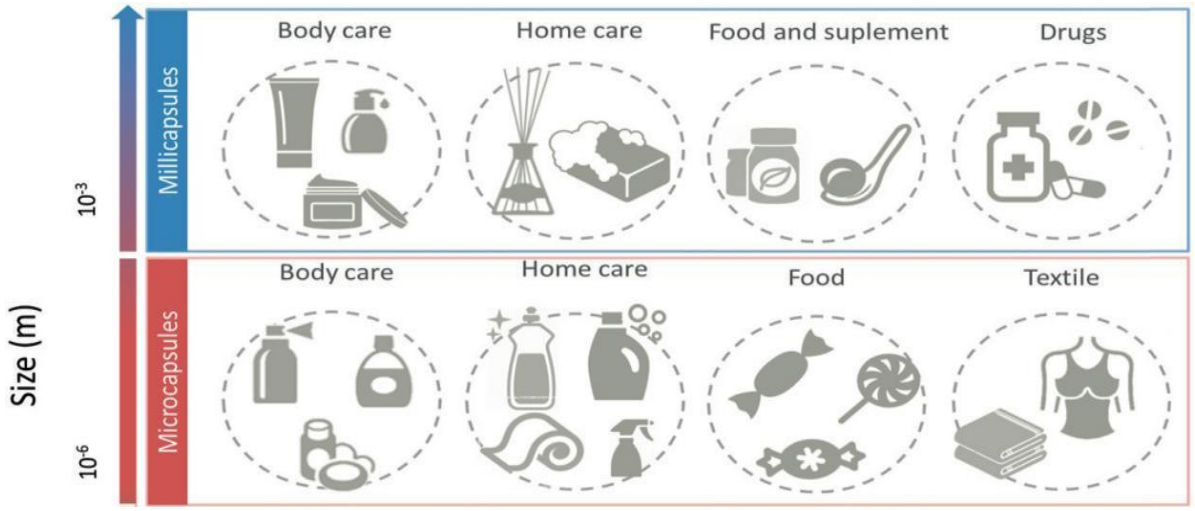

Table 4: Use of micro and milli capsules in selected industrial applications ***(Martins et al., 2017a)***

The term millicapsules (44) is applied to oil reservoirs larger than 1 mm and is used in applications where visualization of the capsule is desired. In addition to protecting the oil from oxidation, millicapsules guarantee an attractive appearance to the final product and are frequently used as a marketing strategy (5).

Microcapsules are capsules between 1 and 1000 μm in size and are generally used in products whose texture and appearance do not need to be radically altered. In some cases, such as in skin and hair creams, shower soaps and household cleaners, visible microcapsules are intentionally added to make the product more attractive. Unlike millicapsules, microcapsules can be used to develop precise active ingredient delivery systems. The general rule that applies to microcapsules is that by decreasing their size, the release of active substance. is faster (45). This means that by controlling the size of microcapsules during the process, it is possible to determine the kinetics of active ingredient release.

2.3 Solid lipid nanoparticles (NLS)

Nanoscale polymer particles have attracted much attention for the development of new formulations for controlled-release systems and for improving oil stability. Polymer-based nanoparticles are classified into nanocapsules and nanospheres (Figure 9a and 9b). They differ from each other in structure. Nanocapsules have a polymeric wall encapsulating the oil core, while in nanospheres, the oil can be conjugated to the wall or to the polymeric matrix(46).

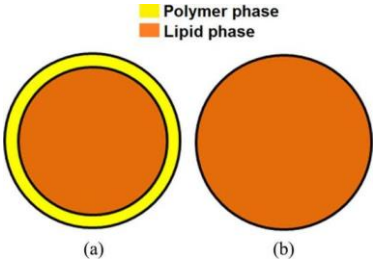

Figure 9 : ***Schematic representation of (a) nanocapsule and (b) nanosphere structures*** *(47)*

Solid lipid nanoparticles (SLNs) are nanometer-sized particles prepared from lipids that are solid at room temperature. The lipid component of NLS can be triacylglycerols or waxes. NLS vary in size from 50 nm to 1 μm. In NLS, the active substances are either in the core or on the membrane (Figure 10). They are ideal for transporting lipophilic active substances. They offer good protection, less salting-out and prolonged release of bioactive agents.

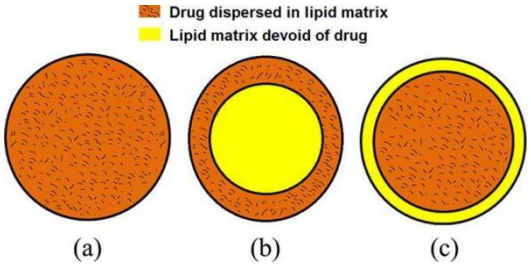

Figure 10 : ***Schematic representation of the different types of solid lipid nanoparticles (a) homogeneous matrix type, (b) active substance-enriched membrane, and (c) active substance- enriched core (48)***

3 Encapsulation methods

3.1 Emulsification

Emulsions are used in a wide variety of food and pharmaceutical products.

Emulsification technology is a key step in the microencapsulation of oils. It is generally applied to encapsulate active substances in aqueous solutions, which can be used directly in their liquid state or dried (by spraying or freeze-drying) to form powders after emulsification. It is therefore part of the microencapsulation process. Basically, an emulsion is made up of at least two immiscible liquids, usually oil (H) and water (E), with one of the liquids dispersed in the form of small spherical droplets in the other (Figure 11). To obtain a kinetically stable emulsion, emulsifiers or texture modifiers are usually added to the formulation. Emulsion droplet diameters range from 0.1 to 100 µm (11). The use of this technology to deliver food components and nutraceuticals has been examined in detail (49). Emulsions are prepared by homogenizing oil, water and emulsifier using a mechanical device known as a homogenizer (high-shear mixer, high-pressure homogenizer, colloid mill, sonicator or membrane homogenizer). The advantages of these systems are relative ease of preparation and low cost, but they have the disadvantages with physical instability (when exposed to heat,cold, freezing,drying, externe Ph and high mineral concentrations) and limited controlled release (49).

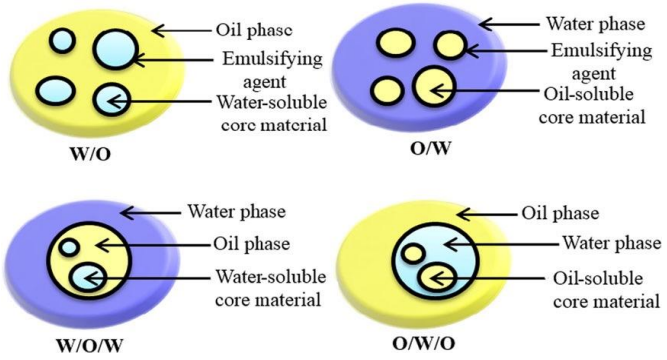

Figure 11 : ***Illustration of the 4 emulsion systems (W/O, O/W, W/O/W and O/W/O).(1)***

3.2 Atomisation

Spray drying is widely used for encapsulating oils in microparticles. It involves rapid atomiza

tion of the solution/emulsion containing the active substance in a high-temperature drying medium (Figure 12).

The temperature is maintained by pumping hot air in the opposite direction to the emulsion spray direction. The sudden change in temperature leads to rapid evaporation of water, and the formation of solid microparticles (50). This is the transformation of a substance in liquid form (solution, emulsion or paste) into a powder by spraying this substance into a hot drying medium (51).

The advantages of this method include the use of heat-sensitive products, easy availability of machines, and easy regulation of microparticle size by adjustments made to the spray nozzle. The disadvantage associated with this method is the use of a high temperature for the drying process. Spray-drying technology requires well-defined operating conditions (52) and a sufficient quantity of liquid containing the active ingredients. The efficiency of microparticle encapsulation in spray drying depends on certain key steps, namely the preparation of the stable oil-in-water emulsion and the atomization of the emulsion into small droplets during drying (10).

Emulsion pulverization and droplet drying depend on emulsion properties. Therefore, the weight ratio of hydrophilic and lipophilic phases, the size distribution of oil droplets in the emulsion, the dry matter content of the emulsion and the viscosity of the emulsion must be optimized prior to spray drying. The success of spray drying is mainly influenced by the size distribution of the oil droplets in the emulsion The choice of polymer is also important, as it constitutes the dry matter of the microparticles (53).

For spray-drying, polymers must have emulsion-forming properties with reasonable viscosityto be pumped and sprayed. They must not be sticky and hygroscopic after drying, otherwise they will affect the stability of the microparticles during storage. The main polymers for spray-drying in the food and pharmaceutical industries are polysaccharides, starches, gums, celluloses and proteins. They have been used alone or in combination.

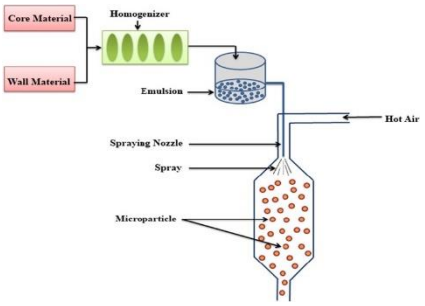

Figure 12 : ***Schematic representation of the spray-drying microencapsulation process.(1)***

3.3 Lyophilization

Freeze-drying is a simple process used to dehydrate almost all heat-sensitive active ingredients and flavors (Figure 13). Prior to drying, the active ingredient is dissolved or dispersed in water and then frozen at between -90°C and -40°C (54,55). The surrounding pressure is then reduced and a sufficient amount of heat is added to allow the frozen water in the active ingredient to sublimate directly from the solid to the gas phase (56).

Freeze-dried active ingredients appear to have maximum retention of volatile compounds compared with spray-drying (57). In addition to protecting heat-sensitive active ingredients, freeze-drying is simple and easy to implement. Freeze-dried samples have been found to be more resistant to oxidation (2). The main disadvantages are high energy consumption, long processing times and high production costs compared with other drying methods (58). Freeze-dried active substances can be more porous, exposing the encapsulated substance to the surrounding environment. However, the porous structures of lyophilized bioactive products enable better release of active substances. (59).

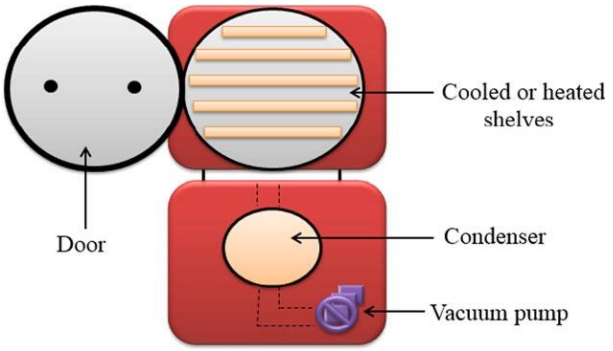

Figure 13 : ***Schematic diagram of a freeze dryer (1)***

3.4 Coacervation

The coacervation technique involves the addition of a desolvation or coacervation agent to a homogeneous polymer solution. During the encapsulation process, the active substance is encapsulated in the polymer-rich phase. Today, coacervation is performed using two methods: simple coacervation and complex coacervation. These two methods are identical, but differ in the way the phases are separated. In simple coacervation, a water-soluble desolvation agent is added to the polymer solution. The desolvation agent separates the aqueous phase from the polymer molecules, affecting their solubility.

The polymer-rich phase is precipitated as spherical droplets. Cross-linking of these spherical droplets leads to the formation of stable microparticles. The choice of cross-linking agents depends on the type of biopolymer used. In general, glutaraldehyde, genipin and calcium salts are widely used as cross-linking agents (7,60). Polymers used in the coacervation process include alginate, chitosan, cellulose derivatives, proteins, etc (61,62,62–68). Polymers used in the coacervation process include alginate, chitosan, cellulose derivatives, proteins, etc (64). On the other hand, complex coacervation involves complexation between two oppositely charged polymers. Complex coacervation involves three fundamental steps (Figure 14). The first stage is the formation of three immiscible phases: the core, the membrane and the manufacturing liquid. Typically, the core is dispersed in a solution of the polymer making up the membrane material. The membrane is rendered immiscible either by adding a desolvent or a salt, or by inducing polymer-polymer interactions, or by modifying the temperature of the polymer solution, or by adding an incompatible polymer. The second step is to deposit the liquid polymer on the core. Finally, the third step involves stabilizing the microcapsules by cross-linking, desolvation or heat treatment. In general, protein-polysaccharide complexes are used in complex coacervation (69–76)

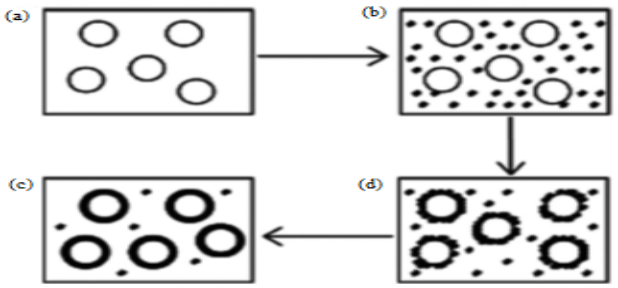

Figure 14 : Schematic representation of the coacervation process. (a) dispersion of the core in a shell polymer solution; (b) separation of the coacervate from the solution; (c) coating of the core with coacervate microdroplets; coalescence of the coacervate to form a continuous shell of the core particles (77)

3.5 Solvent evaporation

In the solvent evaporation method, three phases are present: the core, the membrane material and the manufacturing liquid. Initially, the membrane material is dissolved in a volatile solvent, which is not soluble in the manufacturing liquid. An active substance to be encapsulated is either dissolved or dispersed in the polymer solution, which is added to the manufacturing liquid with stirring, and the mixture is heated to evaporate the polymer solvent. The coating material then shrinks around the core and encapsulates the latter (77). The resulting microparticles are then washed and dried (78). Mineral and vegetable oils can be used as manufacturing liquids for encapsulating active substances. hydrophobic, vitamins, peptides, proteins or food additives such aspigments (79).

3.6 Extrusion

The extrusion method is considered the most common approach to microencapsulation and can be achieved by emulsifying/dispersing hydrophobic active ingredients or dissolving hydrophilic active ingredients in an aqueous solution where ionic or thermal gelation takes place (80). It involves a simple protocol. In this method, the active ingredient is gradually added to the aqueous polymer solution with continuous homogenization. The homogeneous solution or emulsion is then sprayed into a cross-linking solution ($CaCl_2$ or glutaraldehyde solution). Spraying can be performed using a syringe, peristaltic pump or nozzle. The size of the microparticles can be regulated by the size of the nozzle in the sprayer. Emulsion droplets cross-link over time on contact with the cross-linking solution, forming microparticles. The microparticles can be hardened by further incubation in the crosslinking solution. The extrusion method provides a wide choice of polymers and is easily adaptable to large-scale production (6).

Also, the electrospray method is based on an extrusion process that produces multilayer microparticles and nanoparticles ranging in size from a few tens of nanometers to a few hundreds of micrometers by introducing coaxial electrified jets. Previously, a single-axis electrospray method had been devised. Later, technical advances led to the transformation of the single-axis electrospray method into a coaxial electrospray method.

During coaxial electrospray (Figure 15), a coaxial capillary needle is used to simultaneously spray two different liquids through a nozzle (one containing the active substance. and the other containing the membrane materials), under the influence of an electric field into a cross-linking solution to obtain particles by ionic gelation (81). Using this method, it is possible to achieve 100% encapsulation efficiency with precise control of the polymer-core geometry. This process protects fragile therapeutic molecules from denaturation and aggregation (82).

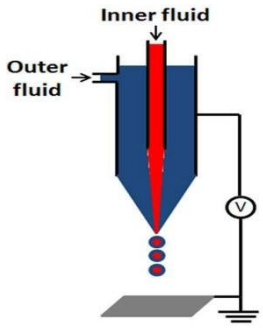

Figure 15 : ***Schematic representation of coaxial electrospray encapsulation synthesis.(83,84)***

3.7 Supercritical fluid technology

Supercritical fluid technology has also been developed to minimize the disadvantages associated with traditional encapsulation methods (Figure 16). It is generally used for oils sensitive to high temperatures, oxygen and chemicals. Supercritical fluid technology is an environmentally-friendly approach in which supercritical carbon dioxide (sc-CO2) is used as a green solvent. This sc-CO2 has ideal properties for encapsulating active substances. Characteristic properties of sc-CO2 are lower viscosity, higher diffusion, lower surface tension, faster processing and high solubility of the active compound (85). This technology can also be described as supercritical solvent impregnation. This process has proven its worth in the encapsulation of oil, perfumes, pharmaceutical ingredients, etc.

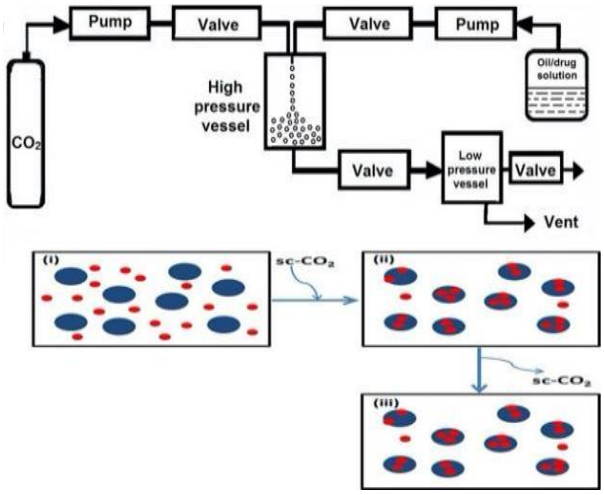

Figure 16 : ***Schematic representation of supercritical fluid technology (86)***

3.8 High-pressure homogenization

This method is used to synthesize NLS. The lipid phase containing the active substance is heated above its melting point. Simultaneously, an aqueous phase containing surfactant(s) was also prepared at the same temperature. Next, an emulsion is formed by adding the aqueous phase to the molten lipid phase and homogenizing it for 30 minutes at a temperature above the lipid's melting point. The hot emulsion is passed through a high-pressure homogenizer at ~800 bar for six cycles. After homogenization, the mixture is cooled to room temperature in an ice bath, resulting in the formation of NLS (7).

3.9 *In situ* and interfacial polymerization

In situ and interfacial polymerization are also used to prepare oil microcapsules. In interfacial polymerization, the membrane is formed by adding a reagent (melanin-formaldehyde combination) inside or outside the core, and polymerization takes place at the interface. The distinctive feature of *in situ* polymerization in encapsulation, compared with any other polymerization process, is that no reagent is included in the core, and all polymerization takes place in the continuous phase (87).

3.10 Fluidized air bed coating

Fluidized-air bed coating is one of the most efficient coating methods, with a growing number of applications in the food and pharmaceutical industries. In this process, ingredients can be mixed, granulated and dried in the same container, reducing material handling and processing times compared with other wet granulation processes. Fluidized air bed coating is also known as "air suspension coating" or "spray coating". It is achieved by suspending solid core particles in an air stream at controlled temperature and humidity, then spraying the membrane material. Over time, it gradually accumulates as a thin layer on the surface of the suspended particles (1). The coating material must have an acceptable viscosity to enable atomization and pumping, must be able to form a suitable film on the surface of a particle and must be thermally stable (88). The amount of material that coats the particles depends on how long the particles remain in the chamber; typically, 5-50% of the coating is applied. The various fluidized-bed coating methods include top spray, bottom spray and tangential spray, as shown in figure 17.

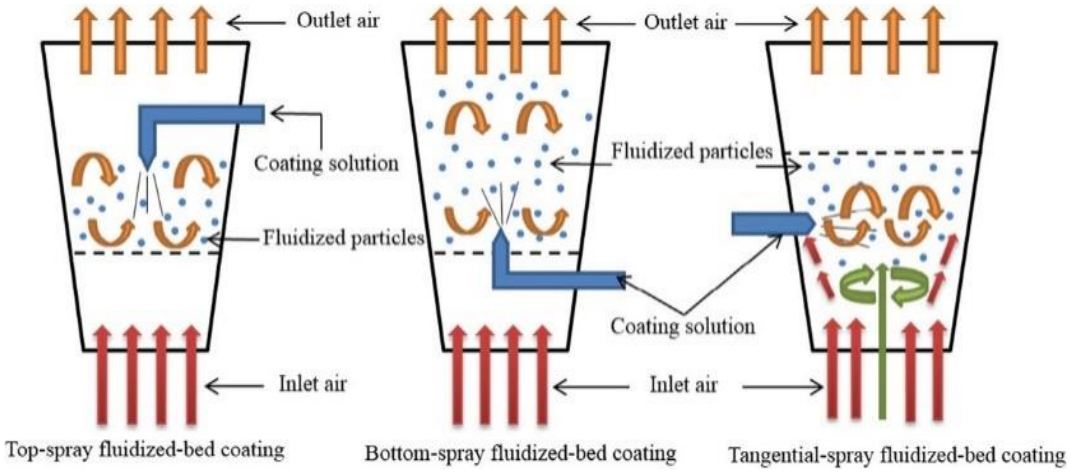

Figure 17 : ***Schematic diagram showing fluidized-bed coating by top (a), bottom (b) and tangential (c) spraying.(1)***

4 Active substance release mechanisms

One of the main objectives of encapsulating active substances is to ensure controlled release. This controlled release must be approached from two angles: delayed release and sustained release. In the first case, this approach includes systems that modify the time or place of release of the active ingredient. They do not increase the potential effect of the active ingredient, but protect it from adverse environments.

In the second case, delivery systems are designed to prolong the release of the active ingredient and, consequently, its potential effect or absorption. This prolongation may also involve improving bioavailability and maintaining nutritional properties (89).

Nanoparticles, microparticles, liposomes and micelles are all examples of sustained-release agents (90). What's more, these systems can be coated with different materials to enable delayed release. Various mechanisms may be involved in the release of active substance encapsulation systems. These include diffusion, dissolution, swelling, degradation/erosion, external forces or various combinations of these mechanisms (91).

A water-soluble active encapsulated in a matrix will mainly be released by diffusion. Conversely, in the case of poorly water-soluble actives, matrix erosion will be the main release mechanism (92).

4.1 Broadcast

This is the most common release mechanism described by Fick's law (Figure 18). In this case, molecules are moved by a concentration gradient from regions of high concentration to regions of low concentration.

In polymer-based encapsulation systems (including reservoir systems, porous-structure matrices), the limiting step is the rate of diffusion of the encapsulated substance (93). The ability to cross the membrane or porous channels depends on the molecule and the medium, with large molecules expected to have lower diffusion than small molecules, while diffusion should be slower in viscous media. Other factors also need to be taken into consideration. The solubility of the active substance. in the polymer system and the geometry in which it is dispersed, also affect the final diffusion pattern. Finally, the rate of release decreased in matrices with a porous structure due to the distance the active ingredient has to travel from the polymer matrix to the barrier of the external environment.

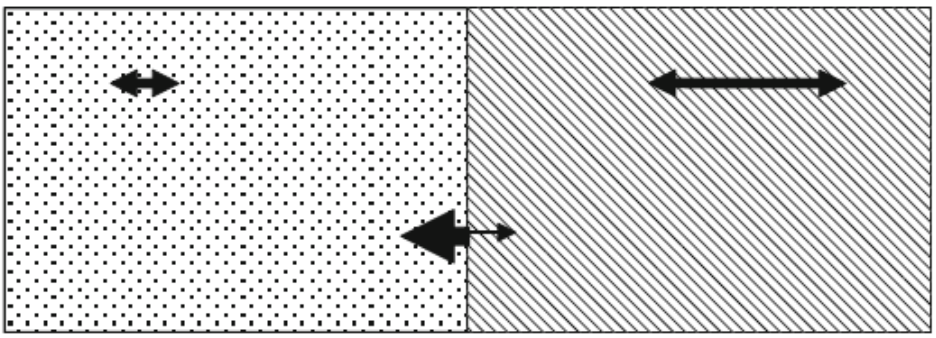

Figure 18 : ***Diffusion mechanism*** *(91)*

Two media are brought into contact. The diffusion coefficient of the active substance. in each medium from the interface is indicated by the length of the corresponding double arrow. At the interface, the active substance chooses to distribute itself in one of the media. The relative frequencies of entry into the two media from the interface are represented by the widths of the arrows pointing to the media. The ratio of the widths of the arrows is the partition coefficient. On entering either medium, the active ingredient diffuses according to the diffusion coefficient of the medium, as shown by the different lengths of the arrows at the interface. In this example, the active substance. diffuses preferentially into the left-hand medium, but diffuses more rapidly into the right-hand medium.

4.2 Dissolution

The rate at which the polymer dissolves in the surrounding environment is the main factor controlling this mechanism. The nature and thickness of the material coating the active substance determines the rate of release, since once the coating is dissolved, the active substance becomes available for dissolution.

The polymers used for these devices are generally water-soluble, but insoluble polymers can also be used. However, the active ingredient may not be exclusively located inside the polymer matrix, but also on the surface (e.g. for a "burst" effect).

In this case, a first stage of dissociation from the surface and solvation with the surrounding medium must take place, followed by a second stage of diffusion from the surface.

When the active ingredient is soluble in the surrounding medium, the first stage occurs more rapidly than the second, forming a concentration gradient. For this reason, some authors suggest that diffusion affects the dissolution mechanism(91).

4.3 Swelling

Swelling is the water absorption process by which the polymer matrix increases in volume. This mechanism may be followed by dissolution of the polymer matrix if it is soluble. If, on the other hand, the polymer matrix is made up of large, cross-linked chains, the matrix remains in place. As the surrounding medium diffuses into the system, the outer layers swell. A point is reached where the mobility of macromolecules increases abruptly (known as polymer chain relaxation or glass transition). This occurs when a specific concentration of the polymer medium is reached, forming a mobile swelling front. In this way, the dissolved active molecules, depending on a concentration gradient, diffuse towards the external medium(94). Other parameters such as temperature, pH... affecting the release of active molecules by swelling-dissolution contribute to the complexity of this mechanism.

4.4 Erosion and degradation

They have been referred to as a combination of mechanisms (the degradation, dissolution and diffusion mechanisms (Figure 19). However, other authors have considered these terms to refer to the process of polymer material loss and subsequent polymer chain cleavage whereby these chains are cleaved into oligomers and monomers, respectively (94).

Two types of erosion process are frequently reported: bulk erosion and surface erosion. Surface erosion depends on the speed with which the releasing medium enters the polymer matrix, as well as its ability to break the bonds between polymer chains. Thus, when the entry of the surrounding medium into the matrix is faster than the scission of the polymer chain, mass erosion occurs. As a result, surface erosion can occur either when medium invasion is slow, or when chain breakage is rapid.

In principle, active substance release is correlated with erosion. Although the idealized mechanisms underlying controlled release by erosion are simply explained, in practice these mechanisms are more complex, as other factors affect release by erosion (e.g. matrix shape, inclusion of erosion activators such as disintegrants..., etc.).

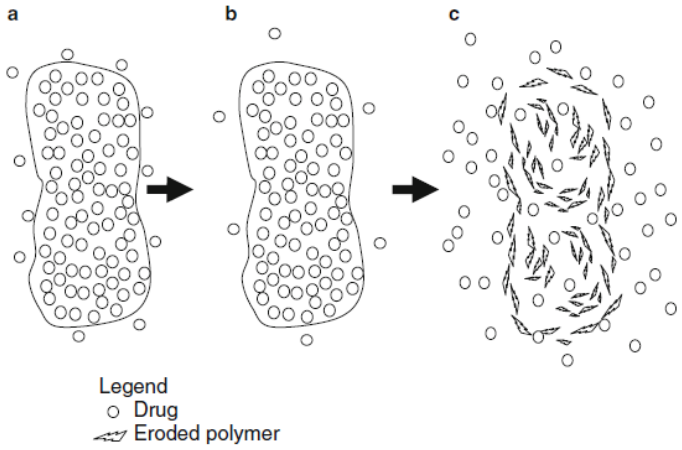

Figure 19 : ***Schematic representation of the three stages of active substance release from polymers*** *(91)*

The first stage (a) corresponds to the active substance being released from the surface of the device or from the pores connected to the surface. A second, latent stage follows, during which there is little polymer degradation and the remaining active substance is trapped (b). In the third stage, the trapped active ingredient is rapidly released as the polymer autocatalytically disintegrates (c).

4.5 External forces

Certain changes in the external environment, such as pH, ionic strength, temperature, humidity, etc, (95–97) can influence drug delivery systems.

4.6 Mathematical modeling

Mathematical modeling of the release process is an important tool for gaining a better idea of the release phenomenon of active substances.

It is used to determine the factors influencing release rate and reduce the number of experimental studies (98). Various mathematical models have been developed, considering swelling, dissolution, erosion/degradation and diffusion processes.

Three kinetic models are frequently used when diffusion is the predominant release step: the zero-order model, the first-order model and the Higuchi model:

$\%Mt / \%M\infty = k.t$ (Zero order) **(1)**

$\%Mt / \%M\infty = 1 - e^{-K.t}$ (First order) **(2)**

$\%Mt / \%M\infty = k.t^{½}$ (Higuchi equation) **(3)**

Where: %Mt is the quantity of active substance released at time t,

$\%R\infty$ is the total quantity of active substance released,

$\%Rt / \%R\infty$ is the fraction of active substance released at time t,

k is a constant linked to the structural and geometric characteristics of the matrix

In certain experimental situations, the release mechanism deviates from the Fick equation, following an anomalous or non-Fickian behavior. In these cases, Peppas (99) used the n value to characterize four types of active substance transport through the matrix. n is the diffusion release exponent that could be used to characterize the different active substance release mechanisms:

$\%Mt / \%M\infty = k.t^n$ *(*Korsmeyer-Peppas equation*)* ***(4)***

Type I transport or Fickian diffusion, when the rate of release is controlled by the diffusion process. **Type II transport,** when bioactive release is controlled by the polymer swelling process. **Abnormal or non-Fickian transport**, when the release rate depends simultaneously on the swelling and diffusion processes.

Super Case II transport, when the release rate is controlled by the polymer erosion/dissolution process under the action of the dissolution medium (100).

Two important parameters need to be taken into account when selecting the appropriate mathematical approach: the geometry of the active substance delivery system and the incorporation of the active substance into this system.Siepmann et *al.,* have shown that in the case of spherical geometries such as nanoparticles (nanospheres/ nanocapsules), microparticles (microspheres/microcapsules), liposomes and micelles, the "n" value indicates the release mechanism. Thus, $n \leq 0.43$, the dominant release mechanism is the Fickian diffusion mechanism (type I transport); $0.43 \leq n < 0.85$ indicates the release mechanism by diffusion and swelling (abnormal or non-Fickian transport) and $n = 0.85$ corresponds to zero-order release kinetics and $n > 0.85$ (super-case II transport). (100).

Conclusion

Encapsulation of plant substances in different formulations has been shown to improve their properties. Encapsulation remains an effective and important tool for preparing high-quality products based on active and health-beneficial plant substances in various industries to improve their chemical properties, and their chemical, oxidative and thermal stability. At the same time, the shelf life, biological activity, functions, properties and bioavailability of the products are improved. The active substances of encapsulated plant origin have been successfully used in various food products, pharmaceuticals, textiles, pesticides… The controlled release of these plant active substances has been made possible in various applications including food, pharmaceutical and cosmetics.

References

1. Bakry AM, Abbas S, Ali B, Majeed H, Abouelwafa MY, Mousa A, et al. Microencapsulation of Oils: A Comprehensive Review of Benefits, Techniques, and Applications. Compr Rev Food Sci Food Saf. 2016;15(1):143-82. DOI: https://doi.org/10.1111/1541-4337.12179

2. Velasco J, Dobarganes C, Márquez-Ruiz G. Variables affecting lipid oxidation in dried microencapsulated oils. Grasas Aceites. 30 sept 2003;54(3):304-14. DOI : https://doi.org/10.3989/gya.2003.v54.i3.246

3. Ajazuddin, Saraf S. Applications of novel drug delivery system for herbal formulations. Fitoterapia. 1 oct 2010;81(7):680-9. DOI: https://doi.org/10.1016/j.fitote.2010.05.001

4. Devi VK, Jain N, Valli KS. Importance of novel drug delivery systems in herbal medicines. Pharmacogn Rev. janv 2010;4(7):27-31.DOI: https://doi.org/10.4103/0973-7847.65322

5. Martins E, Poncelet D, Rodrigues RC, Renard D. Oil encapsulation techniques using alginate as encapsulating agent: applications and drawbacks. J Microencapsul. déc 2017;34(8):754-71. DOI: https://doi.org/10.1080/02652048.2017.1403495

6. Ruiz Ruiz JC, Ortiz Vazquez EDLL, Segura Campos MR. Encapsulation of vegetable oils as source of omega-3 fatty acids for enriched functional foods. Crit Rev Food Sci Nutr. 3 mai 2017;57(7):1423-34. DOI: https://doi.org/10.1080/10408398.2014.1002906

7. Sagiri SS, Anis A, Pal K. Review on Encapsulation of Vegetable Oils: Strategies, Preparation Methods, and Applications. Polym-Plast Technol Eng. 11 févr 2016;55(3):291-311. DOI: http://dx.doi.org/10.1080/03602559.2015.1050521

8. Wakil A, Mackenzie G, Diego-Taboada A, Bell JG, Atkin SL. Enhanced bioavailability of eicosapentaenoic acid from fish oil after encapsulation within plant spore exines as microcapsules. Lipids. juill 2010;45(7):645-9. DOI: https://doi.org/10.1007/s11745-010-3427-y

9. Calvo P, Castaño ÁL, Hernández MT, González-Gómez D. Effects of microcapsule constitution on the quality of microencapsulated walnut oil. Eur J Lipid Sci Technol. 2011;113(10):1273-80. DOI: http://dx.doi.org/10.1002/ejlt.201100039

10. Gharsallaoui A, Roudaut G, Chambin O, Voilley A, Saurel R. Applications of spray-drying in microencapsulation of food ingredients: An overview. Food Res Int. 1 nov 2007;40(9):1107-21. DOI: https://doi.org/10.1016/j.foodres.2007.07.004

11. Fang Z, Bhandari B. Encapsulation of polyphenols – a review. Trends Food Sci Technol. 1 oct 2010;21(10):510-23.DOI: https://doi.org/10.1016/j.tifs.2010.08.003

12. Richard J, Benoît JP. Microencapsulation. In: Techniques de l'Ingénieur Génie des procédés, [Internet]. 2000 [cité 31 mai 2023]. p. 1-20. Disponible sur: https://www.techniques-ingenieur.fr/base-documentaire/archives-th12/archives-formulation-tiajc/archive-1/microencapsulation-j2210/

13. Poncelet D, Dreffier C. Les méthodes de microencapsulation de A Z (ou presque). Microencapsul Sci Aux Technol. 1 janv 2007;23-33.

14. Chaturvedi M, Kumar M, Sinhal A, Saifi A. Recent development in novel drug delivery systems of herbal drugs. Int J Green Pharm IJGP [Internet]. 2011 [cité 31 mai 2023];5(2). Disponible sur: https://www.greenpharmacy.info/index.php/ijgp/article/view/182

15. Dhiman A, Nanda A, Ahmad S. Novel herbal drug delivery system (NHDDS): the need of hour. Int Proc Chem Biol Environ Eng IPCBEE. 2012;49:171-5.

16. Kulkarni G. HERBAL DRUG DELIVERY SYSTEMS: AN EMERGING AREA IN HERBAL DRUG RESEARCH. In 2011 [cité 31 mai 2023]. Disponible sur: https://www.semanticscholar.org/paper/HERBAL-DRUG-DELIVERY-SYSTEMS%3A-AN-EMERGING-AREA-IN-Kulkarni/9d2003647347dd84997489817e76fbf712764c8c

17. Sarangi MK, Padhi, S. Novel Herbal Drug Delivery System: An Overview : Archives of Medicine and Health Sciences. 2018;6(1):171.DOI: http://dx.doi.org/10.4103/amhs.amhs_88_17

18. Chan ES, Yim ZH, Phan SH, Mansa RF, Ravindra P. Encapsulation of herbal aqueous extract through absorption with ca-alginate hydrogel beads. Food Bioprod Process. juin 2010;88(2-3):195-201. DOI: http://dx.doi.org/10.1016/j.fbp.2009.09.005

19. Chao P, Deshmukh M, Kutscher HL, Gao D, Sundara Rajan S, Hu P, et al. Pulmonary targeting microparticulate camptothecin delivery system: anti-cancer evaluation in a rat orthotopic lung cancer model. Anticancer Drugs. janv 2010;21(1):10.1097/CAD.0b013e328332a322.

20. Garg R, Gupta GD. Gastroretentive Floating Microspheres of Silymarin: Preparation and In Vitro Evaluation. Trop J Pharm Res [Internet]. 2010 [cité 20 mai 2023];9(1). Disponible sur: https://www.ajol.info/index.php/tjpr/article/view/52037

21. You J, Cui F de, Han X, Wang Y sheng, Yang L, Yu Y wei, et al. Study of the preparation of sustained-release microspheres containing zedoary turmeric oil by the emulsion-solvent-diffusion method and evaluation of the self-emulsification and bioavailability of the oil. Colloids Surf B Biointerfaces. 1 mars 2006;48(1):35-41.DOI: https://doi.org/10.1016/J.COLSURFB.2005.12.011

22. Xiao L, Zhang Y, Xu J, Jin X. Preparation of floating rutin-alginate-chitosan microcapsule. Chin Tradit Herb Drugs [Internet]. 1994 [cité 22 nov 2023]; Disponible sur:

23. Natarajan V, Krithica N, Madhan B, Sehgal PK. Formulation and evaluation of quercetin polycaprolactone microspheres for the treatment of rheumatoid arthritis. J Pharm Sci. janv 2011;100(1):195-205.DOI: https://doi.org/10.1002/jps.22266

24. Gavini E, Alamanni MC, Cossu M, Giunchedi P. Tabletted microspheres containing Cynara scolymus (var. Spinoso sardo) extract for the preparation of controlled release nutraceutical matrices. J Microencapsul. août 2005;22(5):487-99.DOI: https://doi.org/10.1080/02652040500099919

25. Engel RH, Riggi SJ, Fahrenbach MJ. Insulin: Intestinal Absorption as Water-in-Oil-in-Water Emulsions. Nature. août 1968;219(5156):856-7.DOI: https://doi.org/10.1038/219856a0

26. Jiao J, Rhodes DG, Burgess DJ. Multiple emulsion stability: pressure balance and interfacial film strength. J Colloid Interface Sci. 15 juin 2002;250(2):444-50. DOI: https://doi.org/10.1006/jcis.2002.8365

27. Dams SS, Walker IM. [5] Multiple emulsions as targetable delivery systems. In: Methods in Enzymology [Internet]. Academic Press; 1987 [cité 1 juin 2023]. p. 51-64. (Drug and Enzyme Targeting Part B; vol. 149). Disponible sur: https://www.sciencedirect.com/science/article/pii/0076687987490435

28. Lee GS, Lee DH, Pyo HB. Preparation and characterization of encapsulation of multiple lipid carrier (MLC) using vegetable fat. J Ind Eng Chem. 25 mai 2011;17(3):421-6. DOI:http://dx.doi.org/10.1016/j.jiec.2011.05.017

29. Cournarie F, Savelli MP, Rosilio V, Bretez F, Vauthier C, Grossiord JL, et al. Insulin-loaded W/O/W multiple emulsions: comparison of the performances of systems prepared with medium-chain-triglycerides and fish oil. Eur J Pharm Biopharm Off J Arbeitsgemeinschaft Pharm Verfahrenstechnik EV. nov 2004;58(3):477-82.

30. Kita Y, Matsumoto S, Yonezawa D. Viscometric method for estimating the stability of W/O/W-type multiple-phase emulsions. J Colloid Interface Sci. 15 oct 1977;62(1):87-94. DOI: https://doi.org/10.1016/0021-9797(77)90068-6

31. Morais JM, Rocha-Filho PA, Burgess DJ. Relationship between rheological properties and one-step W/O/W multiple emulsion formation. Langmuir ACS J Surf Colloids. 7 déc 2010;26(23):17874-81. DOI: https://doi.org/10.1021/la103358n

32. Rajesh K, Murugesan SK, Nanjaian M. Multiple Emulsions: A Review. Scribd. 2012;2(1):9-19.

33. Can Karaca A, Low N, Nickerson M. Encapsulation of Flaxseed Oil Using a Benchtop Spray Dryer for Legume Protein–Maltodextrin Microcapsule Preparation. J Agric Food Chem. 29 mai 2013;61(21):5148-55. https://doi.org/10.1021/jf400787j

34. Durante M, Lenucci MS, Laddomada B, Mita G, Caretto S. Effects of sodium alginate bead encapsulation on the storage stability of durum wheat (Triticum durum Desf.) bran oil extracted by supercritical CO2. J Agric Food Chem. 24 oct 2012;60(42):10689-95. DOI:https://doi.org/10.1021/jf303162m

35. Rubilar M, Morales E, Contreras K, Ceballos C, Acevedo F, Villarroel M, et al. Development of a soup powder enriched with microencapsulated linseed oil as a source of omega-3 fatty acids. Eur J Lipid Sci Technol. 2012;114(4):423-33.DOI: https://doi.org/10.1002/ejlt.201100378

36. Gomes MTMS, Santos DT, Meireles M a. A. Trends in particle formation of bioactive compounds using supercritical fluids and nanoemulsions. Food Public Health. 2012;2(5):142-52. doi: 10.5923/j.fph.20120205.05

37. Li X, Anton N, Ta TMC, Zhao M, Messaddeq N, Vandamme TF. Microencapsulation of nanoemulsions: novel Trojan particles for bioactive lipid molecule delivery. Int J Nanomedicine. 2011;6:1313-25.DOI: https://doi.org/10.2147/ijn.s20353

38. Hernandez E. Structured lipids as delivery systems. In: Delivery and Controlled Release of Bioactives in Foods and Nutraceuticals. 2008. p. 135-48.

39. Martins E, Poncelet D, Renard D. A novel method of oil encapsulation in core-shell alginate microcapsules by dispersion-inverse gelation technique. React Funct Polym. mai 2017;114:49-57. DOI: http://dx.doi.org/10.1016/j.reactfunctpolym.2017.03.006

40. Martins E, Renard D, Adiwijaya Z, Karaoglan E, Poncelet D. Oil encapsulation in core-shell alginate capsules by inverse gelation. I: dripping methodology. J Microencapsul. févr 2017;34(1):82-90. DOI: https://doi.org/10.1080/02652048.2017.1284278

41. Martins E, Renard D, Davy J, Marquis M, Poncelet D. Oil core microcapsules by inverse gelation technique. J Microencapsul. 2015;32(1):86-95.DOI: https://doi.org/10.3109/02652048.2014.985342

42. Hom FS, Veresh SA, Ebert WR. Soft Gelatin Capsules II: Oxygen Permeability Study of Capsule Shells. J Pharm Sci. 1 mai 1975;64(5):851-7.DOI: https://doi.org/10.1002/jps.2600640528

43. Liu S, Low NH, Nickerson MT. Entrapment of Flaxseed Oil Within Gelatin-Gum Arabic Capsules. J Am Oil Chem Soc. 2010;87(7):809-15.DOI: http://dx.doi.org/10.1007/s11746-010-1560-7

44. Lidert Z. Microencapsulation: an overview of the technology landscape. Dans R.R. Meyer (dirs). Delivery System Handbook for Personal Care and Cosmetic Products [Internet]. Meyer Rosen. 2005 [cité 23 nov 2023]. 181-190 p. Disponible sur: https://shop.elsevier.com/books/delivery-system-handbook-for-personal-care-and-cosmetic-products/rosen/978-0-8155-1504-3

45. Vasisht N. Chapter 2 - Factors and Mechanisms in Microencapsulation. In: Gaonkar AG, Vasisht N, Khare AR, Sobel R, éditeurs. Microencapsulation in the Food Industry [Internet]. San Diego: Academic Press; 2014 [cité 23 nov 2023]. p. 15-24. Disponible sur: https://www.sciencedirect.com/science/article/pii/B9780124045682000029

46. Bilia AR, Guccione C, Isacchi B, Righeschi C, Firenzuoli F, Bergonzi MC. Essential oils loaded in nanosystems: a developing strategy for a successful therapeutic approach. Evid-Based Complement Altern Med ECAM. 2014;2014:651593.DOI: https://doi.org/10.1155/2014/651593

47. Nimesh S, Gupta N. Perspectives and Challenges of Nanomedicine in Gene Silencing. Pharm Technol. 2 mars 2014;38(3):30-5.

48. Müller RH, Radtke M, Wissing SA. Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) in cosmetic and dermatological preparations. Adv Drug Deliv Rev. 1 nov 2002;54 Suppl 1:S131-155.DOI: https://doi.org/10.1016/s0169-409x(02)00118-7

49. McClements DJ, Decker EA, Park Y, Weiss J. Structural design principles for delivery of bioactive components in nutraceuticals and functional foods. Crit Rev Food Sci Nutr. juin 2009;49(6):577-606. DOI:https://doi.org/10.1080/10408390902841529

50. Roccia P, Martínez ML, Llabot JM, Ribotta PD. Influence of spray-drying operating conditions on sunflower oil powder qualities. Powder Technol. mars 2014;254:307-13. DOI: http://dx.doi.org/10.1016/j.powtec.2014.01.044

51. Zuidam NJ, Shimoni E. Overview of Microencapsulates for Use in Food Products or Processes and Methods to Make Them. In: Zuidam NJ, Nedovic V, éditeurs. New York, NY: Springer New York; 2010 [cité 11 déc 2023]. p. 3-29. Disponible sur: http://link.springer.com/10.1007/978-1-4419-1008-0_2

52. Gallo L, Llabot JM, Allemandi D, Bucalá V, Piña J. Influence of spray-drying operating conditions on Rhamnus purshiana (Cáscara sagrada) extract powder physical properties. Powder Technol. 10 mars 2011;208(1):205-14.DOI: http://dx.doi.org/10.1016/j.powtec.2010.12.021

53. Carneiro HCF, Tonon RV, Grosso CRF, Hubinger MD. Encapsulation efficiency and oxidative stability of flaxseed oil microencapsulated by spray drying using different combinations of wall materials. J Food Eng. avr 2013;115(4):443-51 DOI: http://dx.doi.org/10.1016/j.jfoodeng.2012.03.033

54. Heinzelmann K, Franke K, Jensen B, Haahr AM. Protection of fish oil from oxidation by microencapsulation using freeze-drying techniques. Eur J Lipid Sci Technol. 2000;102(2):114-21. DOI: http://dx.doi.org/10.1002/(SICI)1438-9312(200002)102:2%3C114::AID-EJLT114%3E3.0.CO;2-0

55. Heinzelmann K, Franke K, Velasco J, Marquez-Ruiz G. Microencapsulation of fish oil by freeze-drying techniques and influence of process parameters on oxidative stability during storage. Eur Food Res Technol Z Lebensm-Unters -Forsch A. 1 janv 2000;211(4):234-9.

56. Oetjen Freeze-drying (2nd ed). Wiley-VCH Verlag Gmbh & Co. KGaA. - Recherche Google [Internet]. [cité 11 déc 2023]. Disponible sur: https://www.google.com/search?q=Oetjen+Freeze-drying+%282nd+ed%29.+Wiley-VCH+Verlag+Gmbh+%26+Co.+KGaA.&client=firefox-b-d&sca_esv=589766361&ei=m_t2ZbLXK-CTkdUPlM6miA0&ved=0ahUKEwjykPPFrIeDAxXgSaQEHRSnCdEQ4dUDCBA&uact=5&oq=Oetjen+Freeze-drying+%282nd+ed%29.+Wiley-VCH+Verlag+Gmbh+%26+Co.+KGaA.&gs_lp=Egxnd3Mtd2l6LXNlcnAiQE9ldGplbiBGcmVlemUtZHJ5aW5nICgybmQgZWQpLiBXaWxleS1WQ0ggVmVybGFnIEdtYmggJiBDby4gS0dhQS5IAFAAWABwAHgAkAEAmAEAoAEAqgEAuAEDyAEA-AEB4gMEGAAgQQ&sclient=gws-wiz-serp

57. Krokida MK, Philippopoulos C. Volatility of apples during air and freeze drying. J Food Eng. 1 mars 2006;73(2):135-41.DOI: http://dx.doi.org/10.1016/j.jfoodeng.2005.01.012

58. Desobry SA, Netto FM, Labuza TP. Comparison of Spray-drying, Drum-drying and Freeze-drying for β-Carotene Encapsulation and Preservation. J Food Sci. 1997;62(6):1158-62. DOI: https://doi.org/10.1111/j.1365-2621.1997.tb12235.x

59. Sinha VR, Agrawal MK, Kumria R, Bhinge JR. Influence of operational variables on properties of piroxicam pellets prepared by extrusion-spheronization: A technical note. AAPS PharmSciTech. mars 2007;8(1):E137-41.DOI: https://doi.org/10.1208/pt0801020

60. Maji TK, Baruah I, Dube S, Hussain MR. Microencapsulation of Zanthoxylum limonella oil (ZLO) in glutaraldehyde crosslinked gelatin for mosquito repellent application. Bioresour Technol. mars 2007;98(4):840-4.DOI: https://doi.org/10.1016/j.biortech.2006.03.005

61. Latha MS, Rathinam K, Mohanan PV, Jayakrishnan A. Bioavailability of theophylline from glutaraldehyde cross-linked casein microspheres in rabbits following oral administration. J Controlled Release. 1 avr 1995;34(1):1-7.DOI: http://dx.doi.org/10.1080/02652040110105391

62. Lazko J, Popineau Y, Legrand J. Soy glycinin microcapsules by simple coacervation method. Colloids Surf B Biointerfaces. 15 août 2004;37(1-2):1-8.DOI: https://doi.org/10.1016/j.colsurfb.2004.06.004

63. Mauguet MC, Legrand J, Brujes L, Carnelle G, Larre C, Popineau Y. Gliadin matrices for microencapsulation processes by simple coacervation method. J Microencapsul. 2002;19(3):377-84. DOI: https://doi.org/10.1080/02652040110105346

64. Mohanty B, Bohidar HB. Systematic of Alcohol-Induced Simple Coacervation in Aqueous Gelatin Solutions. Biomacromolecules. 1 juill 2003;4(4):1080-6.DOI: https://doi.org/10.1021/bm034080l

65. Prabaharan M, Mano JF. Chitosan-based particles as controlled drug delivery systems. Drug Deliv. 2005;12(1):41-57.DOI: https://doi.org/10.1080/10717540590889781

66. Rivier M, Méot JM, Ferré T, Briard M. Le séchage des mangues [Internet]. éditions Quae; 2009 [cité 6 mai 2023]. Disponible sur: https://www.quae-open.com/product/11/9782759203420/le-sechage-des-mangues

67. Weiβ G, Knoch A, Laicher A, Stanislaus F, Daniels R. Simple coacervation of hydroxypropyl methylcellulose phthalate (HPMCP) II. Microencapsulation of ibuprofen. Int J Pharm. 19 sept 1995;124(1):97-105.DOI: https://doi.org/10.1016/0378-5173(95)00084-V

68. Wu KG, Xiao Q. Microencapsulation of Fish Oil by Simple Coacervation of Hydroxypropyl Methylcellulose. Chin J Chem. 2005;23(11):1569-72.DOI: https://doi.org/10.1002/CJOC.200591569

69. Burgess DJ, Carless JE. Microelectrophoretic studies of gelatin and acacia for the prediction of complex coacervation. J Colloid Interface Sci. 1 mars 1984;98(1):1-8.

70. F W, R de V, P S, Cg de K. Complex coacervation of whey proteins and gum arabic. Biomacromolecules [Internet]. avr 2003 [cité 23 mai 2023];4(2). Disponible sur: https://pubmed.ncbi.nlm.nih.gov/12625724/

71. Saravanan M, Rao KP. Pectin–gelatin and alginate–gelatin complex coacervation for controlled drug delivery: Influence of anionic polysaccharides and drugs being encapsulated on physicochemical properties of microcapsules. Carbohydr Polym. 2010;3(80):808-16. DOI: http://dx.doi.org/10.1016/j.carbpol.2009.12.036

72. Singh ON, Burgess J. Characterization of albumin-alginic acid complex coacervation. J Pharm Pharmacol. oct 1989;41(10):670-3.DOI https://doi.org/10.1111/j.2042-7158.1989.tb06338.x

73. Thimma RT, Tammishetti S. Study of complex coacervation of gelatin with sodium carboxymethyl guar gum: microencapsulation of clove oil and sulphamethoxazole. J Microencapsul. 2003;20(2):203-10.DOI: http://dx.doi.org/10.1080/00914037.2011.553851

74. Tsung M, Burgess DJ. Preparation and stabilization of heparin/gelatin complex coacervate microcapsules. J Pharm Sci. mai 1997;86(5):603-7. DOI: https://doi.org/10.1021/js9603257

75. Schmitt C, Sanchez C, Thomas F, Hardy J. Complex coacervation between β-lactoglobulin and acacia gum in aqueous medium. Food Hydrocoll. 1 nov 1999;13(6):483-96.DOI https://doi.org/10.1016/S0268-005X(99)00032-6

76. Hwang DS, Waite JH, Tirrell M. Promotion of osteoblast proliferation on complex coacervation-based hyaluronic acid - recombinant mussel adhesive protein coatings on titanium. Biomaterials. févr 2010;31(6):1080-4.DOI: https://doi.org/10.1016/j.biomaterials.2009.10.041

77. Jyothi NVN, Prasanna PM, Sakarkar SN, Prabha KS, Ramaiah PS, Srawan GY. Microencapsulation techniques, factors influencing encapsulation efficiency. J Microencapsul. mai 2010;27(3):187-97. DOI: https://doi.org/10.3109/02652040903131301

78. Yang YY, Chung TS, Ng NP. Morphology, drug distribution, and in vitro release profiles of biodegradable polymeric microspheres containing protein fabricated by double-emulsion solvent extraction/evaporation method. Biomaterials. févr 2001;22(3):231-41.DOI: https://doi.org/10.1016/s0142-9612(00)00178-2

79. Tiwari S, Verma P. Microencapsulation technique by solvent evaporation method (Study of effect of process variables | [Internet]. [cité 11 déc 2023]. Disponible sur: https://www.academia.edu/43594980/Microencapsulation_technique_by_solvent_evaporation_method_Study_of_effect_of_process_variables

80. Yuliani S, Torley P, D'Arcy B, Nicholson T, Bhandari B. Extrusion of mixtures of starch and D-limonene encapsulated with B-cyclodextrin: Flavour retention and physical properties. Food Res Int. 2006;39(3):318-31.DOI: http://dx.doi.org/10.1016/j.foodres.2005.08.005

81. Zhang L, Huang J, Si T, Xu RX. Coaxial electrospray of microparticles and nanoparticles for biomedical applications. Expert Rev Med Devices. nov 2012;9(6):595-612. DOI: https://doi.org/10.1586/erd.12.58

82. Xie J, Ng WJ, Lee LY, Wang CH. Encapsulation of protein drugs in biodegradable microparticles by co-axial electrospray. J Colloid Interface Sci. 15 janv 2008;317(2):469-76. DOI: https://doi.org/10.1016/j.jcis.2007.09.082

83. Xi J, Zhang Q, Myers D, Sun Y, Cao G. Hollow hemispherical titanium dioxide aggregates fabricated by coaxial electrospray for dye-sensitized solar cell application. J Nanophotonics. 1 janv 2012;6:063519.

84. Loscertales IG, Barrero A, Guerrero I, Cortijo R, Marquez M, Gañán-Calvo AM. Micro/nano encapsulation via electrified coaxial liquid jets. Science. 1 mars 2002;295(5560):1695-8. DOI: https://doi.org/10.1126/science.1067595

85. Almeida AP, Rodríguez-Rojo S, Serra AT, Vila-Real H, Simplicio AL, Delgadilho I, et al. Microencapsulation of oregano essential oil in starch-based materials using supercritical fluid technology. Innov Food Sci Emerg Technol. 1 oct 2013;20:140-5. DOI: http://dx.doi.org/10.1016/j.ifset.2013.07.009

86. Parhi R, Suresh P. Supercritical Fluid Technology: A Review. J Adv Pharm Sci Technol. 30 janv 2013;1(1):13-36.

87. Hwang JS, Kim JN, Wee YJ, Yun JS, Jang HG, Kim SH, et al. Preparation and characterization of melamine-formaldehyde resin microcapsules containing fragrant oil. Biotechnol Bioprocess Eng. 1 août 2006;11(4):332-6.DOI: http://dx.doi.org/10.1007/BF03026249

88. Poncelet ET D. Fluid-Bed Coating. In: Encapsulated and Powdered Foods. CRC Press; 2005.

89. Dima C, Pătraşcu L, Cantaragiu A, Alexe P, Dima Ş. The kinetics of the swelling process and the release mechanisms of Coriandrum sativum L. essential oil from chitosan/alginate/inulin microcapsules. Food Chem. 15 mars 2016;195:39-48. DOI: https://doi.org/10.1016/j.foodchem.2015.05.044

90. Ye Q, Asherman J, Stevenson M, Brownson E, Katre NV. DepoFoam technology: a vehicle for controlled delivery of protein and peptide drugs. J Control Release Off J Control Release Soc. 14 févr 2000;64(1-3):155-66.DOI: https://doi.org/10.1016/s0168-3659(99)00146-7

91. Siegel RA, Rathbone MJ. Overview of controlled release mechanisms. In: Fundamentals and Applications of Controlled Release Drug Delivery [Internet]. Springer US; 2012 [cité 23 mai 2023]. p. 19-43. Disponible sur: http://www.scopus.com/inward/record.url?scp=84975838730&partnerID=8YFLogxK

92. Costa P, Sousa Lobo JM. Modeling and comparison of dissolution profiles. Eur J Pharm Sci Off J Eur Fed Pharm Sci. mai 2001;13(2):123-33.DOI: https://doi.org/10.1016/s0928-0987(01)00095-1

93. Huang X, Brazel CS. On the importance and mechanisms of burst release in matrix-controlled drug delivery systems. J Control Release Off J Control Release Soc. 15 juin 2001;73(2-3):121-36. DOI: https://doi.org/10.1016/s0168-3659(01)00248-6

94. Siepmann J, Göpferich A. Mathematical modeling of bioerodible, polymeric drug delivery systems. Adv Drug Deliv Rev. 11 juin 2001;48(2-3):229-47.DOI: https://doi.org/10.1016/s0169-409x(01)00116-8

95. Averina E, Allémann E. Encapsulation of alimentary bioactive oils of the Baikal Lake area into pH-sensitive micro- and nanoparticles. Lebensm-Wiss Ie Technol [Internet]. 2013 [cité 23 mai 2023]; Disponible sur: http://dx.doi.org/10.1016/j.lwt.2013.01.020

96. McClements DJ, Li Y. Structured emulsion-based delivery systems: controlling the digestion and release of lipophilic food components. Adv Colloid Interface Sci. 15 sept 2010;159(2):213-28. DOI: https://doi.org/10.1016/j.cis.2010.06.010

97. Ayala-Zavala JF, Soto-Valdez H, González-León A, Álvarez-Parrilla E, Martín-Belloso O, González-Aguilar GA. Microencapsulation of cinnamon leaf (Cinnamomum zeylanicum) and garlic (Allium sativum) oils in β-cyclodextrin. J Incl Phenom Macrocycl Chem. 2008;3-4(60):359-68. DOI: http://dx.doi.org/10.1007%2Fs10847-007-9385-1

98. Siepmann J, Siepmann F. Modeling of diffusion controlled drug delivery. J Control Release Off J Control Release Soc. 20 juill 2012;161(2):351-62.DOI: https://doi.org/10.1016/j.jconrel.2011.10.006

99. Peppas NA. Analysis of Fickian and non-Fickian drug release from polymers. Pharm Acta Helv. 1985;60(4):110-1.

100. Siepmann J, Peppas NA. Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). Adv Drug Deliv Rev. 11 juin 2001;48(2-3):139-57. DOI: https://doi.org/10.1016/s0169-409x(01)00112-0