# CHAPTER 1
# Introduction

Jamileh M. Lakkis

Encapsulation and controlled-release systems are designed to protect actives from undergoing undesirable interactions while enhancing their functionality and bioavailability. Other objectives include masking the taste of bitter components, ensuring adequate administration of heat- or oxidation-labile health actives, and ensuring their delivery at a predetermined rate to a target site. In foods and nutraceuticals, encapsulation and controlled release have found applications in many categories such as confections, bakery, breakfast cereals, dairy products, beverages, packaging, among others. Markets and Markets Research estimated the value of food-related encapsulation market to reach $39.5 billion by 2020 (http://www.marketsandmarkets.com).

European Directive 3AQ19a defined *controlled release* as a "modification of the rate or place at which an active substance is released." Such modification can be made using materials with specific barrier properties for manipulating the release of the active and to provide unique sensory and/or functional benefits.

The addition of small amounts of nutrients to a food system may not affect its appearance and taste significantly; however, incorporating high levels of nutrients to meet certain requirements or treat an ailment will most often result in unstable and unpalatable foods. Examples of such nutrients include fortification with calcium, vitamins, or polyunsaturated fatty acids, which often results in undesirable sensory changes such as grittiness, medicinal or oxidized taste, and others. Different types of encapsulation and controlled-release systems are currently available to help overcome these challenges and to provide a wide range of release requirements.

A wide variety of cores (encapsulants), wall-forming materials (encapsulating agents), and technologies are commercially available for manufacturing microcapsules and microparticles of different sizes, shapes, morphological properties, and costs, as well as controlling the release of the encapsulated actives.



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## Wall-forming materials

Materials used in microencapsulation as film coating or matrix-forming components include several categories:

1. Lipids and waxes: beeswax, candelilla and carnauba waxes, wax microemulsions and macroemulsions, glycerol distearate, and natural and modified fats
2. Proteins: gelatins, whey proteins, zein, soy proteins, caseins and caseinates, gluten, etc. All these proteins are available in both native and modified forms.
3. Carbohydrates: starches, maltodextrins, chitosan, sucrose, glucose, ethylcellulose, cellulose acetate, alginates, carrageenans, chitosan, etc.
4. Food-grade polymers: polypropylene, polyvinylacetate, polystyrene, polybutadiene, etc.

## Core materials

These materials include flavors, antimicrobial agents, vitamins, minerals, antioxidants, probiotics, colors, acidulants, alkalis, buffers, sweeteners, enzymes, cross-linking agents, yeasts and chemical leavening agents, omega-3 fatty acids, and other nutrients.

## Release triggers

Encapsulation and controlled-release systems can be designed to respond to one or a combination of triggers that can activate the release of the entrapped substance and to meet a desired release target or rate. Triggers can be one or a combination of the following:

1. Temperature: ideally for release of actives from fat/wax matrices, gelatin, and other meltable polymers
2. Moisture: essential for releasing actives entrapped in hydrophilic matrices
3. pH: can release actives from enteric-coated particulates or emulsions (coalescence)
4. Enzymes: can release actives from enteric-coated particulates due to disintegration of the wall material with amylases, proteases, lipases, etc.
5. Shear: chewing, physical fracture, and grinding represent physical means for release of actives during actual consumption
6. Lower critical solution temperature: release takes place at a critical temperature below which the components of a mixture are miscible for all compositions (often encountered in phase diagrams).

## Payload

*Payload* is a term used to estimate the amount of active (core) entrapped in a given matrix or wall material (shell) and is expressed as:

$$\text{Payload } (\%) = [(\text{core})/(\text{core} + \text{shell})] \times 100$$

## Current approaches to encapsulation and controlled release

### Entrapment in carbohydrate matrices

Encapsulation into a carbohydrate matrix generally involves melting a crystalline polymer using heat and/or shear to transform the molecular structure into an amorphous phase. The encapsulant is then incorporated into the meta-stable amorphous phase followed by cooling to solidify the structure and form glass, thus restricting molecular movements.

Carbohydrates are excellent candidates for this type of encapsulation due to several attributes; they (1) form an integral part of many food systems, (2) are cost-effective, (3) occur in a wide range of polymer sizes, and (4) have desirable physicochemical properties such as solubility, melting, phase change, etc.

Sucrose, maltodextrins, native and modified starches, polysaccharides, and gums have been used for encapsulating flavors, minerals, vitamins, probiotic bacteria, as well as pharmaceutical actives. The unique helical structure of the amylose molecule, for example, makes starch a very efficient vehicle for encapsulating lipids and flavors (Conde-Petit et al., 2006). Some carbohydrates such as inulin and trehalose can provide additional benefits for encapsulation applications; inulin is a prebiotic that can enhance the survival of probiotic bacteria, while trehalose serves as support nutrient for yeasts.

Two main technologies—spray-drying and extrusion—are commonly used in large-scale encapsulation applications into amorphous matrices, although different mechanisms are used. In spray-drying, the active is entrapped within the porous membranes of hollow spheres, while in extrusion, the goal is to entrap the active in a dense, impermeable glass.

Encapsulating actives via spray-drying requires emulsifying the substrate into the encapsulating agent. This is especially important for flavor applications, considering the fact that most flavors are made of components of various chemistries (e.g., polarity, hydrophobic-to-hydrophilic ratios), thus limiting their stability when dispersed or suspended in different solvents. Hydrophobicity is one of the most critical attributes that can play a significant role in determining flavors payload as well as their release in food systems.

The basic principle of spray-drying can be found in an excellent book by Masters (1979). Briefly, the process comprises atomizing a micronized (1- to 10-μm droplet size) emulsion or suspension of an active and an encapsulating substance(s) and further spraying into a chamber. Drying takes place at relatively high temperatures (210 $^{o}$C inlet and 90 $^{o}$C outlet), although the active's exposure to these temperatures lasts only few seconds. The process results in free flowing, low bulk density powders of 10 to 100 μm. Optimal payloads of 20% can be expected for flavors encapsulated in starch matrices. Maltodextrins and lower molecular weight sugars, due to their low viscosities and inadequate emulsifying activities, often lead to lower flavor payloads.

Several factors can impact the efficiency of encapsulation via spray-drying, —mainly, those related to the emulsion or dispersion (e.g., solid content, molecular weight, emulsion droplet size, viscosity) and to the process (e.g., feed flow rate, inlet/outlet temperatures, gas velocity). Release of flavors from spray-dried matrices

takes place on reconstitution of the dried emulsion in the release medium (water or saliva). Reasonable prediction of the release behavior should take into consideration the complex chemistry of flavors and prevailing partition and phase transport mechanisms between aqueous and nonaqueous phases (Larbouss et al., 1992; Shimada et al, 1991).

Encapsulation into an amorphous matrix via extrusion has gained wide popularity in the past two decades with applications ranging from entrapping flavors for their controlled release to masking the grittiness of minerals and vitamins. Hot melt extrusion is a process with many unique advantages for encapsulation applications, namely:

1. Extruders are multifunctional systems (many unit operations) that can be manipulated to provide desired processing temperature and shear rate profiles by varying screw design, barrel heating, mixing speed, feed rate, moisture content, plasticizers, etc.
2. There is the possibility of incorporating actives and other ingredients at different points of the extrusion process. Heat-labile actives, for example, can be incorporated via temperature-controlled inlets toward the end of the barrel, and their residence time in the extruder can be minimized to avoid degradation of the active and preserve its integrity.
3. Extruders are also formers; encapsulated products can be recovered in practically any desired shape or size (pellets, rods, ropes, etc.).
4. Only a very limited amount of water is needed to transform carbohydrates from native crystalline to amorphous glassy matrices in an extruder, thus limiting the need for expensive downstream drying.
5. High payload can exceed 30% when encapsulating solid actives in extruded pellets.
6. Favorable economics due to the high throughput, continuous mode, and limited need for drying make extrusion a very attractive process for manufacturing encapsulated ingredients.

Figure 1.1 shows a typical melt extrusion encapsulation process. The carbohydrate (encapsulating matrix), a mixture of sucrose and maltodextrin, is dry fed and melted via a combination of heat and shear in the extruder barrel so that the crystalline structure is transformed into an amorphous phase. The encapsulant (flavor or other active) is added through an opening in a cooled barrel situated toward the die end of the barrel to avoid flashing off of low boiling components. The amorphous mixture exits the die in the form of a rope that can be cooled quickly by air or liquid nitrogen to form a solid glassy material. The latter can be ground to a desired particle size to form compact microparticles of high bulk density. Using this technology, encapsulated products can be designed to achieve almost any desired target glass transition temperature by incorporating plasticizers (reduce $T_g$) or high molecular weight polymers (increase $T_g$).

It should be cautioned, however, that although glass transition (and therefore microcapsule stability) is clearly related to the material properties of the matrix and rates of crystallization, there is growing evidence that in the glass transition region, small molecules are more mobile than might be expected from the high viscosity of the matrix (Parker and Ring, 1995). The mechanism of degradation of molecules

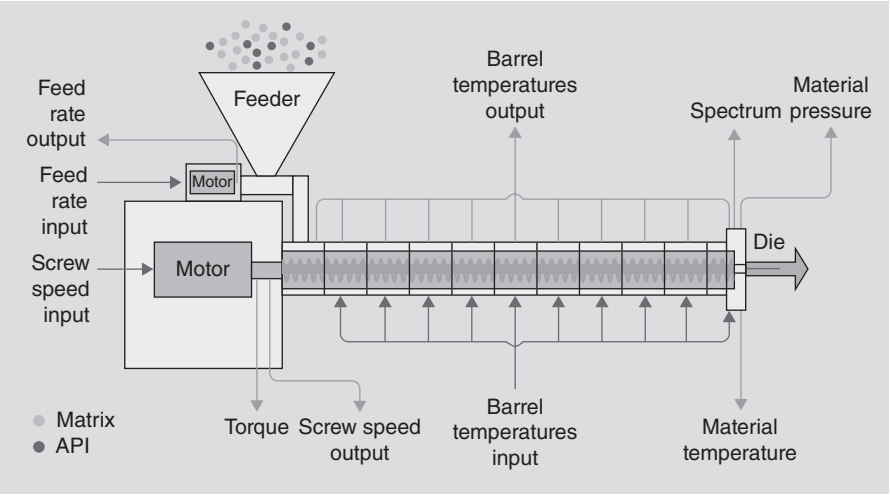


**Figure 1.1** Typical hot-melt extrusion system (courtesy of Siemens, AG).

entrapped in a glassy matrix is not fully understood but is speculated to be due to side chain flexibility and/or diffusion of small molecules such as water and oxygen through the glassy matrix. Other deteriorative mechanisms may include Maillard reaction between the active and the carrier matrix.

Microcapsules manufactured via extrusion and spray-drying may show structural imperfections, thus limiting their shelf-life. The latter is manifested in undesirable handling properties such as stickiness and clumping. The presence of exposed actives on the microparticle surface may have detrimental consequences such as drifts in the release profile and/or loss of active due to oxidation and other deteriorative processes.

A limited number of applications have used freeze-drying or similar evaporative techniques to form carbohydrate glasses from solution where the removal of water molecules takes place via either freezing the solution and subliming the ice as in freeze-drying or evaporation. Freeze-drying forms porous substrates due to transport of water vapor. Unlike starches, sugars lack fixed molecular structure and, thus, collapse on freeze-drying.

Co-crystallization with sugars has been practiced in few unique situations but has not found any commercial success. While crystalline sucrose is a poor flavor carrier, its co-crystallization with flavors forms aggregates of very small crystals, which can incorporate flavors via either inclusion within the crystals or entrapment between them.

Release of actives from amorphous carbohydrate matrices takes place by subjecting the matrix to moisture or high temperatures (i.e., by bringing the matrix to a temperature above its glass transition temperature). Microcapsules entrapped in amorphous structures are preferred for their ease of manufacturing, scalability, and economics compared with other encapsulation technologies. Their use has been adapted to a variety of food systems such as surface sprinkle on breakfast cereals, hot instant drinks, soups, teabags, chewing gum, pressed tablets, etc.

## Complexation into cyclodextrins

Entrapment of actives into cyclodextrins is a unique approach to microencapsulation that is based on molecular selectivity. Cyclodextrins are cyclic oligosaccharides formed of various numbers of α1, 4–linked pyranose subunits with the 6-, 7-, and 8-numberd cyclic structures referred to as α-, ß-, and γ-cyclodextrins, respectively; these molecules vary in their solubility, cavity size, and complexation properties.

The type and degree of complexation in cyclodextrins are determined by two main factors: (1) steric fit of the guest (encapsulant) to the host (cyclodextrin) and (2) thermodynamic interactions, mainly hydrophobic interactions of the guest molecule with the host. Generally, one guest molecule can be included in one cyclodextrin molecule, although for some low molecular weight molecules, more than one guest molecule may fit into the cavity. For molecules with large hydrodynamic radii, more than one cyclodextrin molecule may bind to the guest. In principle, only a portion of the molecule must fit into the cavity to form a complex (Figure 1.2). As a result, 1:1 molar ratios are not always achieved, especially with very high or very low molecular weight guests.

Guest molecules in cyclodextrins are not permanently entrapped, but they occur in a dynamic equilibrium. However, once a complex is formed and dried, it is very stable and often results in a very long shelf-life (up to years at ambient temperatures under dry conditions). Release of the complexed guest takes place by immersing the guest–host complex in aqueous media to dissolve the complex and further release of the guest when displaced by water molecules.

A wide variety of molecules can be entrapped in cyclodextrins, such as fats, flavors, colors, etc. (Martin Del Valle, 2004; Parrish, 1988). Complexation of cyclodextrins with sweetening agents such as aspartame, stevioside, and glycyrrhizin can stabilize these sweeteners and improve their taste as well as eliminate the lingering bitter aftertaste. Cyclodextrins can also be used to entrap undesirable substances such as cholesterol to rid milk, butter, and eggs from this undesirable component (Hedges, 1998; Szetjli, 1998).

## Encapsulation in microporous matrices: physical adsorption

Physical adsorption can only be feasible when an active is adsorbed onto a high-surface-area microporous substrate, commonly referred to as molecular sieves. Cheremisinoff and Morresi (1978) cited two main examples of this category:

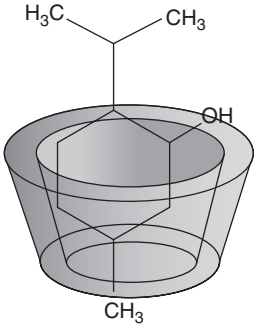


**Figure 1.2** Molecular complexation with cyclodextrin.

activated carbon (500–1400 $m^2/g$) and amorphous silica (100–1000 $m^2/g$). The effectiveness of these materials is demonstrated by the extensive reduction in equilibrium vapor pressure that accompanies physical adsorption of volatile flavors. Despite their efficiency in entrapping volatiles, silica and activated carbon use in foods has been discouraged due to regulatory constraints and is currently limited to packaging applications.

Micronized sugars have been used but with limited success in adsorption applications. Dipping capillary-sized droplets of sucrose or lactose solution into liquid nitrogen followed by freeze-drying can produce amorphous spheres that have the ability to adsorb aromas. Sorption of vapor causes these materials to revert to the more stable crystalline state with accompanying loss of porosity.

## Encapsulation in fats and waxes

Solid particles can be encapsulated in fats or waxes to form reservoir or matrix-type microcapsules by using fluid bed coating or spray chilling techniques, respectively. These technologies are discussed in greater detail in Chapter 8 dealing with encapsulation of bakery leavening agents.

Fluid bed coating is a versatile encapsulation technology where a fat (or aqueous) coating can be applied to particles that are suspended in a temperature- and moisture-controlled chamber. For aqueous or solvent-based coating, an evaporation mechanism is necessary to form a dry coating; for fat-based coating, the molten fat is cooled to solidify the fat film around the coated particles. Multiple layers of fat/wax coating can be applied depending on the goal of encapsulation whether for controlled/targeted release or for taste masking.

In spray chilling, on the other hand, a dispersion of solid particles in a molten matrix is formed and is further sprayed through a nozzle into a cooled chamber to solidify the fat matrix. Despite its benefits in delayed-release applications, spray chilling results in the formation of small spherical particulates with a significant proportion of the active exposed to the outer surface of the particulate. This problem can be minimized by choosing process conditions where the active can bind tightly to the fat matrix or by applying an outer coating using a fluid bed coating system.

## Encapsulation in emulsions and micellar systems

Micelles are described as “reservoirs” or “microcontainers” that entrap insoluble actives for their release at a targeted site, often via diffusional processes. The technique is simply an entrapment of a hydrophobic active in a hydrophilic shell material, thus enhancing the encapsulated particle or droplet solubility. This is no trivial matter when considering problems with bioavailability of many drugs and nutritional actives (fat-soluble vitamins, fish oil, and a host of water-insoluble drug actives). A second important aspect of micelles is their small size, which allows them to evade the body’s screening mechanism, the reticuloendothelial system. Recognition by the reticuloendothelial system is the main reason for removal of many drug-delivery vehicles from the blood before reaching their target site (Sagaowicz et al., 2006). An in-depth discussion on encapsulation into micelles and

emulsion systems can be found in Chapters 6 and 7 of this book by Dr Zuidam et al. and Professor Garti et al., respectively.

Despite the desirable structural characteristics of liposomes for encapsulation applications, one major challenge that often remains unresolved is liposome physical instability, especially during large-scale production and long-term storage (Chaudhury et al., 2012; Chen et al., 2010; Yokota et al., 2012). Lyophilization in the presence of cryoprotectants has been introduced recently as an alternative solution for improving liposome stability. Chaudhury et al. (2012) reported on lyophilizing cholesterol-free PEG liposomes containing the drug carboplatin to a moisture content of ~2.6%, which resulted in a 2-fold increase in the drug loading with no measurable changes in their in vitro release profile compared with their nonlyophilized counterparts. A recent study by Stark et al. (2010) on optimizing conditions for lyophilizing extruded unilamellar liposomes showed that a mixture of glycerol and carbohydrate concentrations of ~1% (w/v), irrespective of the carbohydrate composition, resulted in no significant changes in the bilayer organization, and the transition behavior of lipids during freezing.

Despite the promising data available on the benefits of lyophilization in preserving liposomes' structural integrity and bioavailability of encapsulated actives, this technique is still considered a work in progress and more research is needed to use this technology more effectively, especially in food and health ingredients applications. A broader discussion on lyophilized liposome technology can be found in Chapter 4 by Drs. Pinho and Tamiaso.

## Encapsulation in coacervated polymers

*Coacervation,* as defined by Speiser (1976), is a process of transferring macromolecules with film properties from a solvated state via an intermediate phase, the coacervation phase, into a phase in which a film is formed around each particle and then to a final phase in which this film is solidified or hardened. Two types of coacervation processes are commonly used in encapsulation applications, namely simple and complex:

1. *Simple coacervation* is based on "salting out" of one polymer by the addition of agents (e.g., salts, alcohols) that have higher affinity to water than the polymer. It is essentially a dehydration process where separation of the liquid phase results in the solid particles or oil droplets becoming coated and eventually hardened into microcapsules.
2. *Complex coacervation*, on the other hand, is a process whereby a polyelectrolyte complex is formed. It requires the mixing of two colloids at a pH at which one is negatively charged and the other is positively charged, leading to phase separation and formation of enclosed solid particles or liquid droplets (Rabiskova and Valaskova, 1998).

Several parameters can impact the formation and integrity of coacervates, such as polymer molecular weight, temperature, and processing time. Core materials suitable for coacervation are solids and liquids that are water insoluble so that the active would not dissolve in the aqueous phase. High oil payloads (65–85%) were reported when using surfactants with hydrophilic-to-lipophilic balance (HLB) of 1.8–6.7. Using Tween 61 (HLB 9.6) reduced the oil payload, and Tween 81 (HLB 10) resulted in capsules with no oil entrapped (Rabiskova and Valeskova, 1998). Release

of actives from coacervated systems is primarily a function of the wall type and its thickness (i.e., slower release with increased wall thickness). Chapter 3 of this book by Dr. Thies presents an in-depth discussion on complex coacervation phenomenon and its applications in encapsulation.

## Encapsulation using supercritical fluids

Supercritical fluid (SCF) technology has been used effectively in extracting delicate essences and flavor components due to the process mild extraction conditions and the SCF's unique physicochemical properties. SCFs behave as intermediates between those of liquids and gases. They have similar densities in gas and liquid forms; their viscosities are near that of a gas with an almost zero surface tension, thus allowing their easy diffusion through highly porous nanostructures. Supercritical carbon dioxide (SC-$CO_2$) is considered the most suitable substance for food and drug applications due to its low toxicity, low cost, easy removal, and nonflammability (Bahrami and Ranjibarajan, 2007; Brunner, 2005)

Encapsulation of thermolabile actives using SCF technology is a relatively new introduction to the field of microencapsulation (Chattopadhyay et al., 2006; Cocero et al., 2009; Fraile et al., 2014; Martin and Cocero, 2008; Sanli et al., 2012; Xia et al., 2011). The process consists of applying a polymeric thin film onto particles via simultaneous nucleation of the polymeric material out of a supercritical fluid, encapsulating the particles fluidized in the supercritical fluid, and further curing and binding the material coated on the particles (Silva and Meireles, 2014). One of the important parameters for the successful encapsulation using SCF technology is ensuring the solubility of the active and the polymer matrix in the supercritical fluid. Natural food-grade polymers such as modified starches, dextrins, and inulin have been used successfully in supercritical fluid encapsulation processes.

Supercritical fluid processing has been adapted to encapsulating various health ingredients and actives such as lutein, bixin, β-carotene, astaxanthin, and other carotenoids (Chattopadhya and Gupta, 2002; Martin et al., 2007; Miguel et al., 2008; Xia et al., 2012), plant extracts such as rosemary (Carvallo et al., 2005), cholecalciferol, vitamin D3 (Xia et al., 2011), and quercetin (Fraile et al., 2014). A more elaborate discussion on microencapsulation via supercritical fluids can be found in Chapter 2 of this book by Dr. Cocero and co-workers.

## Encapsulation into hydrogel matrices

Hydrogels are hydrophilic three-dimensional network gels that can absorb much more water than their own weight. Hydrogels consist of (a) polymers, (b) molecular linkers or spacers, and (c) an aqueous solution. Basic high molecular weight polymers include polysaccharides, proteins, chitin, chitosans, hydrophilic polymers, and others (Shahidi et al, 2006). The affinity of hydrogels to aqueous media makes them ideal absorbing matrices for food and agricultural actives.

Encapsulation by hydrogels is simply an entrapment of an active substance in a gel phase for its release in response to external stimuli. Release from hydrogels takes place via diffusion that can be affected by various chemical and physical factors. While chemical factors include H-bonds, ionic bonds, electrostatic interactions,

and hydrophobic interactions between the active and matrix, physical factors include molecular size and conformation. Controlling (extending) the release of an active in a hydrogel matrix can be achieved by decreasing the hydrophilicity and/or diffusivity of the hydrogel structure or by covalently linking the active to the carrier hydrogel matrix.

Ideal hydrogels display a sharp phase transition on swelling in an aqueous solvent in response to environmental stimuli such as temperature, pH, electric field, etc. Release from hydrogels can be predicted from their lower critical solution temperatures (LCT) values. As temperature increases to the hydrogel's LCT, the hydrogel shrinks due to dehydration. Below LCT, hydrogels can take up water, thus increasing their swelling (Ichikawa et al., 1996). Grahm and Mao (1996) categorized the types of materials that cannot be delivered via hydrogels as those actives that are either (1) extremely water soluble due to the risk of uncontrollable quick release and (2) very high molecular weight substances due to the extremely slow release rate to achieve a desired benefit.

## Encapsulation using flow-focusing technology

Production of uniform sized microparticles and nanoparticles is a primary challenge in many encapsulation processes. Given the importance of particle size in predicting release rate, research efforts have been centered on finding new methods suitable for producing monodisperse particles. One approach involves the use of hydrodynamic flow-focusing technology. This technology has been used for years by the ink jet industry and in diagnostic and detection assays but has only recently been adapted to encapsulation applications for the first time by Dr. Alfonso Gañán-Calvo at the University of Seville, Spain.

Flow focusing is in essence a laminar-jet disintegration technology that uses a combination of a specific axisymmetric geometry and hydrodynamic forces to produce droplets of uniform sizes (Freitas et al., 2005; Herrada-Gutierrez et al., 2010). The basic principle of flow focusing involves coaxial focusing of two or more immiscible fluid streams through a small opening where the outer continuous phase is set at a flow rate much higher than the inner disperse phase (Figure 1.3). After passing through the orifice, the central stream is forced to break up into droplets, due to a rapid change in fluid pressure and the prevailing shear stress of the outer continuous phase. To generate microparticles, the droplets often consist of liquid containing dissolved polymers. Once formed, these droplets rapidly undergo the additional step of solvent extraction or solvent evaporation, during which each turns into a particle or microsphere (Schneider et al., 2008). On curing, the drops can form multilayer microcapsules with multiple shells of controllable thickness. Flow-focusing technology is claimed to be scalable by replicating an arbitrary number of flow-focusing heads into an array structure that can result in the formation of monodisperse microencapsulated spheres.

Several advantages have been cited for flow focusing, such as (i) the ability to form monodisperse particles via adjusting flow rates of the two phases, (ii) mild process conditions that allow safe processing of thermolabile actives and (iii) reduction/

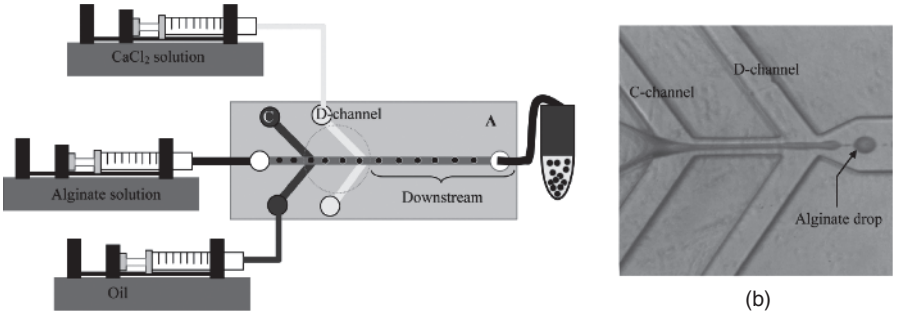


**Figure 1.3** Schematic diagram of (a) flow-focusing microfluidic process for making calcium alginate beads, (b) top view of the flow-focusing channels, C and D, as they pass through the orifice and the subsequent generation of microparticulates (from Hong et al., 2007, with permission).

elimination of clogging of particles exit holes due to the fact that liquid jets do not touch the exit holes, and (iv) unlike other encapsulation dripping techniques, the droplet size is not limited by the orifice diameter. Flow focusing has not yet proved its benefits in encapsulating foods and nutraceuticals actives due to challenges with throughput and high cost.

## Overview of controlled-release systems

Despite the far-reaching applications of encapsulation and controlled-release technologies in many industries, predicting the release of encapsulated actives, especially in biological systems (foods included) remains a challenge. In the human gastrointestinal intestinal tract, for example, the release of microcapsules is a function of not only the microcapsule design and composition but also the physiological conditions, the presence of food, and the physicochemical properties of the ingested dosage.

One of the essential requirements for predicting release mechanisms of microencapsulated dosages is identifying parameters involved in mass-transport and diffusion of the actives from a region of high concentration (dosage) to a region of low concentration in the surrounding environment. Encapsulation and controlled release systems can be classified into: (a) matrix and (b) reservoir, or (c) their combination (Figure 1.4). It should be noted that in either system, the active is not covalently enclosed in the polymer matrix.

### Matrix systems

In a matrix or monolithic delivery system, the active is dispersed or dissolved within a rate-controlling polymer matrix. Such systems can best be represented by microparticles prepared by extrusion or fat-congealed capsules (spray-chilled) where

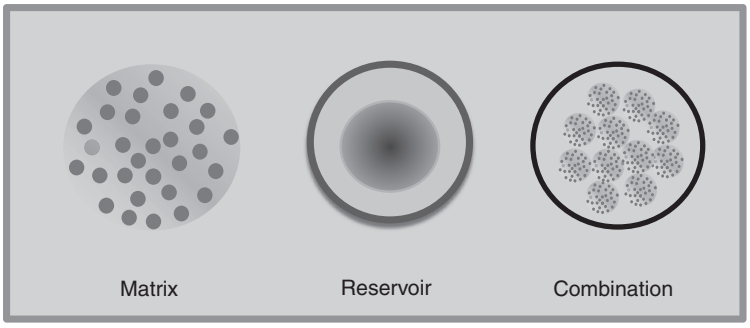


**Figure 1.4** Typical microencapsulation systems: matrix, reservoir, and their combination.

the active is uniformly dispersed in the encapsulating medium (carbohydrate, fat, or other matrices). Matrix systems can be swellable (hydrogel) or nonswellable. In such systems, release is controlled by diffusion from the matrix through small pores. Some active particles or droplets lodged at the surface of the microcapsule will be readily released, leading to a small "burst" effect. However, diffusion of the remaining active particles located inside the microcapsule takes place at a slower pace as they need to travel a longer distance before they are released from the delivery device. Application of a coating material over a monolithic microparticle can help eliminate burst release, although it might change the release profile. Other treatments include washing microparticles to extract active particles exposed to the microcapsule surface. Compared with reservoir systems, matrix systems require less quality control and, hence, lower manufacturing cost.

## Reservoir systems

Reservoir systems are simply described as delivery devices where an inert membrane surrounds an active agent that, on activation, diffuses through the membrane at a finite controllable rate (Siepmann et al., 2012). The active's release rate is mainly a function of the physicochemical properties of the active and the polymer (e.g., thickness, molecular weight, integrity, etc.). In reservoir systems, the purpose of the membrane is to mediate diffusion of the active; therefore, release of the active takes place via its initial partition into the surrounding membrane followed by diffusion. Because of their simple mechanism and ability to produce zero-order release, reservoir systems would seem to be highly advantageous. However, these systems can be difficult to fabricate reliably and often small defects or cracks in the membrane lead to dose dumping as discussed above, release of actives from a reservoir-type system is controlled by the physicochemical properties of the encapsulating polymer (e.g., composition, molecular weight, etc.) and the active (e.g., molecular weight, particle size, solubility, etc.).

## Combination systems

Examples of this category can best be illustrated by congealed microcapsules or extruded microparticles with additional coating (enrobing) film. This technique is most useful for manufacturing extremely "delayed-release" profiles.

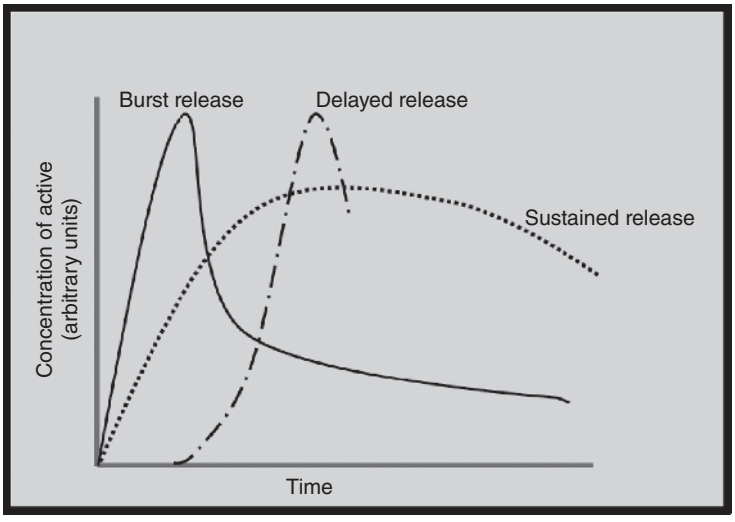


**Figure 1.5** Principal modes of controlled release, burst, delayed, and sustained.

## Release mechanisms

In designing microcapsules for controlled-release applications, it is critical to identify the desirable release profile so that adequate materials and technology can be chosen. The principal modes of controlled release are "delayed," "sustained," and "burst" release (Figure 1.5).

In the "delayed-release" mode, the release of an active substance is delayed from a finite "lag time" up to a point where its release is favored and is no longer hindered. Examples of this category include encapsulating probiotic bacteria for their protection from gastric acidity and subsequent release in the lower intestine, flavor release on microwave heating of ready-meals, or the release of encapsulated sodium bicarbonate on baking of a dough or cake batter.

"Sustained release," on the other hand, aims at maintaining the release of constant concentrations of an active at its target site for a desired time. Examples of this mode include encapsulating flavors and sweeteners for chewing gum applications so that their rate of release is maintained throughout the time of chewing.

"Burst release" is simply described by a high initial delivery of an entrapped active. This type of release is desirable for delivering instantaneous burst of flavors or fragrances. However, it may be detrimental to other systems such as encapsulated drugs and may lead to high toxicity levels and ineffective administration of the drug.

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