Encapsulation and Controlled Release Technologies in Food Systems

Edited by Jamileh M. Lakkis

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Jamileh M. Lakkis, Ph.D., has 14 years experience in the food, dietary supplements, and consumer products industries. She served as Senior Project Manager at Pfizer/Cadbury-Schweppes, Morris Plains, NJ, focusing on designing confectionery products as delivery systems for oral care benefits. As a Senior Encapsulation Specialist for General Mills, Inc., Minneapolis, MN, Dr. Lakkis designed several microencapsulation processes for stabilizing and masking the taste/aroma of a variety of functional and nutraceutical actives for their applications in breakfast cereals, dairy, confections, and shelf-stable bakery products. Her professional experience also includes engagements as Senior Research Scientist at Land O'Lakes, Inc., Arden Hills, MN. Dr. Lakkis co-organized the first IFT symposium on microencapsulation and controlled release applications in food systems. She is an active member of the Controlled Release Society and serves on the society's newsletter editorial board representing the Consumer and Diversified Products Division.

Blackwell Publishing Professional
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Web site: www.blackwellprofessional.com

Blackwell Publishing Ltd.
9600 Garsington Road, Oxford OX4 2DQ, UK
Tel.: +44 (0)1865 776868

Blackwell Publishing Asia
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Tel.: +61 (0)3 8359 1011

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I dedicate this book to LEBANON
Which had not been my country, I'd have chosen it to be

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Contributors

Ingrid A.M. Appelqvist
Unilever Food and Health Research Institute
Unilever R&D Vlaardingen
The Netherlands
Chapter 3

Abraham Aserin
Casali Institute of Applied Chemistry
The Institute of Chemistry
The Hebrew University of Jerusalem
Jerusalem, Israel
Nutralease Ltd., Mishor Adumim, Israel
Chapter 2

Kathy Brownlie
Manager, Global Programme
Frost & Sullivan
Oxford, England, UK
Chapter 10

Tugba Cevik
Department of Chemical Engineering
Section of Food Technology
Gebze Institute of Technology
Gebze-Kocaeli, Turkey
Chapter 9

Kun-Nan Chen
Department of Mechanical Engineering
Tung Nan Institute of Technology
Taipei, Taiwan
Chapter 4

Ming-Ju Chen
Department of Animal Science
National Taiwan University
Taipei, Taiwan
Chapter 4

Nissim Garti
Casali Institute of Applied Chemistry
The Institute of Chemistry
The Hebrew University of Jerusalem
Jerusalem, Israel
Nutralease Ltd., Mishor Adumim, Israel
Chapter 2

Matt Golding
Unilever Food and Health Research Institute
Unilever R&D Vlaardingen
The Netherlands
Chapter 3

Qingrong Huang
Department of Food Science
Rutgers University
New Brunswick, NJ
Chapter 6

Nicolaas Jan Zuidam
Unilever Food and Health Research Institute
Unilever R&D Vlaardingen
The Netherlands
Chapter 3

Yan Jiang
Department of Food Science
Rutgers University
New Brunswick, NJ
Chapter 6

Jamileh Lakkis
Senior Project Manager
Formerly with Pfizer/Cadbury-Schweppes
Morris Plains, NJ
Chapter 1
Chapter 5
Chapter 8

Murat Ozdemir
Department of Chemical Engineering
Section of Food Technology
Gebze Institute of Technology
Gebze-Kocaeli, Turkey
Chapter 9

Eli Pinthus
Nutralease Ltd., Mishor Adumim, Israel
Adumim Food Ingredients
Mishor Adumim, Israel
Chapter 2

Aviram Spernath
Casali Institute of Applied Chemistry
The Institute of Chemistry
The Hebrew University of Jerusalem
Jerusalem, Israel
Chapter 2

Curt Thies
Thies Technology
Henderson, Nevada
Chapter 7

Rob Vreeker
Unilever Food and Health Research Institute
Unilever R&D Vlaardingen
The Netherlands
Chapter 3

Xiaoyong Wang
Department of Food Science
Rutgers University
New Brunswick, NJ
Chapter 6

Preface

Encapsulation and controlled release technologies have enjoyed their fastest growth in the last two decades. These advances, pioneered by pharmaceutical companies, were a result of: (1) the rapid change in drug development strategies to target specific organs or even cells, (2) physicians' growing concern about patient non-compliance, and (3) pharmaceutical companies desire to extend their market monopoly on new drugs for a certain period of time as provided by the US and international patent laws.

Despite this progress, encapsulation and controlled release technologies have only been recently adopted by the food industry. Food researchers and technologists have often been confronted with the dilemma of how to translate all these advances from the drug arena into practical applications in food systems. By searching the literature, one can find volumes of books and specialized publications on encapsulation and controlled release technologies. Unfortunately, most of these publications have dealt with theoretical aspects of these technologies with little emphasis on real applications in consumer and food products.

This book attempts to illustrate various aspects of encapsulation and controlled release applications in food systems using practical examples. These examples will give the reader an appreciation for the delicate art of designing encapsulated ingredients and the enormous challenges in incorporating them into food formulations. Most of the practical examples in this book were borrowed from the patent literature. This approach might be questioned based on the fact that patents applications are never peer reviewed, but seems justifiable considering the frantic effort by both industry and academia to protect their discoveries and to gain limited-time monopoly on their innovations, thus limiting the availability of such information in peer-reviewed articles.

This publication has several potential uses. It is a reference book for scientists in the food, nutraceuticals and consumer products industries who are looking to introduce microencapsulated ingredients into new or existing formulations. It is also a post-graduate text designed to give students some comprehension of various aspects of encapsulation and controlled release in food systems.

This book is organized in such a way that each chapter treats one major application of encapsulation and controlled release technologies in foods.

Chapter 1 introduces the readers to various encapsulation and controlled release technologies, as well as release mechanisms, suitable for applications in foods, nutraceuticals and consumer products.

Chapter 2 by Professor Nissim Garti and his collaborators discusses a novel approach to encapsulation and controlled release via reverse microemulsion technique referred to as nanosized self-assembled liquids (NSSL). Such systems are shown to provide exceptional thermodynamic stability in a wide pH range. In addition to enhancing bioavailability of functional active ingredients, NSSL systems, by virtue of their unique transparent appearance, are excellent candidates for beverage applications.

Chapter 3, by Dr. Klaas-Jan Zuidam and co-workers, presents an elaborate approach to understanding emulsions and their benefits as delivery systems in food applications. This chapter discusses various mechanisms of emulsion stabilization and destabilization and

how they can best be designed for targeted delivery of flavors and functional ingredients in the human gastrointestinal system.

Chapter 4 on encapsulation and controlled release of probiotics by Drs. Chen and Chen reports on approaches for encapsulating probiotic bacteria in dairy products as well as in the human gastrointestinal tract. This chapter also discusses novel optimization techniques for stabilizing these beneficial bacteria and enhancing their survival rates.

Chapter 5, written by the editor of this book, highlights current approaches to encapsulation and controlled release technologies for bakery products applications. Current encapsulation practices such as hot-melt particle coating and spray chilling are discussed. Examples of the performance of encapsulated leavening agents as well as sweeteners and flavors are presented in shelf-stable bakery applications.

Chapter 6 on nanoencapsulation technology by Dr. Huang and his collaborators deals with novel approaches to encapsulate enzymes and nutraceuticals. Specific examples are presented on stabilization of phytochemicals and their enhanced bioavailability via incorporation into nanoemulsions and bioconjugation systems.

Chapter 7 on flavor encapsulation via complex coacervation is written by Dr. Curt Thies. Discussion is focused on the basic principle of complex coacervation technique as a liquid–liquid polymer phase separation phenomenon. Guidance on polymer selection and subsequent implications on the physicochemical properties of capsules as well as their release behavior is provided.

Chapter 8, written by the editor of this book, details techniques used for delivering therapeutic as well as functional actives and flavors via confectionery products. Technologies and subsequent applications discussed in this chapter have wide applications in the food, nutraceuticals, as well as pharmaceutical arenas. Mechanisms and challenges specific to targeted release in upper gastrointestinal tract, especially the mouth and throat areas will be described in great detail.

Chapter 9 discusses encapsulation and controlled release of actives in packaging applications by Dr. Ozdemir and collaborator. In this contribution, the authors provide examples on embedding fragrances, pigments as well as antimicrobial and insect repellent agents into food packaging films.

Chapter 10, authored by Ms. Kathy Brownlie, provides a marketing perspective of microencapsulation technologies and their potential impact on the food industry. Ms. Brownlie offers an in-depth assessment of market drivers as well as constraints that are still hindering wider implementation of these technologies in food manufacturing.

This book has definitely surpassed my vision and expectations thanks to the contributors that I am grateful to all of them for their expertise, commitment, and dedication. It is my hope that this book will prove itself a useful source on encapsulation and controlled release in a wide range of food and consumer product applications.

Many thanks to the editorial staff at Blackwell Publishing Co., especially to Mark Barrett and Susan Engelken for their valuable help and advice throughout this project.

Last but not least, I would like to thank my parents who taught me the importance of working hard, having clear goals, and standing for what I believe is right. It is a lesson that guides me in everything I do.

Jamileh M. Lakkis

Encapsulation and Controlled Release Technologies in Food Systems

1 Introduction

Jamileh M. Lakkis

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

Addition of small amounts of nutrients to a food system, for example, may not affect its properties significantly; however, incorporating high levels of the nutrient either to meet certain requirements or to treat an ailment will most often result in unstable and often unpalatable foods. Examples of such nutrients include fortification with calcium, vitamins, polyunsaturated fatty acids, and so on, and the associated grittiness, medicinal and oxidized taste, respectively. Different types of controlled-release systems have been formulated to overcome these challenges and to provide a wide range of release requirements.

The two principal modes of controlled release are delayed and sustained release (Figure 1.1).

- *Delayed release* is a mechanism whereby the release of an active substance is delayed from a finite "lag time" up to a point when/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 further release in the lower intestine, flavor release upon microwave heating of ready-meals or the release of encapsulated sodium bicarbonate upon baking of a dough or cake batter.
- *Sustained release* is a mechanism designed to maintain constant concentration of an active at its target site. Examples of this release pattern include encapsulating flavors and sweeteners for chewing gum applications so that their rate of release is reduced to maintain a desired flavor effect throughout the time of chewing.

A wide range of cores (encapsulants), wall-forming materials (encapsulating agents), and technologies for controlling the interactions of ingredients in a given food system and for manufacturing microcapsules and microparticles of different size, shape, and morphological properties are commercially viable.

Wall-Forming Materials

Materials used in film coating or matrix formation include several categories:

1. Waxes and lipids: beeswax, candelilla and carnauba waxes, wax micro- and wax macroemulsions, glycerol distearate, natural and modified fats.
2. Proteins: gelatins, whey proteins, zein, soy proteins, gluten, and so on. All these proteins are available both in native and modified forms.

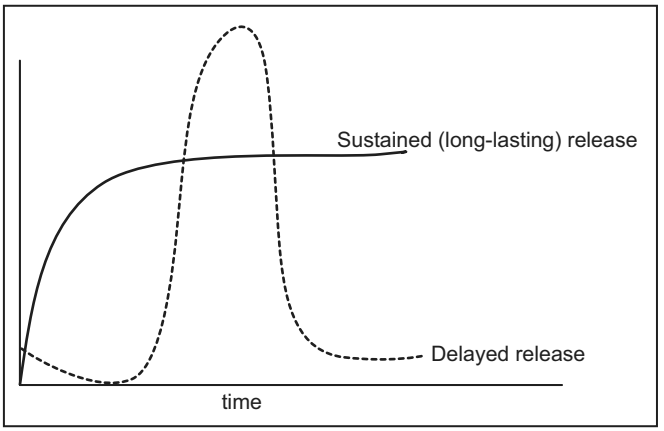

Figure 1.1. Generic representation of "sustained" and "delayed" release profiles.

3. Carbohydrates: starches, maltodextrins, chitosan, sucrose, glucose, ethylcellulose, cellulose acetate, alginates, carrageenans, chitosan, and so on.
4. Food grade polymers: polypropylene, polyvinylacetate, polystyrene, polybutadiene, and so on.

Core Materials

Core materials include flavors, antimicrobial agents, nutraceutical and therapeutic actives, vitamins, minerals, antioxidants, colors, acids, alkalis, buffers, sweeteners, nutrients, enzymes, cross-linking agents, yeasts, chemical leavening agents, and so on.

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:

- temperature: fat/wax matrices
- moisture: hydrophilic matrices
- pH: enteric coating, emulsion coalescence, and others.
- Enzymes: enteric coating as well as a variety of lipid, starch and protein matrices.
- Shear: chewing, physical fracture, and grinding
- lower critical solution temperature (LCST) of hydrogels.

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

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

Entrapment of Actives in Food Matrices

Entrapment in an Amorphous Matrix

Encapsulation of active into an amorphous 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 metastable amorphous phase followed by cooling to solidify the structure and form glass, thus restricting molecular movements.

Carbohydrates are excellent candidates for encapsulation applications due to the several attributes possessed by them.

1. They form an integral part of many food systems.
2. They are cost-effective.
3. They occur in a wide range of polymer sizes.
4. They have desirable physicochemical properties such as solubility, melting, phase change and so on.

Sucrose, maltodextrins, native and modified starches, polysaccharides, and gums have been used in 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 molecules like lipids, flavors, and so on (Conde-Petit et al., 2006). Some carbohydrates such as inulin and trehalose can provide additional benefits for encapsulation applications. Inulin, for example, is a prebiotic ingredient that can enhance survival of probiotic bacteria while trehalose serves as a support nutrient for yeasts.

Two main technologies—spray drying and extrusion—have been used in large-scale encapsulation applications into amorphous matrices, though using different mechanisms. In spray drying, for example, the active is trapped within 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 important for flavor applications, in particular, considering the fact that most flavors are made up of components of various chemistries (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 has been adequately covered by Masters (1979). Briefly, the process comprises atomizing a micronized (1–10 micron droplet size) emulsion or suspension of an active and an encapsulating substance and further spraying the same into a chamber. Drying takes place at relatively high temperatures (210°C inlet and 90°C outlet), though the emulsion's exposure to these temperatures lasts only for few seconds. The process results in free flowing, low bulk density powders of 10–100 micron size. Optimal payloads of 20% can be expected for flavors encapsulated in starch matrices. Maltodextrins and sugars with lower molecular weight, due to their low viscosities and inadequate emulsifying activities, result in lower flavor payloads.

Several factors can impact the efficiency of encapsulation via spray drying, mainly those related to the emulsion (solid content, molecular weight, emulsion droplet size, and viscosity) and to the process (feed flow rate, inlet/outlet temperature, gas velocity, and so on).

Release of flavors from spray-dried matrices takes place upon reconstitution of the dried emulsion in the release medium, water most often. Reasonable prediction of the release behavior should take into consideration the complex chemistry of flavors and the prevailing partition and phase transport mechanisms between aqueous and non-aqueous phases (Larbouss et al., 1991; Shimada et al., 1991).

Encapsulation into an amorphous matrix via extrusion has gained wide popularity in the last 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 highly integrated 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, and so on.
2. 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 to preserve its integrity.
3. Extruders are also formers—encapsulated products can be recovered in practically any desired shape or size (pellets, rods, ropes, and so on).
4. Only very limited amount of water is needed to transform carbohydrates from their native crystalline structure to amorphous glassy matrices in an extruder, thus limiting the need for expensive downstream drying.
5. High payload—up to 30% can be expected when encapsulating solid actives in extruded pellets.
6. Economics—attributes such as high throughput, continuous mode, and limited need for drying make extrusion a very attractive process for manufacturing encapsulated ingredients.

Figure 1.2 describes a typical melt extrusion encapsulation process. Carbohydrate (encapsulating matrix), a mixture of sucrose and maltodextrin, is dry fed and melted by 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 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 any desired target glass transition temperature by incorporating plasticizers (reduce T_g) or high-molecular weight polymers (increase T_g). It should be cautioned that although glass transition and associated microcapsule stability are 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). Mechanism of degradation of molecules entrapped in a glassy matrix is not fully understood but is speculated to be due to side-chain flexibility (e.g. enzymes) 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.

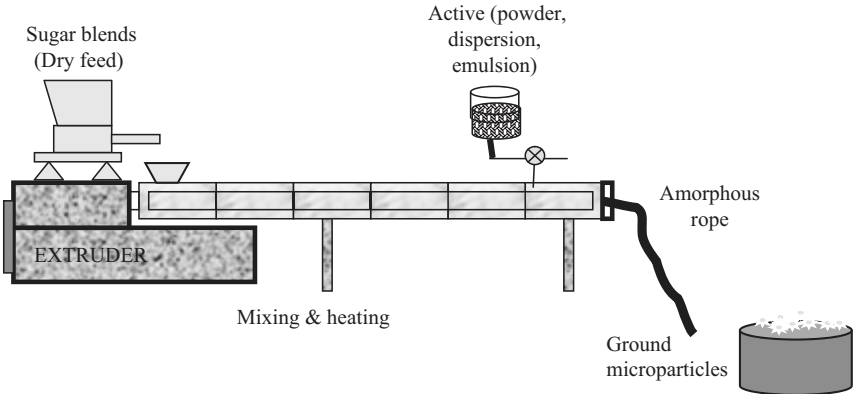

Figure 1.2. Encapsulation into amorphous carbohydrate matrices using hot melt extrusion.

Microcapsules manufactured via spray drying and extrusion may show structural imperfections, thus limiting their shelf life. While spray-dried microcapsules tend to have low bulk density, extruded granules may show stickiness and clumping. In addition, the presence of exposed active 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 employed freeze drying or other evaporative techniques to form carbohydrate glasses from solution. Here, the removal of water molecules takes place either by freezing the solution and subliming the ice as in freeze drying or by evaporation. Freeze drying forms porous substrates due to transport of water vapor. Unlike starches, sugars lack fixed molecular structure; thus they collapse upon freeze drying.

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

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

Complexation of Actives 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 α-(1,4) linked pyranose subunits. The 6-, 7-, and 8-numbered cyclic structures are referred to as α-, β-, and γ-cyclodextrins, respectively; these molecules vary in their solubility, cavity size, and complexation properties (Table 1.1).

Table 1.1. Selected physicochemical properties of cyclodextrins (adapted from Martin Del Valle 2004)

Attribute	α-Cyclodextrin	β-Cyclodextrin	γ-Cyclodextrin
Number of glucopyranose units	6	7	8
Molecular weight (g/mol)	972	1135	1297
Solubility in water at 25°C (% w/v)	14.5	1.85	23.2
Cavity diameter (Å)	4.7–5.3	6.0–6.5	7.5–8.3
Cavity volume $(Å)^3$	174	262	427

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) their thermodynamic interactions, mainly hydrophobic type.

Generally, one guest molecule is included in one cyclodextrin molecule, although for some molecules with low molecular weight, more than one guest molecule may fit into the cavity (Figure 1.3). 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. As a result, one-to-one molar ratios are not always achieved, especially with high- or low-molecular-weight guests.

Guest molecules in cyclodextrins are not permanently entrapped but occur in a dynamic equilibrium. However, once a complex is formed and dried, it is very stable and often results in 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 promoting the release of the guest when displaced by water molecules.

A wide variety of molecules can be entrapped in cyclodextrins such as fats, flavors, colors, and so on (Martin Del Valle, 2004; Parrish, 1988). Complexation of cyclodextrins with

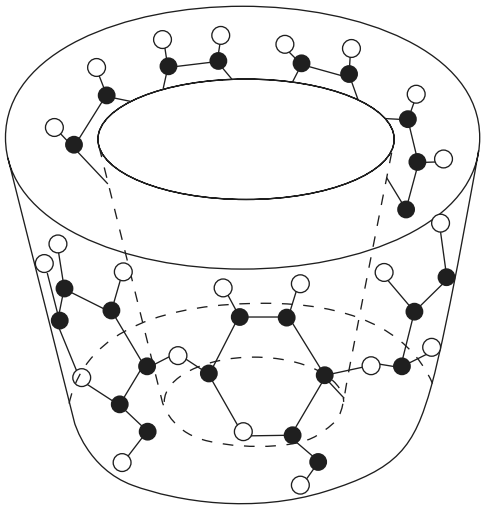

Figure 1.3. Schematic representation of a molecule entrapped in cyclodextrins.

sweetening agents such as aspartame can also stabilize the molecule and improve its taste as well as eliminate the bitter aftertaste of other sweeteners such as stevioside and glycyrrhizin. Cyclodextrins can entrap undesirable substances such as cholesterol from products such as milk, butter, and eggs (Szetjli, 1998; Hedges, 1998).

Encapsulation in Microporous Matrices—Physical Adsorption

Physical adsorption can only be feasible when an active is adsorbed onto a large surface area, microporous substrate, commonly referred to as molecular sieve. Examples of this category include activated carbon (500–1400 m^2/g) and amorphous silica (100–1000 m^2/g) (Cheremisinoff and Morresi, 1978). Despite their efficiency in entrapping volatiles, silica and activated carbon usage in foods has been discouraged due to regulatory constraints and is currently limited to packaging applications. The effectiveness of these materials is demonstrated by extensive reduction in equilibrium vapor pressure which accompanies physical adsorption of volatile flavors.

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 Fat- or Wax-Based Matrices

Entrapment of functional actives in fat-based matrices can be achieved using two main technologies, hot-melt fluid bed coating and spray congealing. Actives can best be entrapped via mixing them with a fat/wax carrier followed by spray congealing. These technologies have been adequately discussed in Chapter 5 which deals with the encapsulation of bakery leavening agents.

Encapsulation in Emulsions and Micellar Systems

Encapsulation via micelles is a convenient approach to enhance the solubility of insoluble or slightly soluble actives. This technique involves the simple entrapment of a hydrophobic active in a hydrophilic shell material, thus rendering the particle or droplet soluble in aqueous media. This is no trivial matter when considering the problems with bioavailability of hydrophobic drugs and nutritional actives (fat-soluble vitamins, fish oil, and a host of water-insoluble drug actives).

A second important function of micelles is their small size which allows them to evade the body's screening mechanism, the reticuloendothelial system (RES). Recognition by RES is the main reason for removal of many drug delivery vehicles from the blood before reaching their target site (Sagalowicz et al., 2006).

Micelles serve as drug "reservoirs" or "microcontainers" that ultimately release drugs via diffusional processes. An in-depth discussion on encapsulation into emulsion systems can be found in Chapters 2 and 3 of this book by Professor Garti and Dr. Zuidam and their respective coworkers.

Encapsulation in Cross-Linked or 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 addition of agents (salts, alcohols) that have higher affinity to water than the polymer. It is essentially a dehydration process whereby 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 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 the polymers' molecular weight, their w/w ratios, 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. One of the approaches to achieving high oil payloads is by using hydrophobic surfactants (Rabiskova and Valeskova, 1998).

The release of actives from coacervated systems is primarily a function of the wall type and its thickness (slower release with increased wall thickness). Chapter 7 of this book presents an in-depth discussion on coacervation for flavor encapsulation applications.

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 so on (Shahidi et al., 2006). The affinity of hydrogels to aqueous media makes them ideal absorbing matrices for food and agricultural actives.

The principle of encapsulation by hydrogels is simply to entrap an active substance and to further release it via gel-phase changes in response to external stimuli. Grahm and Mao (1996) categorized the types of materials that cannot be delivered via hydrogels as: (i) extremely water-soluble actives due to the risk of uncontrollable quick release and (ii) very high-molecular-weight substances due to the extremely slow release rate to achieve a desired benefit.

Release of actives from hydrogels takes place via diffusion. The latter can be impacted by various chemical and physical factors such as the prevailing chemical bonds (H-bonds, ionic bonds, electrostatic interactions, and hydrophobic interactions) between the active and the 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 upon swelling in an aqueous solvent in response to environmental stimuli such as temperature, pH, electric field, and so on. Release from hydrogels can be predicted from their LCT (lower critical solution temperatures) 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).

Overview of Release Mechanisms

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 tract (GIT), for example, the release of microcapsules is a function of the physiological conditions, presence of food as well as the physicochemical properties of the ingested dosage.

One of the essential requirements for predicting release mechanisms of microencapsulated dosages is by 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 two main types: reservoir and matrix systems and, in some cases, combinations of both.

Reservoir-Type Systems

Reservoir-type systems are simply described as delivery devices where an inert membrane surrounds an active agent which upon activation diffuses through the membrane at a finite controllable rate (Figure 1.4a). Reservoir-type systems are capable of achieving zero-order rates provided that constant thermodynamic activity is maintained inside the coating material. Reservoir-type systems are subject to shifts to a "burst-like" mechanism due to minor flaws in the membrane integrity.

Matrix Systems

Matrix or monolithic delivery systems can best be represented by microparticles prepared by extrusion or fat-congealed capsules where the actives are dispersed in the encapsulating

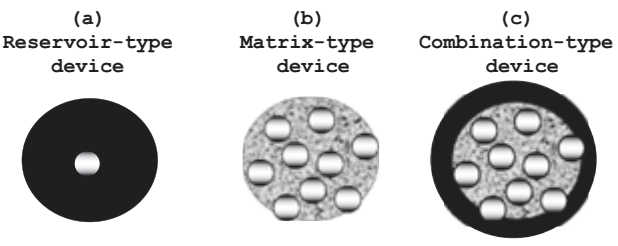

Figure 1.4. Schematic representation of encapsulation systems: (a) reservoir-type, (b) matrix-type, and (c) combination-type.

medium (carbohydrate, fat, or other matrices). Matrix systems can be swellable (hydrogel) or non-swellable. Compared to reservoir systems, matrix systems require less quality control, hence lower manufacturing cost (Figure 1.4b).

Combination Release Mechanism

Examples of this category can best be illustrated by congealed microcapsules or extruded microparticles with additional film. coating (enrobing). This technique is most useful for manufacturing extremely "delayed release" profiles (Figure 1.4c).

Burst Release Mechanism

Burst release is simply described by a high initial delivery of an entrapped active, before the release reaches a stable profile, thus reducing the system's effective lifetime and complicating the release control. Although burst release may be preferred for flavor high-impact applications, in drugs this mechanism may lead to high toxicity levels and ineffective administration of the active.

Burst release can most often take place in reservoir and hydrogel systems, though it can still take place in matrix designs. Reasons for this range from cracks in the protective capsule shell to storage effect where the membrane becomes saturated with the active substances or due to very high active loading. When placed in a release medium, the active can quickly diffuse out of the membrane surface causing a burst effect (Huang and Brazel, 2001). Low-molecular-weight actives frequently undergo burst release, a result of high osmotic pressure and increased concentration gradient. Other reasons include: processing conditions, surface characteristics of host material, sample geometry, host/drug interactions, morphology, and porous structure of dry material.

Application of a coating material over a monolithic microparticle can help eliminate burst release, though might change the release profile. Other treatments include washing microparticles to extract surface droplets of actives.

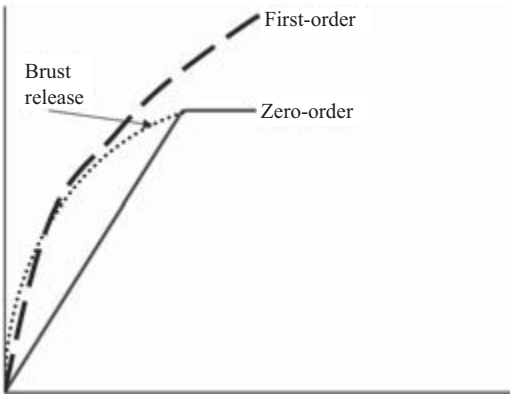

Figure 1.5. Release rates (zero-order, first-order, and burst) of microencapsulated systems.