

Chapter 2

Factors and Mechanisms in Microencapsulation

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2.1 INTRODUCTION

Microencapsulation technology serves two key applications in the food industry. The technology is used extensively for providing stability of the active ingredient in food products, which may otherwise render undesirable functionality. Whether the product relates to flavors, chewing gum, candies, coffee, probiotics, health foods, vitamins, minerals, or enzymes, the governing principles to achieving desirable product stability can be managed by controlling the structural design of the microcapsule that offers improved performance in the food products.

Another primary application of microencapsulation technology is to bring a desired physicochemical change in sensory perception in the food product at the desired time or by using a suitable triggering mechanism. Having an improved understanding of the molecular and physicochemical interaction of the active ingredient and material composition is critical to creating such a *dynamic* system.

This chapter describes the factors and the theoretical mechanisms that impact the stability, mass transport, and offer triggered release. The major building blocks for developing food-grade delivery systems are given. This section is followed by design concepts for the microcapsule structure. Because food products are complex, multicomponent systems, a discussion of multivariant characteristics of the factors is presented. The chapter concludes with a comparison of the theory and industry practice with regards to release mechanisms.

2.2 STRUCTURAL DESIGN OF THE MICROCAPSULE

A microcapsule comprises many different components of which the active ingredient and the matrix polymer are the two key components that control the rate of diffusion. Understanding the morphology, physicochemical compatibility, and thermodynamics of both the active and matrix polymer is important.

In food systems, the microcapsule shell can provide several different functionalities for stability:

- Protection of sensitive active ingredients such as flavors, vitamins, minerals, unsaturated lipids, essential oils, and salts from oxygen, water, and light.
- Processing convenience by converting difficult-to-handle liquids to powdered food systems.
- Separation of two components during storage hold time.

From a morphological or structural standpoint, the factors affecting the stability and release are type, size, shape, and payload of the microcapsules. Also, molecular weight of the active, functional moiety and surface charge, concentration, solubility, wettability, and temperature are important parameters and they will be discussed in the following sections.

2.3 MICROCAPSULE OR MICROSPHERE TYPE

Morphological configuration in which the active ingredient is configured into a microcapsule with a distinct matrix wall around the active ingredient, or in microsphere morphology where the active ingredient is contained in a number of small discrete droplets or particles that are dispersed in the matrix material, can significantly impact stability and release of the active ingredient. One may also envision that the small droplets in a microsphere are so small that the active may be inherently soluble in the matrix polymer. Figure 2.1 shows the different structural configurations of microencapsulated systems and presents how the active ingredient is distributed in the matrix polymer, however, both microcapsule and microsphere morphologies must be free of defects, pin holes, or high curvatures to provide enhanced stability. The presence of defects can cause oxidative or hydrolytic degradation over longer periods of time.

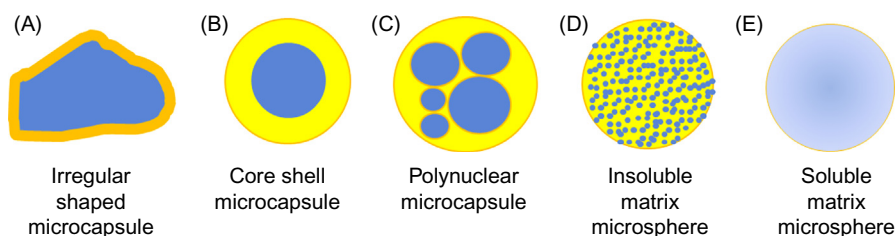


FIGURE 2.1 Microcapsule (A, B, and C) versus microsphere (D and E) morphology.

2.4 MICROCAPSULE SIZE, SHAPE, AND PAYLOAD

Particle size is one of many parameters that may be adjusted to control release rates of encapsulated ingredients, as shown in Figure 2.2.

The size of the microcapsule (or microsphere) and its corresponding active payload are interrelated. For a defined microcapsule size, a lower active loading in a microcapsule will offer better protection than a high loading, because the thickness of the matrix wall increases dramatically with a decrease in loading. Table 2.1 shows how the volume of the thickness of the shell wall is impacted by the size of the microcapsule and loading. This is also described in a plot in Figure 2.3. As the microcapsule shell thickness increases, the ability of the microcapsule to provide barrier properties increases.

Note that as the microcapsule dimensions become smaller and smaller, the thickness approaches infinitesimal values (i.e., nanoscale). In other words, large microcapsules of the same active loading offer the advantage of greater stability because the surface area per unit mass of the active is significantly higher as the surface area of transport increases as a square of the radius of the microcapsule. Figure 2.4 describes the relationship between the microcapsule size and the

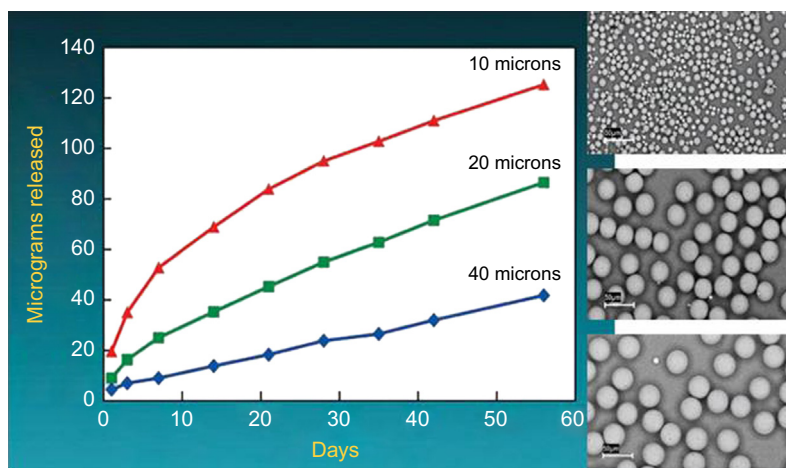
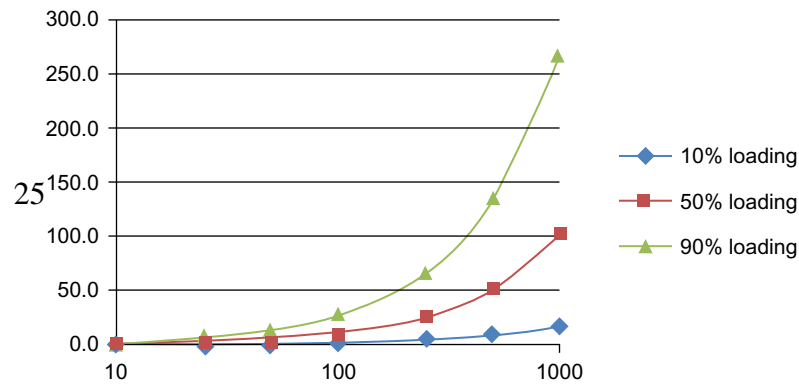
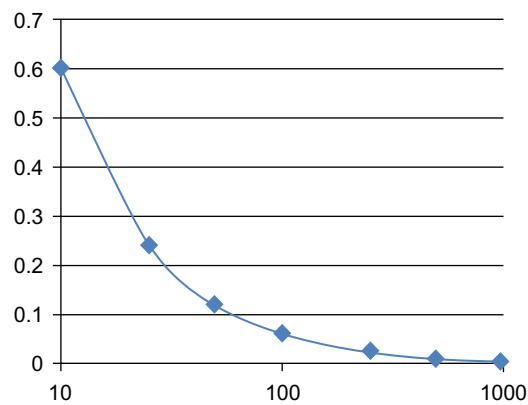


FIGURE 2.2 Impact of size of the microsphere in controlled release.

TABLE 2.1 Effect of Thickness of the Shell Wall on the **Microcapsule** Volume and Loading

Diameter (μm)	Vol. Microcapsule (μm^3)	Thickness (μm) @ 90% Load	Thickness (μm) @ 50% Load	Thickness (μm) @ 10% Load
1000	523,600,000	17.3	103.1	267.9
500	65,450,000	8.6	51.6	134.0
250	8,181,250	4.3	25.8	67.0
100	523,600	1.7	10.3	26.8
50	65,450	0.9	5.2	13.4
25	8181.25	0.4	2.6	6.7
10	523.6	0.2	1.0	2.7
5	65.45	0.1	0.5	1.3
2.5	8.18125	0.0	0.3	0.7
1	0.5236	0.0	0.1	0.3

**FIGURE 2.3** Microcapsule thickness as a function of microcapsule diameter.**FIGURE 2.4** Microcapsule size and the surface area relationship.

total surface area (as demonstrated by number of microcapsules) at the same payload. The figure shows that when the size of the microcapsules is small, the surface area is significantly high as compared to the size of the microcapsules. In such a situation, it is inherently difficult to design a sustained release formulation. As a result, sustain release formulations are often designed with surface area/volume ratios less than approximately 0.2.

2.5 PHYSICOCHEMICAL FACTORS

From a physicochemical compatibility perspective, the factors affecting the microcapsule stability and release are as follows.

2.5.1 Molecular Weight of the Active Agent

Often one cannot alter the size once the active ingredient for the food product is ascertained. In this context, it is simply important to know that size of the active ingredient is important. Typical food active ingredients have molecular weights that are less than 500 Da. Because of the small molecular dimension, these molecules can slip through tortuosity of the matrix polymer interstitial space or through the polar heads of the phospholipids in the case of a liposome. As the molecular size increases, the diffusion decreases exponentially. This means that larger molecules, such as proteins and peptides, cannot diffuse quickly.

2.5.2 Functional Moiety and Surface Charge

Glucose enters cells much faster than other sugars, facilitated by a carrier protein specific for glucose. This concept is also known as facilitated diffusion and has applications in the pharmaceutical drug industry, although its use in the food industry is rare. In contrast, the ionic surface charge on the active ingredient can play a significant role in retarding the rate of diffusion by electrovalent binding to the matrix polymer moieties. Changing the ionic properties often results in a change in solubility of the active ingredient in the matrix phase. Thermodynamics also affects microcapsule stability and release. Thermodynamic properties such as concentration, temperature, solubility, and interfacial properties are all key factors contributing to the performance and stability of the microcapsule.

2.5.3 Concentration

Molecules are in constant motion and tend to move from regions where they are in higher concentration to regions where they are less concentrated. Microcapsules are no exception. The active ingredient moves from areas of high concentration of that material into areas of low concentration of that material. As the concentration gradient between the inside of the microcapsules increases as compared to the surrounding food outside, the rate of diffusion increases. This is important from two standpoints. First, because the initial concentration gradient in a microcapsule is high, this is a contributing cause for a burst effect. Also, as the concentration gradient decreases, the driving force associated with release decreases and, therefore, such a system exhibits a first order release.

2.5.4 Solubility

In most product development efforts, one often needs to make a decision whether the active ingredient must be in a solubilized state or a dispersed state. When the active is in a solubilized state, one can expect faster release. The concepts for such a release and its kinetics are presented in the next chapter. Microcapsules with active ingredients in a dispersed state require a balance between the stability and release rate. This is particularly relevant when the active has low solubility in the food product in which the microcapsule is placed.

As the solubility of the active ingredient increases in the matrix, the active ingredient can move through the matrix more easily. The solubility is characterized by partition (P) or distribution (D) coefficients. These coefficients are a measure of the difference in solubility of the active ingredient in an aqueous versus oil phase. Normally, one of the solvents used is water, while the second is hydrophobic, such as octanol. Hence, both the partition and distribution coefficients are measures of how hydrophilic (“water loving”) or lipophilic (“oil loving”) an

active ingredient is. The logarithm of the ratio of the concentration is called $\log P$. The $\log P$ value is also known as a measure of lipophilicity.

$$\text{Log } P = \log[(C \text{ in octanol})/(C \text{ in water})]$$

2.5.5 Wettability

The wettability of the active ingredient impacts dissolution and subsequent release. If the aqueous media cannot wet the surface of the active ingredient, no release will occur. To quantitate the wettability, Griffin in 1954 defined the term hydrophilic–lipophilic balance (HLB) and a useful scale between 0 and 20 that allows one to explore how wettable the active would be with water. Griffin proposed a mathematical equation as follows:

$$\text{HLB} = 20 * \text{Mh}/\text{Mw}$$

where Mh is the molecular mass of the hydrophilic portion of the active ingredient molecule and Mw is the molecular mass of the entire molecule, giving a result on a scale of 0 to 20 (Garti, 1996). An HLB value of 0 means completely lipophilic, while a value of 20 corresponds to completely hydrophilic. Using this scale, the HLB value can be used to predict the surfactant properties of a molecule, as presented in [Table 2.2](#).

In addition to these properties, scientists also use solubility parameters to take into account hydrogen bonding between water and the hydroxyl groups.

TABLE 2.2 Griffin's HLB Guidance Chart

Ingredient	HLB Guidance
Oil soluble	<10
Water soluble	>10
Antifoaming agents	>4 and < 8
W/O (water-in-oil) emulsifier	>7 and <11
O/W (oil-in-water) emulsifier	>12 and <16
Wetting agent	>11 and <14
Detergent	>12 and <15
Solubilizing agent	>16 and <20

2.5.6 Temperature

Temperature is the most critical thermodynamic property that influences the release of the active ingredient. In most cases, increase in temperature causes molecules to move faster, therefore enhancing diffusion. The temperature also allows the matrix to undergo entropic relaxation from a metastable state to an equilibrium state. As the density increases, the molecule undergoes fewer collisions; this allows for faster diffusion. Similarly, lowering the temperature will lower the diffusion rate by lowering the energy of each particle. As a result, microcapsules stored at room temperatures or under refrigeration offer greater stability than those kept at elevated temperatures.

Because temperature is a controllable property, its impact on matrix polymers cannot be undermined. Polymer matrices typically undergo phase transition with respect to temperature, thus changing from a crystalline to amorphous state, glassy to rubbery state, or solid to molten state, and sol to gel state. In each of the phase transition states, the product release profiles differ. Obviously, the selection of the matrix material becomes a key factor in microencapsulation design. The selection criteria for the matrix polymer are described in Chapter 16.

TABLE 2.3 Critical Process Control Parameters That Influence Release and Stability

Process	Critical Process Control Parameter
Atomization	Mixing time, mixing energy, evaporation rate, thermal profile, feed rate, air flow
Ionic gelation	Mixing time, mixing energy, salt content, zeta potential, cooling temperature, cool rate, gel point, feed ratio
Coacervation	Mixing time, mixing energy, pH control/zeta potential, cooling temperature, cool rate, gel point
Liposome	Mixing energy, pH, ionic charge, thermal conditions, freezing cycling
Fluid bed	batch size, evaporation rate, thermal profile, feed rate, air flow rate, feed ratio

2.5.7 Process Factors

Each microencapsulation process uses its specific critical control variable, and so a detailed description of all processes that can lead to a change in release profile is not possible. However, common pitfalls for an ill-designed microcapsule structure that result in high porosity or lower density are described in [Table 2.3](#).

2.6 MECHANISM OF DIFFUSION

The mechanism of diffusion or mass transport has been a topic of extensive research over the past 70 years ([Crank, 1975](#)). Despite years of history, one skilled in the state-of-the-art must construct an assessment for the target food product. Because food products are complex, diffusion mechanisms are controlled by several attributes. Diffusion entails several steps:

- Surface wetting
- Hydration or swelling of the matrix composition or layer
- Disintegration or erosion of the matrix
- Dissolution of the active ingredient to induce molecular diffusion or mobility
- Permeation of the active ingredient in the matrix phase
- Permeation of the active ingredient through the matrix phase into the bulk food phase

Each of the steps has the potential to control the rate and amount of release, and depending on the release duration, the rate controlling step may change over time. As an example, the microencapsulation of a water-insoluble food active ingredient in a poorly erodible matrix may provide the stability protection one needs, but the rate of release will be significantly compromised because the rate and amount of the active release will undergo two critical rate controlling steps: rate of erosion followed by solubilization of the active ingredient. Fundamentally, the rate controlling step in a complex food product ultimately defines the release kinetics.

However, in most engineering practices, the standard approach is to consider the rate controlling step, which can potentially dominate over the others. The rate controlling step depends on the choice of matrix material, morphology, physicochemical properties of the active and matrix polymer, and system in which the microcapsule is placed. With respect to practical considerations, one must recognize that using a single rate controlling step as a basis may not mimic a superimposition of several kinetics. A number of methods are described to determine the kinetic model of diffusion ([Benita, 1984](#)). Some of the tools used include gradients of chemical potential ([Dash et al., 2010](#)), equilibrium analyses ([Donbrow et al., 1988](#)), cell dynamics models ([Ghosal et al., 1992](#)), Monte-Carlo simulation ([Jalsenjak, 1992](#)), and non-regression analyses ([Higuchi, 1963](#); [Thies, 1982](#); [Nixon, 1984](#)).

An excellent starting point to understand the different kinetic release profiles is to consider concepts of zero order diffusion, Fickian diffusion, first order diffusion, Higuchi's diffusion model, and case II diffusion ([Figure 2.5](#)).

2.6.1 Zero Order or Pseudo-Zero Order Diffusion Model

A zero order diffusion rate is independent of the concentration of the active ingredient. Increasing the concentration will not speed up the rate of release, nor does the reduction in concentration slow down the diffusion. This is

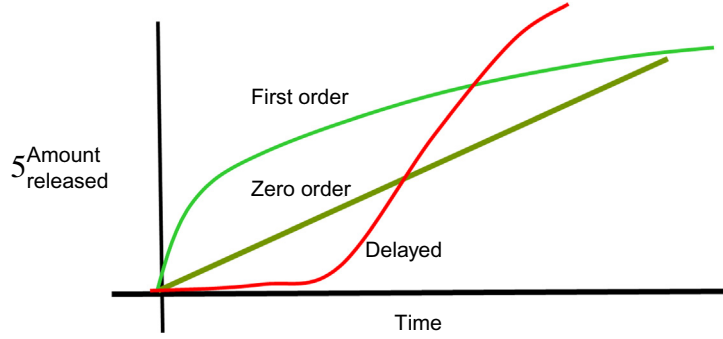


FIGURE 2.5 Schematic release profiles for microencapsulated systems.

counterintuitive. In a zero order diffusion model, the hypothesis is that the amount of active loading is infinite. In other words, one can achieve zero order diffusion when the release amount is extremely slow as compared to the amount of active loaded in the microcapsule. Zero order release in diffusion is described as the amount released is directly proportional to time. As shown in Figure 2.5 and mathematically:

$$C\alpha t \quad (2.1)$$

$$dC_t/dt = k_0 \quad (2.2)$$

where C_t is the amount of active ingredient released in time t , and k_0 is a zero order constant.

By integration of Eq. 2.2:

$$(C_t - C_0) = k_0 \cdot (t - 0) \quad (2.3)$$

where C_0 represents the initial release at $t \rightarrow 0$ for a fixed volume in which the release is measured:

$$C_t = C_0 + k_0 \cdot t \quad (2.4)$$

This equation is called the integrated zero order rate law.

It must be pointed out that a true zero order kinetics is often rare in the food industry, because of the short desirable release time, solubility of the active agent in the matrix, surface activity, and desirability for a burst release from the microcapsule.

2.6.2 Fickian Diffusion Model

Fickian diffusion postulates that the diffusive flux, J , goes from regions of high concentration to regions of low concentration, with a magnitude that is proportional to the spatial concentration gradient. In terms of one-dimensional spherical coordinates relating to a microsphere morphology, *Fick's first law* is:

$$J = (1/A) \cdot dC/dr = -D dC/dr \quad (2.5)$$

where J is the diffusion flux or mass flow of the active ingredient under the assumption of steady state, D is the diffusion coefficient, r is the radius of the designed microcapsule, and A is the surface area of the microcapsule. The negative sign in Eq. 2.5 is because diffusion occurs in the direction opposite to that of increasing concentration. It must be emphasized that the equation is consistent only for an isotropic medium, where the diffusion properties do not change in other spherical coordinates.

Equation 2.5 can be simplified with the knowledge that the concentration difference between the inside and outside of the microcapsule is:

$$dC/dr = -D \cdot A \cdot (\Delta C)/R \quad (2.6)$$

where $(\Delta C) = C_{oM} - C_{iM}$, and where C_{oM} is the concentration of the active agent on the outside of the microcapsule while C_{iM} is the concentration of the active agent on the inside of the microcapsule. R is the thickness of the microcapsule.

Comparing Eqs. 2.2 and 2.6, one can show that Fickian diffusion will approximate zero order diffusion when:

$$k_0 = -DA(\Delta C)/R \quad (2.7)$$

In essence, for constant release, a pseudo-zero order rule can be used for a practical approximation. The higher the k_0 , the faster the rate of diffusion. One also concludes that the rate of diffusion can be increased by an increase in diffusion coefficient, surface area, and concentration driving force, while it can be decreased by increasing the thickness of the microcapsule wall.

2.6.3 First Order Diffusion Model

First order diffusion depends on the concentration of the active agent. The rate law for a first order diffusion is:

$$dC/dt = k_1 C \quad (2.8)$$

where k_1 is the first order rate constant, which has units of 1/s.

The integrated first order rate gives:

$$\ln C - \ln C_0 = -k_1 t \quad (2.9)$$

A plot of $\ln C$ versus time t gives a straight line with a slope of $-k_1$.

2.6.4 Higuchi's Diffusion Model

In 1961, Higuchi published the derivation of an equation that allowed for an active agent to diffuse from a matrix phase when the active is a finely dispersed drug into a perfect sink. He based his equation on a pseudo-steady state where the cumulative amount released is proportional to the square root of time. His model is based on the hypotheses that:

1. Initial active ingredient concentration in the matrix is much higher than the solubility in the matrix.
2. Diffusion takes place only in one dimension.
3. There is no surface contamination with the active agent (edge effect must be negligible) and the active agent particles are much smaller than the microcapsule system.
4. No swelling or dissolution of the matrix occurs.
5. Diffusivity of the active agent is constant.
6. Perfect sink conditions are always attained in the release environment.

Initially conceived for planar systems, it was then extended to different geometrics and porous systems. For a one-dimension system, the following equation can be used:

$$C_t = -[DA(2C_0 - C_s)C_s t]^{1/2} \quad (2.10)$$

where C_s is the solubility of the active in the matrix, D is the diffusion coefficient, C_t is the concentration of the active released at time t , and A is the surface area through which the release occurs.

The major benefit of this equation is that a formulator could be used to facilitate microsphere optimization, where the active agent is well dispersed in the microsphere matrix rather than using a microcapsule morphology to understand the release mechanism.

2.6.5 Case II Diffusion

In many cases, the diffusion mechanism of an active ingredient cannot be described adequately. This is particularly true when diffusion of the active agent occurs in a glassy polymer matrix in contrast to the rubbery state. In essence, the phase transition point, such as glass point, plays a significant role in the type of diffusion mechanism the active agent will exhibit from the microsphere. Such form of diffusion is known as non-Fickian case II diffusion.

Unlike Fickian diffusion, which is controlled by diffusion coefficient, in case II diffusion the parameter is a constant velocity front, which marks the boundary of the swollen gel and the unswollen glassy matrix. [Korsmeyer et al. \(1983\)](#) derived a simple relationship based on power law that allows for the release of the active agent from a polymeric matrix. They presented the diffusional release in a power law relationship, as shown in [Table 2.4](#).

2.6.6 Osmosis

Osmosis is a specialized case of diffusion that involves the passive transport of water. In this case, water moves through a selectively permeable membrane from a region of its higher concentration to a region of its lower concentration.

TABLE 2.4 Interpretation of Diffusional Release Mechanisms from Polymeric Films

Transport Mechanism	Power Law Release Exponent (n)	Release Rate as a Function of Time
Fickian diffusion	0.5	$t^{-0.5}$
Non-Fickian transport	$0.45 < n = 0.89$	t^{n-1}
Case II transport	0.89	Zero order release
Super case II transport	Higher than 0.89	t^{n-1}

The key to designing an osmotic release system is to select a polymer membrane that selectively allows passage of certain types of molecules while restricting the movement of others. Although each molecule moves down its own concentration gradient, from a region of its high concentration to a region of its low concentration, the rate of release is impacted because of backpressure exerted by other molecules such as water. Changing the ionic solute concentration changes the way the membrane behaves.

Osmosis as a mechanism of release can be used for triggered release (Deasy, 1984). In an ill-designed microcapsule product, which has defects and holes, osmotic pressure can be used to provide sustained release by virtue of the osmotic pressure. The pressure required to stop osmosis is called the osmotic pressure. Osmotic pressure arises when two solutions of different concentrations, or a pure solvent and a solution, are separated by a semipermeable membrane.

In dilute solutions, osmotic pressure (Π) is directly proportional to the molarity of the solution. The Van't Hoff equation provides osmotic pressure calculations as:

$$\Pi = MRT \quad (2.11)$$

where:

Π = osmotic pressure

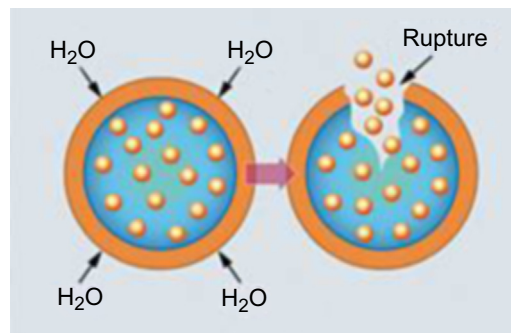
M = molarity = moles $\div$ volume (L)

R = 8.3145 J/k mol is the normal gas constant ($R' = 0.0821$ L atm/K mol is the gas constant expressed in terms of liters and atmospheres)

T = temperature (K)

A schematic that demonstrates osmotic release being triggered by the absorption of water into the microcapsule core is presented in [Figure 2.6](#). At the pressure where osmotic pressure is exceeded, subsequent swelling ruptures the microcapsule shell.

In this chapter, while most of the discussion is focused on the physics of mass transport versus diffusion concepts, almost any mechanism that induces a structural change to the microcapsule can be used as a triggering mechanism. [Figure 2.7](#) depicts many such triggered release concepts. The most common triggering mechanisms are temperature, pH, use of salts, osmotic pressure, and light.


FIGURE 2.6 Concept of burst release by osmotic pressures.

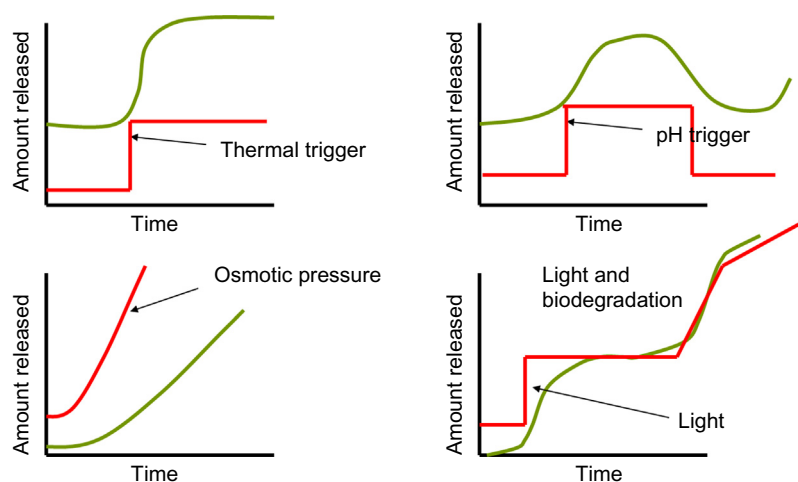


FIGURE 2.7 Nondiffusion release mechanisms.

Depending on the triggering and the morphological difference in the microcapsules, the response release curve may be sigmoidal, waveform, or asymptotic in nature. Release profiles such as these are unique to different food products in the food industry.

2.7 CONCLUSION

In this chapter, the different rate controlling factors were presented. The mechanisms of release are subject to how the microencapsulation is conducted, that is, method or process, shell composition, physicochemical state, and morphological properties. The versatile technologies that have resulted from the evolution of this technology can improve product performance and provide better controlled delivery of ingredients. Understanding of the molecular and physicochemical interaction of the active ingredient and material composition is critical to creating such a *dynamic* system. Selection and development of microencapsulated food ingredients for controlled delivery require a careful balance of physical and chemical properties and processing of ingredients, available techniques, and regulatory guidelines. Finally, there are no all-encompassing techniques or approaches that apply to the microencapsulation of food ingredients.

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