Fundamental aspects of controlled release in foods

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The fundamental equations governing the controlled release of active ingredients and the application of controlled-release technology in food systems are reviewed in this article. The method of microencapsulation, among others, can be applied to achieve controlled release in foods. Some of the release mechanisms employed in the food industry involve one or a combination of the following stimuli: a change in temperature, moisture or pH; the application of pressure or shear; and the addition of surfactants. Encapsulation is a method of protecting food ingredients that are sensitive to temperature, moisture, microorganisms or other components of the food system. Such food ingredients include flavors, sweeteners, enzymes, food preservatives and antioxidants, and are encapsulated using carbohydrates, gums, lipids and/or proteins. With a properly designed controlled-release delivery system, the food ingredient is released at the desired site and time at a desired rate.

Food ingredients may be of natural origin or chemically prepared. In some cases, the natural ingredients can be less potent than the chemical counterparts. On the other hand, the permitted levels of chemical ingredients are low. In either case, it may be difficult to achieve the desired effect without adding high levels of the ingredient. Controlled release is a novel technology that can be used to increase the effectiveness of many ingredients. The performance of natural ingredients can be improved, thereby offering viable alternatives to the less acceptable chemical additives. The technology of controlled release, with its initial roots in the drug industry, has spread to other areas such as the agrochemicals, fertilizers, veterinary drugs and food industries.

Controlled release may be defined as a method by which one or more active agents or ingredients are made available at a desired site and time at a specific rate. With the emergence of controlled-release technology, some heat-, temperature- or pH-sensitive additives can be used very conveniently in food systems. Such additives are introduced into the food system mostly in the form of microcapsules.

The additive present in the microcapsule is released under the influence of a specific stimulus at a specified stage. For example, flavors and nutrients may be released upon consumption, whereas sweeteners that are susceptible to heat may be released towards the end of baking, thus preventing undesirable caramelization in the baked product. Also, carbon dioxide is released when an acid reacts with sodium carbonate during baking. Thus, controlled-release delivery systems may be categorized according to whether they involve physical or chemical methods of release of the active agent. Some of the physically and/or chemically controlled delivery systems that are available are presented in Fig. 1. This article first describes the variety of controlled-release mechanisms available, then gives some food industry applications, focusing especially on alternative approaches to microencapsulation, the most commonly used controlled-release system in the food industry.

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Methods of achieving controlled release in foods

The most commonly used method to achieve controlled release in the food industry is microencapsulation. Microencapsulation is defined as the technology of packaging solid, liquid or gaseous materials in miniature sealed capsules that release their contents at controlled rates under the influence of certain stimuli. The shape and size of the microcapsule depend on the shape of the food-additive material. The simplest microcapsule may consist of a core surrounded by a wall or barrier of uniform or non-uniform thickness. The core may be composed of just one or several different types of ingredients, and the wall may be single or multi-layered.

The techniques used for microencapsulation are spray drying, coating, extrusion, liposome entrapment, coacervation and freeze drying[2]. Of these methods, spray drying is the most commonly used. Generally, water-soluble polymers are used to encapsulate organic core materials and water-insoluble polymers for aqueous core materials. Because few suitable polymers have been approved for use in foods, certain food materials can be modified to increase their porosity and to alter other characteristics, thus enabling their use as coating materials in microencapsulation[3].

Other methods of achieving controlled release of food ingredients, besides microencapsulation, are molecular inclusion, adsorption and co-crystallization[2].

The advantages of controlled release are[3,4]:

- the active ingredients are released at controlled rates over prolonged periods of time;
- loss of ingredients, such as vitamins and minerals, during processing and cooking can be avoided or reduced;
- reactive or incompatible components can be separated.

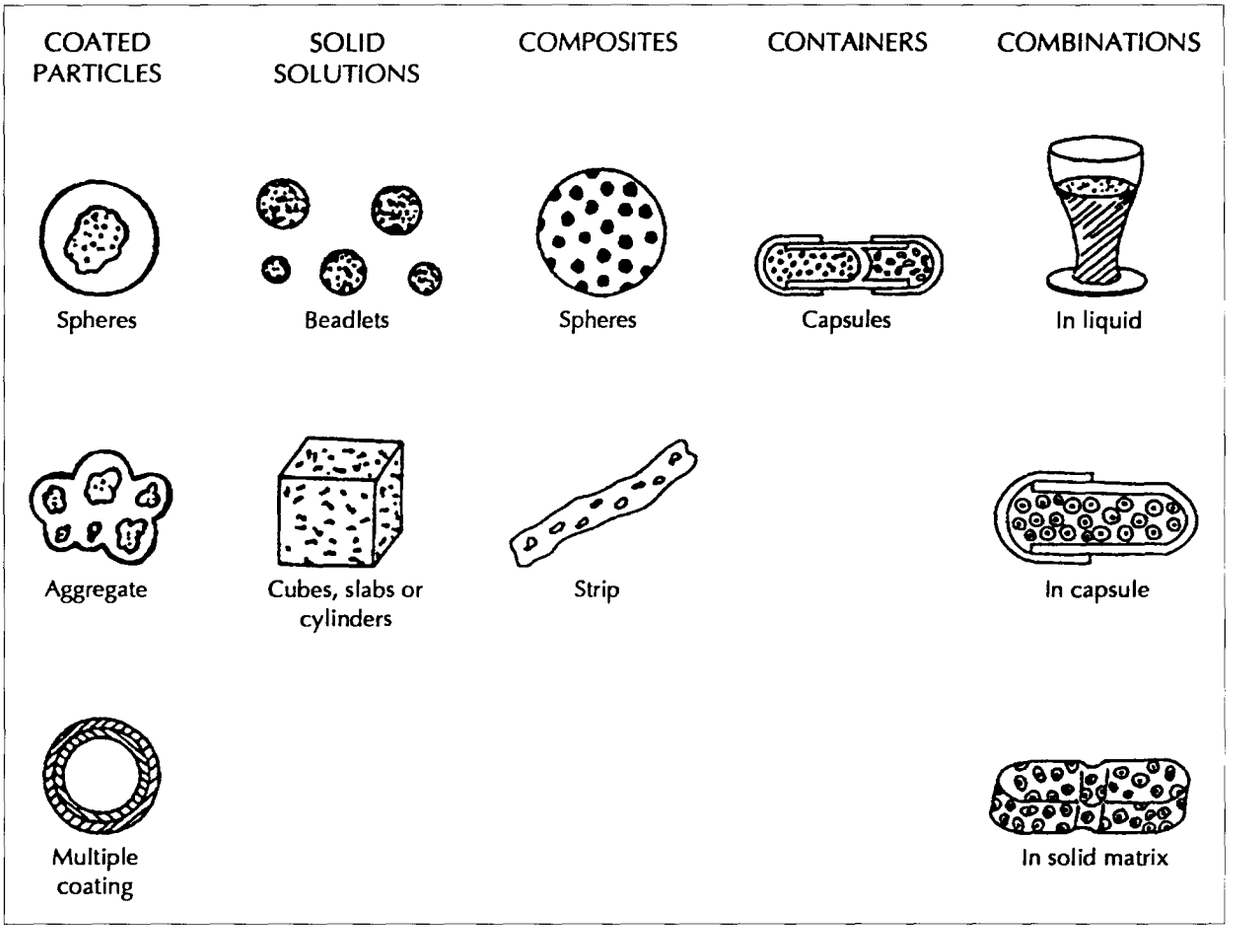


Fig. 1
Physical and chemical types of controlled-release systems. Adapted from Ref. 1.

The active agent is released from the controlled-release delivery systems by diffusion, biodegradation, swelling or osmotic pressure.

Release of active agent by diffusion

Reservoir systems

A reservoir system consists of an active agent contained within a rate-controlling barrier (Fig. 2a). Barriers may be microporous, macroporous or non-porous[6]. The most commonly used barrier is the non-porous homogeneous film[7]. The release rate from a reservoir system depends on the thickness, the area and the permeability of the barrier[5] (Fig. 3a). In a reservoir containing an excess of active agent, the release rate follows zero-order kinetics (i.e. the release rate is constant).

The principal steps in the release of an active ingredient from a reservoir system are[8]:

- diffusion of the active agent within the reservoir;
- dissolution or partitioning of the active agent between the reservoir carrier fluid and the barrier;
- diffusion through the barrier and partitioning between the barrier and the elution medium (i.e. the surrounding food);
- transport away from the barrier surface into the food.

The rate-limiting step in the release of the active ingredient is diffusion through the polymer. Several excellent reviews of the mathematical equations describing the rates of release of active ingredients in reservoir systems have been published[5,6,8,9]. The final form of the mathematical equations is presented here. The pattern of release of the active agent depends on the geometry of the system. The reservoir system containing the active agent is considered as the source, and the medium into which the active agent is released is termed the sink. If the amount of active agent present in the reservoir system is relatively high and the solubility of the active agent relatively low, the system is considered as an infinite source. Three idealized situations for the reservoir system (source) and the medium into which the active ingredient is released (sink) are

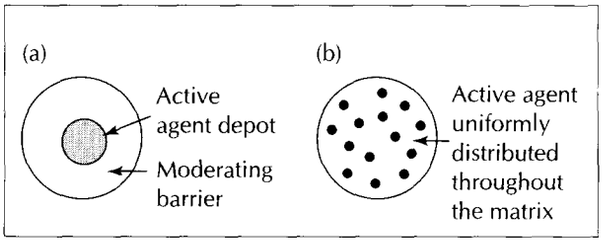
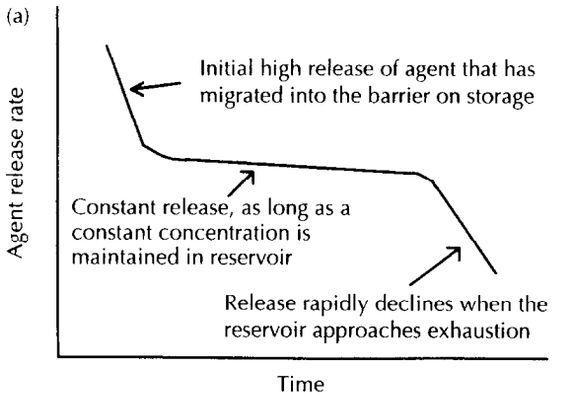
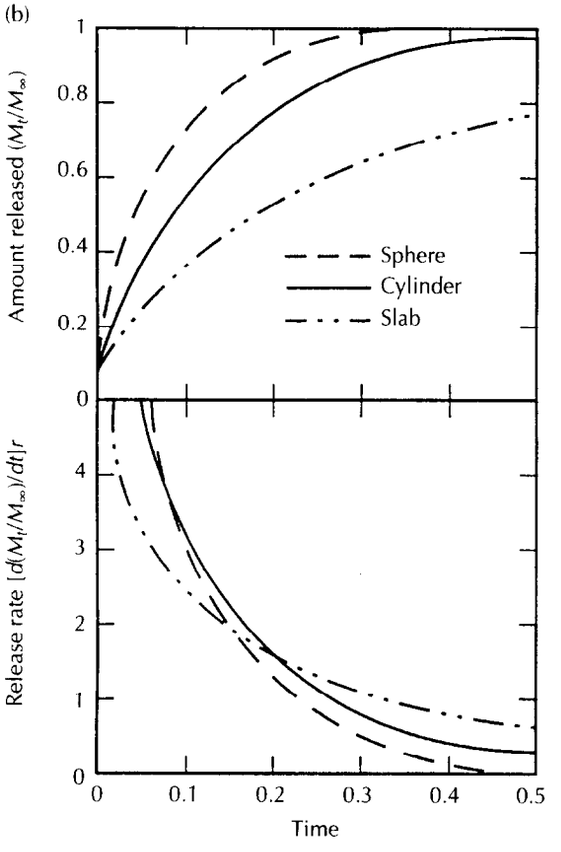


Fig. 2
Simple reservoir-type (a) and matrix-type (b) systems. Reproduced with permission from Ref. 5.





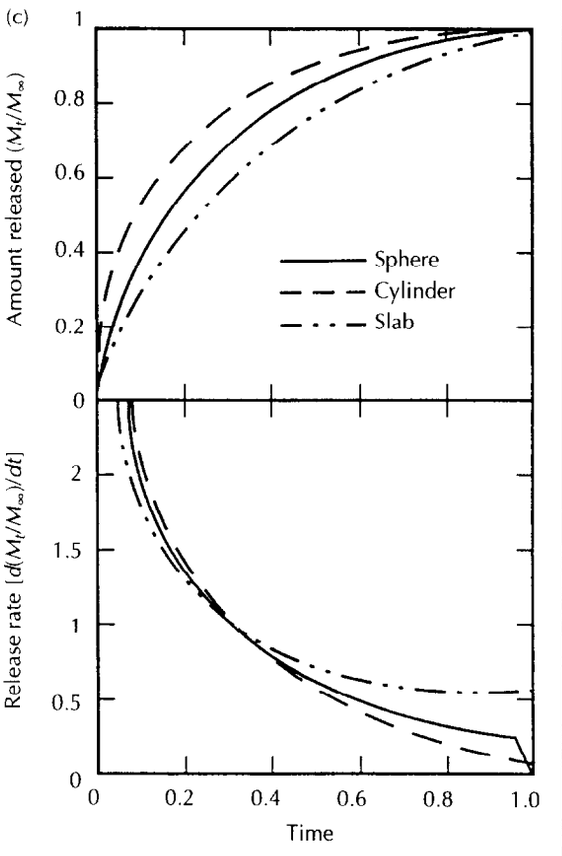


Fig. 3
(a), Rate of release of an active agent from a reservoir system. Reproduced with permission form Ref. 5. (b), Release pattern of an active agent dissolved in a slab-shaped, cylindrical or spherical matrix. Reproduced with permission from Ref. 9. (c), Release pattern of an active agent dispersed in a slab-shaped, cylindrical or spherical matrix. Reproduced with permission from Ref. 9. M_t is the amount of active agent released in time t; M_∞ is the total amount of active agent that can be released; r is the radius of the matrix.

considered. The amount of active agent released, M_t, in time t is given by the following equations[8]:

(1) for an infinite, well-agitated source and an infinite well-agitated sink:

$$M_t = \frac{AD_m k(C_1 - C_2)t}{\delta} \quad (1)$$

(2) for a finite source and a finite sink:

$$M_t = \frac{M_1V_2 - M_2V_1}{V_1 + V_2}\left\{1 - \exp\left[\frac{(V_1 + V_2)AD_m kt}{V_1V_2\delta}\right]\right\} \quad (2)$$

(3) for a sink and source that are not well-agitated, such that the boundary-layer resistance on the inner surface of the barrier has to be accounted for:

$$M_t = \frac{AC_{1\infty}t}{\frac{1}{k_1} + \frac{\delta}{K_1D_m} + \frac{K_2}{K_1k_2}} \quad (3)$$

where A is the barrier area, D_m is the diffusion coefficient of the active agent through the barrier, k is the mass transfer coefficient, C_1 and C_2 are the respective concentrations of the active agent in the source and in the sink, δ is the thickness of the barrier, M_1 and M_2 are the respective masses of the active agent in the source and in the sink, and V_1 and V_2 are the respective volumes of the source and the sink, $C_{1\infty}$ is the concentration in the bulk of the reservoir, k_1 and k_2 are the mass transfer coefficients on the reservoir and sink side, respectively, and K_1 and K_2 are the partition coefficients on the reservoir and sink side, respectively[8,9].

When the sink and source are not well-agitated, boundary-layer resistances on the surface of the barrier have to be considered. The release of the active agent in a system with boundary-layer resistance may be controlled either by barrier diffusion or by boundary-layer diffusion. If the time for diffusion of the active agent through the barrier is greater than the time for mass transfer across the boundary layers, the system is essentially barrier-diffusion controlled[8].

Barrier-diffusion-controlled reservoir systems are more efficient than most of the other controlled-release systems. The system can be designed so that the active agent makes up 90% of the volume of the system. However, such core-and-shell-type delivery systems are not commonly used in the food industry because manipulation of the release rate of the active ingredient is not simple, and leaks may alter the release rates[5].

Matrix systems

In matrix systems, the active agent is homogeneously dissolved or dispersed throughout the polymer mass (Fig. 2b). The release pattern depends on the geometry of the system, the type of carrier material and the loading of the active agent. The principal steps involved in the release of the active agent from a matrix system depend on whether the active agent is dissolved or dispersed in the matrix.

The steps involved in the release of an active agent that is dissolved in the matrix are[8]:

- diffusion of the active agent to the surface of the matrix;
- partition of the active agent between the matrix and the elution medium (i.e. the surrounding food);
- transport away from the matrix surface.

The simplest way to model the release rate from such a system is to consider an infinite, flat matrix system of thickness δ and with the active agent dissolved in the polymer at or below the saturation concentration. The amount of active agent released when the device is dissolved in a well-agitated, infinite medium is given by[6]:

$$\frac{M_t}{M_\infty} = 1 - \sum_{n=0}^{\infty} \frac{8}{(2n+1)^2 \pi^2} \exp\left[\frac{-D_m (2n+1)^2 \pi^2 t}{\delta^2}\right] \quad (4)$$

where M_∞ is the amount of active agent released at infinite time. During the early stages of release, when M_t/M_∞ is <0.6, the release rate varies as $t^{-0.5}$, whereas during the later stages of release when M_t/M_∞ is >0.6 and <1.0, the release rate decays exponentially with time (Fig. 3b).

The steps involved in the release of an active agent that is dispersed in the matrix are[8]:

- dissolution into the matrix;
- diffusion to the surface;
- transport away from the surface of the matrix.

Assuming pseudo steady-state release kinetics, the amount of active agent released at the surface of the polymer is given by[6]:

$$M_t = A[D_m C_{as}(2C_{ao} - C_{as})t]^{\frac{1}{2}} \quad (5)$$

where C_{as} is the solubility of the active agent in the polymer, and C_{ao} is the concentration of the active agent in the polymer (Fig. 3c).

Manipulation of the release rates from matrix systems is easier than from reservoir systems. Unlike the case with reservoir systems, leaks do not substantially alter the release rate from a matrix system.

Release of active agent by biodegradation

Biodegradable systems may be reservoir-type or matrix-type delivery systems. In a matrix-type delivery system, the active agent is dispersed within the polymer and is released when the polymer degrades or erodes[8] (Fig. 4a). Biodegradation of the polymer must result in the formation of nontoxic components. For one class of biodegradable polymers, the surface area of the matrix decreases with time, resulting in decreasing release rates. Such systems are designed to contain a higher concentration of the active agent in the interior than in the surface layers. For a second class of biodegradable polymers, the polymer degrades very slowly in the initial stages, but the degradation rate increases rapidly in the later stages owing to autocatalysis, and the bulk erodes over a comparatively short period.

The release of an active agent from a matrix-type delivery system may be controlled by diffusion, erosion or a combination of both. If erosion of the matrix is much slower than diffusion, the release kinetics can be predicted by Eqns 4 and 5. In addition, erosion-controlled processes may involve heterogeneous or homogeneous erosion. Heterogeneous erosion occurs when degradation is confined to a thin layer at the surface of the delivery system, whereas homogeneous erosion is a result of degradation occurring at a uniform rate throughout the polymer matrix. The type of erosion, heterogeneous or homogeneous, depends on the hydrophobicity and morphology of the polymer. Heterogeneous erosion is more common with hydrophobic polymers, whereas homogeneous erosion is common with hydrophilic polymers.

Heterogeneous erosion is more desirable because it can lead to a constant release rate that is independent of the chemical and physical properties of the active agent. The release rate can be varied by varying the active-agent loading while maintaining the integrity because erosion is limited to the surface. The amount of active agent released in heterogeneous erosion is given by[6]:

$$\frac{M_t}{M_\infty} = 1 - \left[1 - \frac{k_0 t}{C_0 r}\right]^n \quad (6)$$

where M_∞ is the total amount of active agent that can be released, k_0 is the erosion rate constant, C_0 is the initial

concentration of active agent in the matrix, r is the radius of a spherical or cylindrical matrix or the half-thickness of a slab (rectangular) matrix and $n = 3$ for a spherical, $n = 2$ for a cylindrical and $n = 1$ for a slab-shaped matrix.

Release of active agent by swelling

In swelling-controlled systems, the active agent dissolved or dispersed in a polymeric matrix is unable to diffuse to any significant extent within the matrix. When the polymer matrix is placed in a thermodynamically compatible medium, the polymer swells owing to absorption of fluid (penetrant) from the medium. The active agent in the swollen part of the matrix then diffuses out[8]. In diffusion-controlled systems the barrier or matrix is assumed to be unaffected during the release process, whereas in swelling-controlled systems, the membrane undergoes a transition from a glassy to a gel state upon interaction with the penetrant. The polymer chains in the gel state, being more mobile than those in the glassy state, allow the active agent to diffuse out of the matrix more rapidly. The release rate is determined by the glass-to-gel transition process. The quantity of active agent, M_t, released at any time t is given by[10]:

$$\frac{M_t}{M_\infty} = k_a t^n \qquad (7)$$

where M_∞ is the initial active-agent loading of the polymer, and k_a and n are system parameters that depend on the nature of the polymer–penetrant–active-agent interaction.

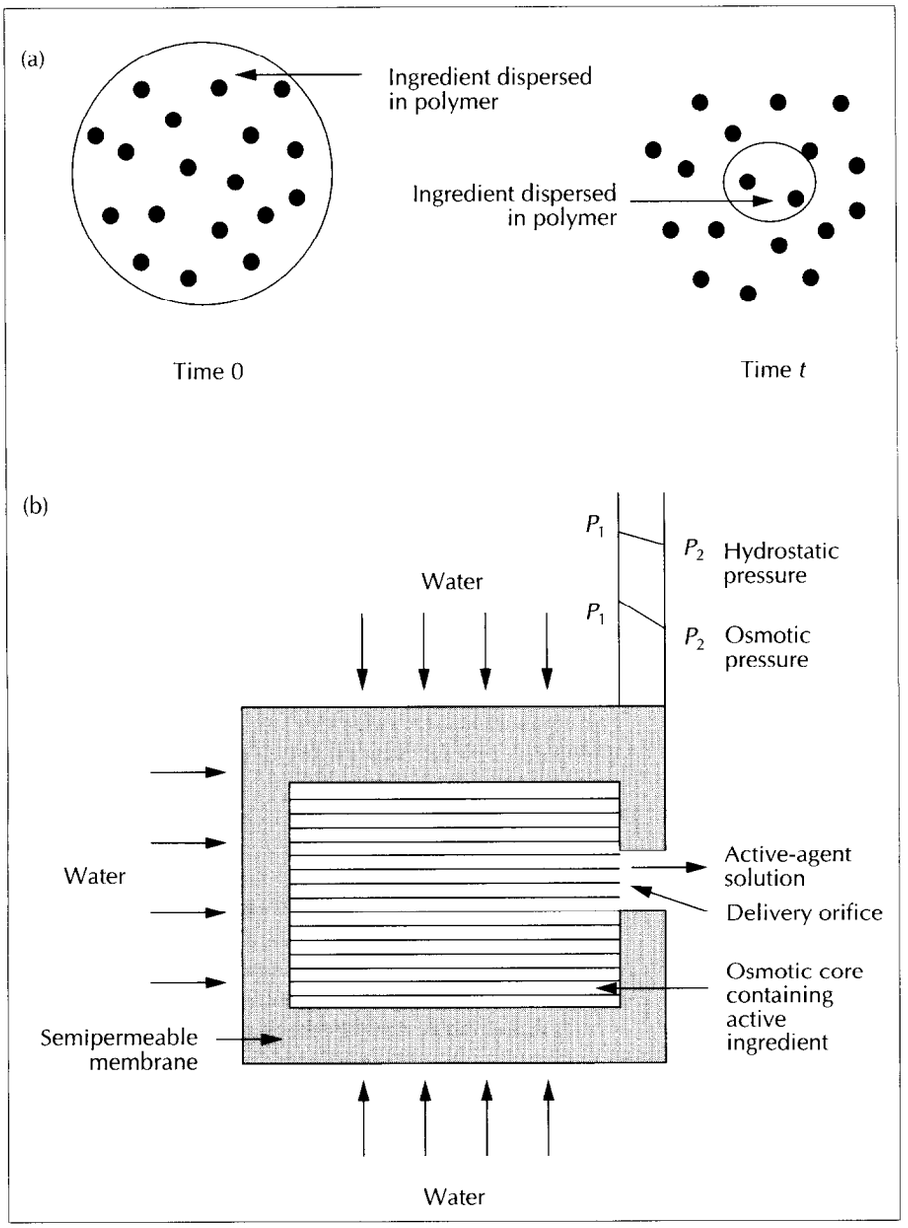


Fig. 4
(a), Erosion-controlled system; (b), elementary osmotic pump. Reproduced with permission from Ref. 8.

The parameter n can take a range of values that indicate the type of active-agent transport. When $n = 0.5$, the active agent is released by simple Fickian diffusion. When $n = 1.0$, diffusion is described as 'case II diffusion'. In case II diffusion, the rate of solvent uptake by the polymer is largely determined by the rate of swelling and relaxation of the polymer chains[5]. 'Super case II transport' occurs when $n > 1.0$. In the $0.5 < n < 1.0$ region, diffusion is a combination of Fickian and non-Fickian diffusion, and is known as anomalous diffusion. A summary of the different types of active-agent transport based on the n values is given in Table 1 (Ref. 8).

The swelling membrane consists of three zones. Adjacent to the solvent surface is the completely swollen gel; next is a fairly thin swelling zone in which the polymer chains are relaxing; and, finally, there is a layer of unswollen, completely dehydrated rigid polymer matrix in the glassy state. The swelling zone moves into the membrane at a uniform rate, and solvent gain in the polymer increases with time. The rate of relaxation of the polymer chains from the glassy state to the gel state is the slowest step in the sorption process.

Release of active agent by osmotic pressure

In an osmotic system, the active agent is released from the microcapsule at a controlled rate by utilizing osmotic pressure as the driving force (Fig. 4b). The active agent (core) is enclosed in a selectively water-permeable polymeric membrane with a small orifice. The membrane is impermeable to the active agent. In

Table 1. Swelling-controlled release systems[a]

n	Type of active agent transport	Time (*t*) dependence of diffusional release
0.5	Fickian	$t^{-0.5}$
$0.5 < n < 1.0$	Non-Fickian (anomalous transport)	t^{n-1}
1.0	Case II transport	Time independent
$n > 1.0$	Super case II transport	t^{n-1}

[a] Data taken from Ref. 8
n, The system parameter

an aqueous environment, water permeates through the membrane into the core. If the active agent has high solubility in water, a large osmotic pressure is created inside the microcapsule. The active agent is released when the osmotic pressure exceeds the maximum force that the walls of the microcapsule can tolerate[3,8].

The net volumetric flux of water, J_w, into the core is given by[8]:

$$J_w = \frac{L_p \sigma RT(C_{a2} - C_{a1})}{\delta} - \frac{L_p(P_2 - P_1)}{\delta} \qquad (8)$$

where L_p is the hydraulic permeability of the membrane, σ is the reflection coefficient of the membrane, $RT(C_{a2}-C_{a1})$ is the osmotic pressure difference, C_{a2} is the concentration of active agent in the surrounding medium, C_{a1} is the concentration of active agent within the microcapsule, (P_2-P_1) is the hydrostatic back pressure, and δ is the thickness of the barrier. The reflection coefficient characterizes the porosity of the membrane, with $\sigma = 1$ for an ideal semipermeable membrane, and $\sigma = 0$ for a porous membrane.

Controlled release in foods

The food industry is taking advantage of the technology of controlled release for food additives including flavoring agents (flavor oils, spices, seasonings), sweeteners, colors, nutrients (vitamins, amino acids, minerals), essential oils, acids, salts, bases, antioxidants, antimicrobial agents, preservatives, ingredients with undesirable flavor and crosslinking agents[11,12]. Controlled release helps to overcome both the ineffective utilization and the loss of food additives during the processing steps. The release of an active agent may be based on one or a combination of release mechanisms[13]; these can be time specific, site specific, rate specific and/or stimulus specific.

Brannon-Peppas categorized the release mechanisms as follows[3].

- Diffusion-controlled release: active ingredient is released by diffusion through the polymer (carrier of the system) or through the pores pre-existing in the polymer [analogous to the 'matrix systems' described in Eqns 4 and 5].
- Barrier-controlled release: release of active ingredient depends on the concentration difference across the wall of the microcapsules, thickness of the wall, permeability through the wall, and diffusion coefficient of the active ingredient in the surrounding environment [analogous to the 'reservoir systems' described in Eqns 1–3].
- Pressure-activated release: active ingredient is released when pressure is applied on the walls of the microcapsules [an example would be the release of sweetener and/or flavor in gum when chewed; the release kinetics cannot easily be characterized because of the nature of the activation mechanism].
- Solvent-activated release: active ingredient is released when the food material comes in contact with a solvent, resulting in swelling of the microcapsule [analogous to the 'swelling-controlled systems' described in Eqn 7].
- Osmotically-controlled release: active ingredient is released owing to large osmotic pressures created inside the microcapsules [see Eqn 8].
- pH-controlled release: active ingredient (e.g. an enzyme) is released at a specific pH [this system can be used alone or may be combined with solvent-activated or osmotically controlled release systems].
- Temperature-sensitive release: active ingredient is released owing to a change in temperature [temperature may affect the melting rate (see below), the osmotic pressure, the glassy or gel state of the polymer in 'swelling-controlled systems', and the partition coefficients in some other systems].
- Melting-activated release: fat or wax used as a coating material melts when the food product is heated and the active ingredients are released.
- Combined systems: active ingredient is released as a result of the combination of different mechanisms.

Controlled-release systems in foods are developed based on the above-mentioned fundamental concepts and release mechanisms [the classification scheme of Brannon-Peppas does not clearly include the case of biodegradation (Eqn 6); the closest case is the solvent-activated system, but here the release is due to swelling, not to erosion]. The development of a controlled-release system that will adequately protect the food additive and release it at the desired time and site at a desired rate presents quite a challenge.

Applications of controlled release in foods

Food additives, such as acidulants, flavoring agents, sweeteners, colorants, lipids, vitamins, minerals, enzymes, microorganisms, gases such as carbon dioxide in candies, antioxidants and food preservatives are sometimes used in encapsulated form in the food industry[12].

The food additive (active agent) can be encapsulated using carbohydrates, gums, lipids, proteins, polymers such as poly(vinyl) acetate (PVA), a fiber matrix made of polymers, and/or liposomes[11,13–16]. One or more materials may be used for encapsulation depending on the type of application.

The active agent is released by one or a combination of the release mechanisms described earlier. In an ideal system, the release of the active agent from the system may follow zero-, half- or first-order kinetics. Zero-order release (constant release rate) occurs when the core is a pure material that is released from the system as a pure material. Half-order release generally occurs with matrix particles, and first-order release occurs when the core is actually a solution. In practical systems, the release rate of the active agent might not be zero, half or first order[11]. Thus, the kinetics of the release of the active agent is complicated. However, the release mechanisms and release-rate equations described earlier provide a basis for the design of controlled-release systems. The application of controlled release in the use of additives, such as flavors, sweeteners, enzymes, food preservatives and antioxidants, will be discussed.

Flavors

The loss of flavors during the processing or storage of foods is a very common occurrence in the food industry. Flavors are very volatile, react with other components and are susceptible to heat and moisture. Because flavor is a desirable characteristic of foods, it is necessary to find methods that allow flavors to be retained in food for a longer time period. Microencapsulation and controlled release offer a method for protecting flavor compounds.

When a flavor is added to chewing-gum base in the 'free' form, only 5–40% of the flavor is released upon chewing; the remainder becomes irreversibly bound to the gum base and cannot be chewed out. It is desirable to be able to obtain increased intensities and the controlled release of such flavors.

Encapsulation is one method that can be used to achieve both improved and prolonged release of flavor compounds and other food additives. Encapsulation by spray drying and extrusion are the two major processes used commercially. Freeze drying, coacervation, fat or wax encapsulation, plating and inclusion in cyclodextrins are less commonly used for commercial purposes[17]. Flavor encapsulation by spray drying, extrusion, coacervation and molecular inclusion in cyclodextrins has been reviewed by Reineccius[17].

Some methods utilizing fat or wax encapsulation have been described in patents by Cherukuri *et al.*[18], Rutherford *et al.*[19], and Reed and Hook[20]. Fat-encapsulated cheese flavor used in microwave popcorn gives uniform distribution of the flavor[21]. The flavor is released when the temperature rises to 57–90°C. Flavors that are released at microwave temperatures have the potential to become popular.

Molecular inclusion is one of the methods of avoiding the loss of flavors during storage of the food product or as a result of exposure to light or oxygen. Molecular inclusion with β-cyclodextrin is a suitable method for reducing the loss of coffee flavors as well as for reducing the bitterness of coffee drinks[22]. Cyclodextrin, a modified starch derivative, behaves like an empty molecular capsule with the ability to entrap 'guest' molecules of appropriate geometry and polarity. The guest molecules are protected from light, heat and oxidation when the complex is in the dry state. The entrapped molecules are released from the molecular-inclusion system on contact with water[23]. Molecular inclusion of coffee flavors improves the storage stability, heat stability and UV-light stability compared with an unprotected (exposed) system composed of coffee flavor adsorbed onto lactose. Although cyclodextrins offer good protection to flavoring agents, the cost of cyclodextrins is a limiting factor in their applicability on a commercial scale. It is estimated that the cost of cyclodextrins cannot be reduced below $5.5–$6.6 per kg (Ref. 17). Also, cyclodextrins do not have 'generally recognized as safe' (GRAS) status[17].

Controlled-release systems may be designed to change the composition of the flavor mixture being released with time, thus compensating for the differential rates of the loss of the components of the original food flavor[12]. The delivery system described in Eqn 4 considers the change in the rate of release of active agent with time.

Sweeteners

Artificial sweeteners are widely used in a variety of foods such as chewing gum and confectionery products, pharmaceutical preparations, and oral hygiene products such as mouthwash and toothpaste. One of the commonly used sweeteners is L-aspartyl-L-phenylalanine methyl ester (aspartame or APM). The delivery system described by Chau *et al.*[24] consists of 0.01–60% sweetener, 40–93% PVA, 0.1–20% waxy material and 0.1–20% emulsifying agent. Like flavor compounds, APM is susceptible to heat, moisture and other components of the food. Sweeteners, in general, are protected by encapsulation in fat, PVA, starch, zein or shellac, amongst others.

Encapsulation by spray drying or by using fluidized-bed techniques requires both an investment in equipment with sophisticated process controls and skilled operating personnel. Another method believed to be more economical for producing encapsulated sweetener has been described in a patent by Zibell *et al.*[25] The method involves mixing uncoated APM with an agglomerating agent, such as hydroxypropyl methyl cellulose, and dampening it with water so that it is dust free, non-flowable, non-extrudable and crumbly. The mixture is then dried, ground and sieved to produce a maximum particle size of 0.43 mm. The release rate of the sweetener when incorporated in chewing gum depends on the particle size (Table 2). More than one agglomerating agent, each with different solubility properties, may be used to obtain a stepped release of the sweetener.

Table 2. Dependence of particle size on the rate of release of sweetener[a]

Particles <0.074 mm in the mixture (%)	Sweetener released in 6 min (%)
10	22
27	50
65	52
Unencapsulated	84

[a] Data taken from Ref. 24

Active agents such as sweeteners, acidulants and flavors can also be encapsulated by dispersion throughout a fiber matrix[26]. The fiber matrix is made up of polyethylene, PVA, polyester or chitosan. The fibers (+60 mesh) have open ends, exposing the active ingredients. Gradual release of the active agent occurs when the fiber is brought into contact with a solvent. The fiber is either insoluble or less soluble in the solvent than the active agent. The active agent at the openings of the fiber ends is dissolved by the solvent, resulting in the creation of channels within the fiber. The solvent fills the channels and dissolves the newly exposed active agent. Thus, the release of the active agent is based on swelling of the delivery system.

The incorporation of several controlled-release delivery systems that release the sweetner at different rates can provide improved and prolonged sweetener intensities in a food system.

Enzymes

One of the methods of controlling the release of enzymes is to encapsulate them in liposomes. A liposome is a versatile carrier system used in the food industry, mainly for the encapsulation of enzymes. Liposomes are artificially made, microscopic barrier vesicles, consisting of one or more concentric layers of lipid, generally phospholipid. The permeability, stability, affinity and surface activity of liposomes depend on the size of the vesicle and the lipid composition[13]. The encapsulation efficiency, defined as the fraction of the aqueous compartment sequestered by the lipid layers, is directly proportional to the lipid concentration; when more lipid is present, more solute can be sequestered within the liposome[27]. Liposome-encapsulated enzymes can be used in two different ways[14]: (1) as delivery systems for the controlled release of enzymes in food systems, and (2) as enzyme reactors for immobilizing and improving the stability of an enzyme while allowing the entry and exit of substrates and products.

Liposome encapsulation of the enzyme neutrase reduces the enzyme requirement by 100-fold and the time required for ripening of Cheddar cheese by 50% compared with the conventional ripening processes[28]. In the conventional cheese ripening process, the enzyme is added before or at the curd stage. Addition of neutrase before the curd stage results in the premature breakdown of casein into amino acids and also loss of the enzyme, amino acids and protein to the whey. Addition of the enzyme at the curd stage avoids premature breakdown of casein, but produces cheese that has a crumbly texture after three months. Addition of liposome-encapsulated enzyme to cheese milk prevents the premature breakdown of casein and loss of the enzyme to the whey. The enzyme is released after the removal of the whey and is uniformly distributed in the milk. The cheese obtained develops the Cheddar flavor much earlier than when free enzyme is used. In addition, the normal Cheddar texture is retained for at least eight months when encapsulated enzyme is used. Although the rate of ripening of the cheese is higher when the enzyme is used in the free form, use of encapsulated enzyme is more favorable because the resultant cheese has a better texture.

The enzymes lysozyme and pepsin, encapsulated in liposome, are released by one or a combination of the following stimuli: change in pH from 1.5 to 2.5, temperature change, or the addition of surfactants[29], such as Tween 80, and food-grade additives, such as Ca^{2+} ion. Tween 80 exerts a mild effect on the release of the enzymes at 10°C while increasing the release rate at 37°C. Addition of Ca^{2+} (25 mM) results in 17–25% of the lysozyme and pepsin being pulse released during the first hour. Very little additional release of enzyme takes place with an increase in the temperature. There is no change in the activities of the enzymes when present in the encapsulated form.

Liposomes are used as enzymatic reactors to remove the undesirable phenolic compounds from food products, drinking water and waste streams. Liposomes offer the advantages of structural versatility, biodegradability, stability under storage, nontoxicity and the ability to encapsulate more than one active ingredient[14].

Encapsulated amylases and proteases may be used for taste modification and texture control[10]. Lipases, lipoxidases and isomerases may be important in aroma formation[10].

Food preservatives

The addition of large amounts of preservatives to intermediate-moisture foods is not desirable from a sensory point of view. One alternative is to concentrate the preservative at the surface, and to use one or more layers of edible coating, such as zein, on the surface of the food. The zein coating acts as a barrier regulating the diffusion of the food preservative from the surface into the bulk; the preservative diffuses into the food through the coating at a rate that depends on the thickness of the zein layer. The thickness of the zein coating varies in the range 0.03–0.04 mm. The surface becomes more susceptible to contamination as the concentration of the preservative at the surface decreases[30].

When the bulk of the food material needs to be protected from contamination, encapsulated organic acids such as citric acid, ascorbic acid and lactic acid can be used as antimicrobial agents. The acid may be encapsulated in a matrix comprising PVA, recently approved for

use in foods (S.M. Faust, pers. commun.), and an emulsifier. The molecular weight of PVA chosen depends on the water solubility of the acid (Table 3). The emulsifier may be lecithin, stearates, palmitates or ester derivatives of stearates. The acid is released when the system swells in the presence of water. The food acid amounts to 20–40% (w/w) of the controlled-release delivery system[16].

Levi and Karel[31] studied the release of an organic volatile probe (*n*-propanol) incorporated in crystallizing or non-crystallizing amorphous carbohydrate glasses. The temperature at which the glasses were held, the glass transition temperature (T_g), moisture content and matrix deformation under gravity had significant effects on the retention of the probe. The release rates of the probe as a function of temperature above T_g can be well predicted by using the William–Landel–Ferry equation. Food ingredients such as acidulants and preservatives can be incorporated in these types of glass matrices.

Lysozyme encapsulated in liposomes is used to prevent spoilage due to spore-forming bacteria in Gouda, Edam and Emmental cheeses[13]. The bacteria produce undesirable flavor and texture changes in cheese as a result of butyric acid fermentation. The application of free lysozyme is limited because it binds with casein in the milk, thereby reducing its efficacy to prevent microbial spoilage. Also, the use of nitrates in many countries for the control of bacterial spoilage is a matter of health concern. Liposome-encapsulated nisin is instead used to prevent the growth of *Listeria monocytogenes* in low-fat cheeses[13].

Antioxidants

The recent trend in food consumption has resulted in the replacement of saturated fat with unsaturated fats in the diet. However, unsaturated fats are prone to the problem of oxidation. The natural lipid-soluble α-tocopherol (vitamin E) can be used as an antioxidant. α-Tocopherol can be regenerated from its oxidized form using ascorbic acid, but in a food system, the α-tocopherol is soluble in the lipid phase and cannot interact with the water-soluble ascorbate. Therefore, the food industry uses lipid-soluble derivatives of ascorbate. Unfortunately, however, the effective dispersal of the lipid-soluble derivatives of vitamin C requires high temperatures, thus increasing the risk of oxidation of the unsaturated fats[32].

The problem of the solubility of ascorbate and the recent ban on the use of synthetic antioxidants has led to the use of liposome-encapsulated natural antioxidants such as α-tocopherol. The liposome-encapsulated system is used as an emulsifier to stabilize an oil-in-water food emulsion[13] (Fig. 5). α-Tocopherol is incorporated into the liposome barrier whereas the ascorbate is entrapped in the aqueous interior. The encapsulated system is added to the aqueous phase and encouraged to accumulate at the water–oil interphase. Thus, the antioxidant can be targeted at the site where oxidative reactions generally occur, and also avoid the reaction of ascorbate with other food ingredients[33].

Table 3. Water solubilities of food acid based on molecular weight[a]

Water solubility of the food acid	Molecular weight of poly(vinyl) acetate (Da)
Low	2000–18 000
Medium	15 000–25 000
High	20 000–65 000

[a] Data taken from Ref. 16

Miscellaneous additives

A leavening system is used to provide a porous and cellular structure in baked products. The porous structure is imparted to the product by a gas being released under appropriate conditions of moisture and temperature. A leavening system, commonly consisting of sodium carbonate or bicarbonate and an acid, is found in self-raising flours, prepared baking mixes, household and commercial baking powders and refrigerated dough products. The acid is either present in the dough or is incorporated as an additive. Leavening acids used in foods include potassium acid tartarate, sodium aluminum sulfate, δ-gluconolactone, and ortho- and pyrophosphates. The reaction between acid and bicarbonate results in the release of carbon dioxide, which imparts the porous structure to the product. To allow the slow release of carbon dioxide, slow-acting leavening acids such as monocalcium phosphate coated with alkali metal phosphates are used[34].

Changes in flowability, solubility and water sorption can be avoided by encapsulating salts, including sodium chloride. Encapsulation of salt also helps to avoid the catalytic peroxidation of lipids[10].

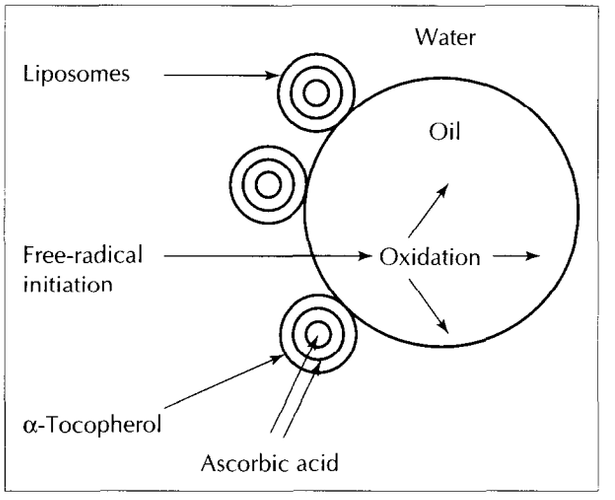


Fig. 5
Protection of a food emulsion by the liposome antioxidant system. Reproduced with permission from Ref. 13.

Concluding remarks

Some of the fundamental aspects of controlled-release technology have been discussed, and the basic equations used to predict the rate of release of active agents from various delivery systems have been reviewed. It is quite a challenge to apply the knowledge gained from the encapsulation of drugs to the food industry. It is possible to incorporate more than one food additive in the controlled-release delivery system; for example, sweetener and flavor compounds may be combined by encapsulating flavors in a matrix comprising sweetener enhancers such as thaumatin, monellin or dihydrochalcones[18].

Because few polymers have been approved by the US Food and Drug Administration for use in the food industry, research is still being conducted to modify food polymers to facilitate the encapsulation of active ingredients. Some of the applications of controlled-release delivery systems in foods mentioned here are patented information. It is not clear whether these systems are used on a commercial basis.

References

1 Zeoli, L.T. and Kydonieus, A.F. (1983) in *Controlled Release Technology* (Das, K.G., ed.), pp. 61–120, John Wiley & Sons
2 Jackson, L.S. and Lee, K. (1991) *Lebensm.-Wiss. Technol.* 24(4), 289–297
3 Brannon-Peppas, L. (1993) in *Polymeric Delivery Systems: Properties and Applications* (ACS Symposium Series 520) (El-Nokaly, M.A., Piatt, D.M. and Charpentier, B.A., eds), pp. 42–52, American Chemical Society
4 Dziezak, J.D. (1988) *Food Technol.* 42, 136–151
5 Baker, R.W. (1986) *Controlled Release of Biologically Active Agents*, Wiley-Interscience
6 Langer, R. and Peppas, N. (1983) *JMS-Rev. Macromol. Chem. Phys.* C(23), 61–126
7 Langer, R. and Karel, M. (1981) *Polym. News* 7, 250–258
8 Fan, L.T. and Singh, S.K. (1989) *Controlled Release: A Quantitative Treatment*, Springer-Verlag
9 Baker, R.W. and Lonsdale, H.K. (1974) in *Controlled Release: Mechanisms and Rates in Controlled Release of Biologically Active Agents* (Tanquary, A.C. and Lacey, R.E., eds), pp. 15–71, Plenum Press
10 Peppas, N. (1984) in *Recent Advances in Drug Delivery Systems* (Anderson, J.M. and Kim, S.W., eds), pp. 279–298, Plenum Press
11 Shahidi, F. and Han, X-Q. (1993) *CRC Crit. Rev. Food Sci. Nutr.* 33(6), 501–547
12 Karel, M. (1987) in *Biotechnology and Food Process Engineering* (IFT Basic Symposium Series) (Schwartzberg, H.G. and Rao, M.A., eds), pp. 277–293, Marcel Dekker
13 Kirby, C. (1991) *Food Sci. Technol. Today* 5(2), 74–78
14 Anon. (1988) *Food Flavor. Agents Packag. Process.* 10(8), 31–35
15 Song, J.H. and Courtright, S.B. (1992) US Patent 5 128 155
16 Cherukuri, S.R., Mansukhani, G. and Faust, S.M. (1991) US Patent 5 057 328
17 Reineccius, G. (1994) in *Source Book of Flavors* (Reineccius, G., ed.), pp. 605–625, Chapman & Hall
18 Cherukuri, S.R., Faust, S.M. and Orlandi, D.A. (1989) US Patent 4 803 082
19 Rutherford, H.J., Desai, N., McDermott, K. and Wiener, C. (1992) US Patent 5 116 627
20 Reed, M.A. and Hook, J.S. (1992) US Patent 5 100 678
21 Tan, C-T., Kang, Y.C., Sudol, M.A., King, C.K. and Schulman, M. (1991) US Patent 5 064 669
22 Szente, L. and Szejtli, J. (1986) *J. Food Sci.* 51(4), 1024–1027
23 Szente, L. and Szejtli, J. (1988) in *Flavor Encapsulation* (ACS Symposium Series 370) (Risch, S.J. and Reineccius, G.A., eds), pp. 148–157, American Chemical Society
24 Chau, T.L., Cherukuri, S.R. and Tolliver, E. (1992) US Patent 5 108 763
25 Zibell, S.F., Pate, M.M., Dave, J.C. and Payne, R.A. (1993) US Patent 5 221 543
26 Song, J.H. and Copper, C.M. (1992) US Patent 5 165 944
27 Deamer, D.W. and Uster, P.S. (1983) in *Liposomes* (Ostro, M.J., ed.), p. 27, Marcel Dekker
28 Kirby, C.J., Brooker, B.E. and Law, B.A. (1987) *Int. J. Food Sci. Technol.* 22, 355–375
29 Koide, K. and Karel, M. (1987) *Int. J. Food Sci. Technol.* 22, 707–723
30 Torres, J.A. (1987) in *Water Activity: Theory and Applications to Food* (Rockland, L.B. and Beuchat, L.R., eds), pp. 329–368, Marcel Dekker
31 Levi, G. and Karel, M. (1995) *J. Food Eng.* 24(1), 1–14
32 Reineccius, G.A. (1991) *Food Technol.* 45(3), 144–146
33 Kirby, C. (1990) *Chem. Br.* 26, 847–850
34 Lindsay, R.C. (1985) in *Food Chemistry* (Fenemma, O.R., ed.), pp. 629–687, Marcel Dekker