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Modeling the release of food bioactive ingredients from carriers/nanocarriers by the empirical, semiempirical, and mechanistic models

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Abstract

The encapsulation process has been utilized in the field of food technology to enhance the technofunctional properties of food products and the delivery of nutraceutical ingredients via food into the human body. The latter application is very similar to drug delivery systems. The inherent sophisticated nature of release mechanisms requires the utilization of mathematical equations and statistics to predict the release behavior during the time. The science of mathematical modeling of controlled release has gained a tremendous advancement in drug delivery in recent years. Many of these modeling methods could be transferred to food. In order to develop and design enhanced food controlled/targeted bioactive release systems, understanding of the underlying physiological and chemical processes, mechanisms, and principles of release and applying the knowledge gained in the pharmaceutical field to food products is a big challenge. Ideally, by using an appropriate mathematical model, the formulation parameters could be predicted to achieve a specific release behavior. So, designing new products could be optimized. Many papers are dealing with encapsulation approaches and evaluation of the impact of process and the utilized system on release characteristics of encapsulated food bioactives, but still, there is no deep insight into the mathematical release modeling of encapsulated food materials. In this study, information gained from the pharmaceutical field is collected and discussed to investigate the probable application in the food industry.

KEYWORDS

controlled release, empirical, mathematical modeling, mechanistic, release parameters

1 | INTRODUCTION

Encapsulation is a process in which valuable bioactive food ingredients (vitamins, flavorings, sweeteners, minerals, amino acids, antioxidants, colorants, essential oils, enzymes, etc.) are protected from physical (e.g., crystallization, precipitation, and evaporation), chemical (oxidation), and biological degradation reactions by using a coating material or matrix, providing a barrier for various bioactive ingredients in food products (Assadpour & Jafari, 2019; Rezaei, Fathi, & Jafari, 2019). Nowadays, one of the most critical applications of encapsulation is the controlled release of the bioactive substances during preservation or digestion, where there have been substantial improvements in this field over the past three decades (Dima, Assadpour, Dima, & Jafari, 2020; Garavand,

Rahaee, Vahedikia, & Jafari, 2019). The release mechanism of encapsulated food bioactives is governed by the composition and nature of the wall and active material characteristics, the release media, and the physical properties of the carriers such as size, shape, and morphological characteristics (Alehosseini & Jafari, 2019; Bahrami, Delshadi, Jafari, & Williams, 2019).

The term "controlled release" is a property that aids the release process of the encapsulated bioactives to the target site, where its functional characteristics should be delivered. The other benefit of a controlled release system is representing a predesigned release rate in the specified time intervals. The main and early application of this process was in drug delivery. Some problems existed there because of the conventional dosing regimen in the long period of usage. One of the concerns was the accumulation of the drugs in the human body resulting in toxicities, side effects, and abrupt fluctuations or ineffective concentrations of active material exposures. This problem could be resolved using the controlled release strategy including targeted delivery, drug protection from early removal across the coating matrix, and directing the active substances to the targeted site of action (Giri et al., 2012; Siegel & Rathbone, 2012). The same applications are considered in food technology when dealing with functional bioactive compounds such as food additive and ingredients such as sweeteners, flavorings, enzymes, antibacterial and antioxidant agents, and food preservatives that might be sensitive to moisture, heat, microorganisms, or the other conditions exist in food systems (Koshani & Jafari, 2019; Rafiee, Nejatian, Daeihamed, & Jafari, 2019). These bioactive agents can be encapsulated using carbohydrates, gums, lipids, or proteins with a prespecified delivery behavior that can release the bioactives at a desired time and site with a suitable rate (Pothakamury & Barbosa-Cánovas, 1995).

Two important release mechanisms are used in food applications. First, "delayed release" helps to protect some bioactive substances such as probiotic bacteria from degradation in the upper gastrointestinal tract (GIT) in the human body and deliver them to the targeted site of action (colon). The second mechanism is "sustained release," which is applicable when a constant release rate is desired such as aroma, flavor, antioxidant, or antimicrobial agents release in food products. Besides, controlled release can decrease the loss of food additives and ingredients during thermal or acidic processes (Katouzian & Jafari, 2016). This characteristic can help use natural food ingredients that are very popular but their practical application is limited due to instability compared to chemical additives, and sensorial or toxicological issues because of using too high or too low concentrations of bioactive agents (Anandharamakrishnan, 2015; Mastromatteo, Mastromatteo, Conte, & Del Nobile, 2010). One of the most popular applications of controlled release is designing antimicrobial food packaging (active packaging) (Vahedikia et al., 2019). In this case, the antimicrobial packaging should be designed in a way that the rate of bioactive migration and microbial growth should match. If the antimicrobial agent migration rate is faster than the rate of microbial growth, after depletion of the antimicrobial agent, the antimicrobial activity of the packaging material is lost and the microorganisms begin to grow. On the other hand, if the rate of active antimicrobial agents is very slow, it cannot prohibit microbial growth (Ju et al., 2019).

In the case of delivery of food nutrients into GIT, the breakdown process of food and release of nutrients to the gastric fluid can be explained similarly to drug delivery systems. Some of the models to predict drug performance have been utilized successfully to model the release kinetics of nutrients in food delivery systems. Because of similarities existed between the applications of targeted/controlled release in food and drug products, the discoveries in the field of pharmaceutical could be used to design and enhance the release of encapsulated food ingredients. The current state of the art of mechanistic realistic and empirical and semiempirical models is reviewed in this study. The most common applied mathematical models are introduced and the recent literature in the field of food is discussed in terms of applying pharmaceutical principles to improve and design novel technologies such as active packaging and targeted nutraceutical delivery systems in food products.

2 | AN OVERVIEW OF RELEASE MODELING

A model is a proposition that describes the relationship between process parameters using mathematical equations (Shargel & Andrew, 2015). In other words, the model is a mathematical metaphor of several features of reality that, in the case of controlled release, is identified by various phenomena that leads to the release kinetics (Dash, Murthy, Nath, & Chowdhury, 2010). Because of remarkable improvement in information technology, mathematical modeling is increasingly utilized in several academic and industrial fields of science such as biology, medicine, engineering, genetics, psychology, economy, and technology and it is predicted that it would have a great future perspective potential. The aims of mathematical modeling in release studies are (a) designing new products with a defined controlled release using the release kinetics (e.g., in the field of active packaging design); (b) prediction of the release rate and profile to avoid unnecessary experiment trials; (c) optimization of the release process (e.g., in

nutraceutical delivery in functional food); (d) determination of the physical mechanisms for bioactive release by comparing the actual release data with mathematical models; and (e) defining the probable effects of design parameters such as shape, size, and composition on the overall release rate.

Modeling of release data has been performed using various approaches such as empirical, semiempirical, and analytical or mechanistic realistic techniques (Jafari, Katouzian, Rajabi, & Ganje, 2017). In the case of empirical/semiempirical ones, the model is not based on the real physicochemical or biological phenomena involved and it is to some extent descriptive. The underlying mechanisms are not also purely defined and a good prediction is not usually achieved. Also, this kind of model cannot predict the effects of parameter changes on process conditions. These theories help to compare two or more release profiles using a predefined kinetic parameter such as release rate constant (Mehrnia, Jafari, Makhmal-Zadeh, & Maghsoudlou, 2017). If there is a lack of suitable theoretical concepts, and limited information, on the other hand, more realistic models are complex to be solved mathematically, then using empirical models is appropriate (Costa & Lobo, 2001). In other words, their usage is limited to simple curve fitting. Contrarily, the fundamental basis of mechanistic models is real phenomena occurring during the release process such as diffusion, erosion, swelling, dissolution, precipitation, and so on. In these models, the mechanism involved in the process is studied more clearly and the controlling mechanism is defined. In realistic models, the impact of processing parameters such as dimensions, geometry, and formulation on the release kinetics could be quantitatively predicted better than empirical models.

Selecting an appropriate mathematical function that defines the proper relationship between dominant factors authorizing the kinetic process determines the capability of the model prediction. Usually, fitting the models to variables or experimental data would estimate the most important parameters in the release process (e.g., k or rate constant of the models). So, these parameters are also dependent on the method of experiments, analysis, and the selected model. These functions present a relationship between the dependent and independent variables using such parameters. For instance, such models predict the amount of dissolved concentration of the bioactive substance (C, dependent variable) as a function of time (t, independent variable). By fitting the set of time versus concentration of released substance data, a model is proposed to predict released rate with respect to time, and the relationship between time and the concentration is defined by kinetic rate constant k (Shargel & Andrew, 2015).

According to Siepmann and Siepmann (2008), four critical aspects should be considered carefully in the mathematical modeling of controlled release: (a) the more phenomena are taken into account in the model, the more accurate prediction capability of the model. However, it should be noted, application of too complex models with several system-specific parameters is difficult. So, it is better to take into account only the controlling mechanisms within the process in the model to have a balance between prediction accuracy and solution complexity. (b) Comparison between theoretical and experimental data should be made either by fitting the model to the experimental results or comparing theoretical data with independent experimental data. In the first case, optimization of model parameters is done in such a way that there would be a minimum difference between theoretical and experimental data, which would often yield a good fit between experiment and theory, even though the model might not be efficient. In this case, the complete release profile should be described, not just one part of the process. In the second case, which defines the validity of the developed model, system-specific parameters would be defined by using several sets of experimental data and after that, the effect of different conditions on release kinetics is determined. (c) None of the proposed models can be utilized for all types of systems. Some of them are usable for a wide range of systems, whereas others might have limited application for specific types of systems. And finally, (d) sometimes certain experimental evidence is not in agreement with the model results, despite good agreements between various experimental and theoretical results (Siepmann & Siepmann, 2008).

3 | RELEASE MECHANISMS AND DEFINITIONS

Although there are several mechanisms such as magnetic, osmotic, and electric phenomena that might affect the controlled release, four main mechanisms involved in releasing bioactive ingredients from the encapsulation matrix are dissolution, diffusion through the food matrix, swelling, and degradation or erosion (Jafari, Esfanjani, Katouzian, & Assadpour, 2017; Leong & Langer, 1988). Defining the controlling mechanism is proportional to the encapsulation matrix. In nonbiodegradable polymers, the dominant mechanism is diffusion, but in biodegradable polymers, swelling and erosion are also involved. Mathematical models of controlled release are often developed based on this categorization. The mechanisms underlying controlled release are proportional to the type and dose of the bioactive agent, the release media conditions, geometry, size, and several other factors.

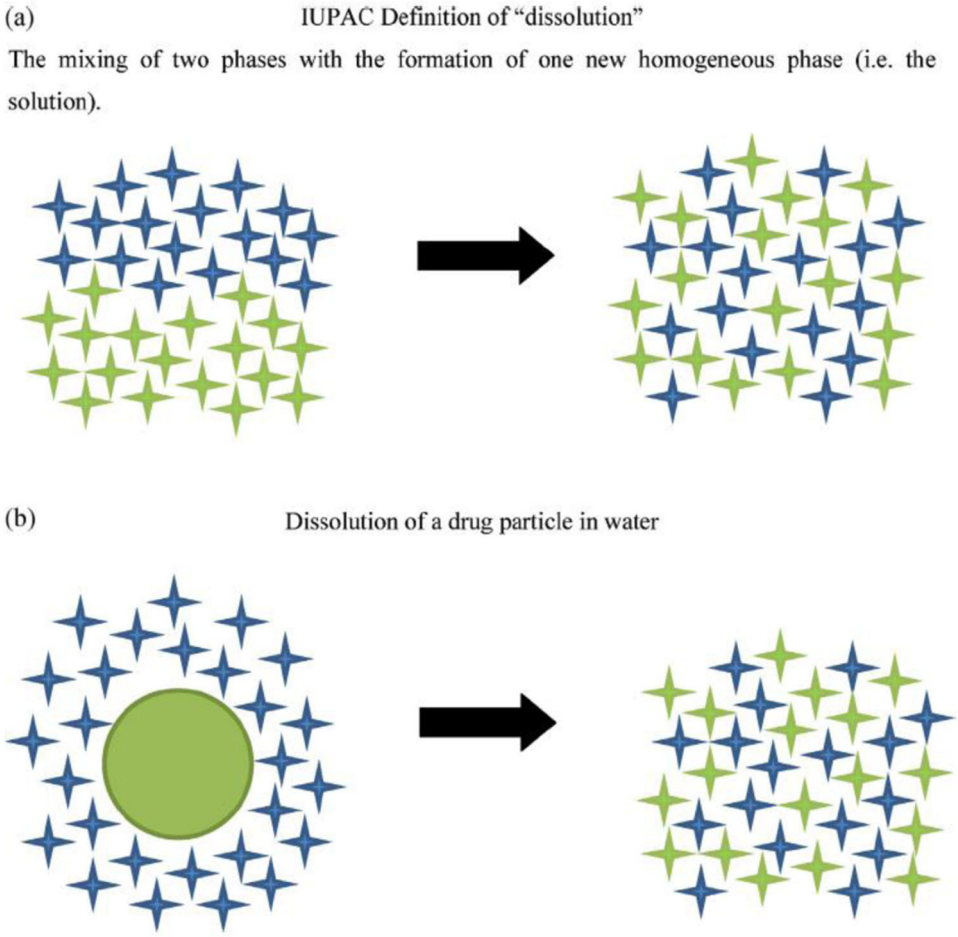


FIGURE 1 Schematic definition of dissolution: (a) mixing of two phases to form a new phase (IUPAC definition of the term "dissolution"); (b) dissolution of a bioactive agent in release media from. Reproduced with permission from Siepmann and Siepmann (2013)

3.1 | Dissolution

Dissolution is the process of dissolving a solute in a solvent (e.g., a bioactive agent in the release media). In this phenomenon, the ions/molecules of the bioactive agent (solid-state) are transferred to the surrounding environment. The term "dissolution" is also applied when two phases mix in order to form a new phase (IUPAC definition), as shown in Figure 1 (Siepmann & Siepmann, 2013). Dissolution is continued in a medium until reaching the saturation. The limiting factors of dissolution are the surface area of the solute, the boundary layer thickness, type of the solvent, and the coefficient of diffusion.

In the dissolution process, molecules of the solid phase are removed when it is placed in contact with the solvent; they move to the surrounding media and a boundary layer is formed around the solute. So, the concentration of the solute increases in the surrounding media, which decreases the dissolution rate because of saturation in the dissolution medium. After a specific time, the created boundary layer is removed and a new solvent comes in contact with the solid solute, which leads to an increase in the dissolution rate. The dissolution rate is predicted using the difference between the solute concentration inside and outside of this boundary layer. The thickness of the boundary layer has an adverse effect on the dissolution rate (Parmar & Sharma, 2018). The mathematical form of the dissolution rate is based on Equation (1):

$$\text{Dissolution rate} = \frac{dC}{dt}. \tag{1}$$

The dissolution rate depends on the size of solute particles, agitation, viscosity, and the temperature of dissolution media. The mathematical definition of dissolution is based on the following equation:

$$\frac{dC}{dt} = DA(C_s - C), \tag{2}$$

where $\frac{dC}{dt}$ is the dissolution rate, D is the coefficient of diffusion, A is the solid surface area, C is the solubility

of the solid, and C_s is its concentration. If the boundary layer thickness (l) is taken into account, the dissolution rate would be expressed by Equation (3):

$$\frac{dC}{dt} = \frac{DA}{l}(C_1 - C_2), \tag{3}$$

where (C_1 – C_2) is the difference between bioactive concentration inside (C_1) and outside (C_2) of the boundary layer.

3.2 | Diffusion

Before introducing empirical and semiempirical models, it is worthy to introduce Fick's law of diffusion, which is the basis of various empirical and theoretical mathematical models of release in literature. Diffusion is defined as the total transport of atoms or molecules from higher concentration fields to lower concentration ones. The driving force for diffusion is the spatial concentration gradient of the involving species. Fick (1855) was one of the first scientists who proposed equations for mass transfer phenomena, which are already called as Fick's first and second laws of diffusion. The mass flux (J) is defined as the amount of mass (M) passing through a surface (S) during the time (t), which is expressed by Equation (4):

$$J = \frac{dM}{S.dt}. \tag{4}$$

The steady state diffusion is described by Fick's first law of diffusion. It is assumed that the concentration within the control volume does not change over the processing time and it is only proportional to the position. This law in one-dimensional geometry is as follows:

$$J = -D\frac{\partial C}{\partial x}, \tag{5}$$

where J is the flux of diffusion (mol/m^2/s), C is the concentration (mol/m^3, position dependent), and D is the diffusion coefficient (m^2/s). x represents the position. As the process occurs in the direction of the concentration gradient, a minus sign is contained in the equation.

In the case of unsteady state diffusion, in one-dimensional geometry, the Fick's second law is written by Equation (36):

$$\frac{\partial C}{\partial t} = -D\frac{\partial^2 C}{\partial x^2}, \tag{6}$$

where C represents the position- and time-dependent concentration.

In modeling the release of bioactive agents from the food matrices, some researchers consider the release process to be Fickian diffusion where Fick's first and second law describes the diffusion as the dominant transport process using the concentration gradient as the driving force (Ganje, Jafari, Tamadon, Niakosari, & Maghsoudlou, 2019). Some studies took into account other processes such as mass transport by the pressure gradient, dissolution, chemical degradation, and so on along with the diffusion in order to describe the whole process more realistically. This approach is called "non-Fickian modeling," which includes more mechanisms than just diffusion. The non-Fickian approach is much more complex than Fickian modeling (Ford Versypt, Pack, & Braatz, 2013; Irfan et al., 2018).

3.3 | Swelling

The driving force for swelling phenomena is the interaction between hydrophilic ingredients and water molecules that is observed generally in macromolecules (Jafari et al., 2017). The three-dimensional matrix of the polymers expands when surrounded by water and results in the formation of chemical or physical bonds. In this process, water penetrates the polymer matrix rapidly, whereas the polymer slowly dissolves into the water. Swelling is an important phenomenon in reservoir systems. In the starting point of bioactive agent release, the volume and thickness of the polymeric matrix are enhanced because of water uptake and consequently, disentanglement of the polymeric chain and dissolution of the bioactive agent or other ingredients occur. This process leads to the decrement of matrix volume and may sometimes diminish the whole swelling matrix (swellable soluble matrix). In some cases, the entire matrix does not disappear due to the existence of long chains that can form cross links and a polymeric network.

3.4 | Erosion

Some polymeric systems show erosion behavior when they interact with the surrounding media. Erosion may be classified as surface, heterogeneous, bulk, or homogenous erosion. The first case occurs when a high rate of system hydrolysis or slow water invasion is observed. In such a system, the rate of polymeric matrix degradation is much faster than the penetration of water into the polymeric matrix. In the latter case, the penetration of water is faster than hydrolysis. Figure 2 shows an illustration of the diffusion-, swelling-, and erosion-controlled systems.

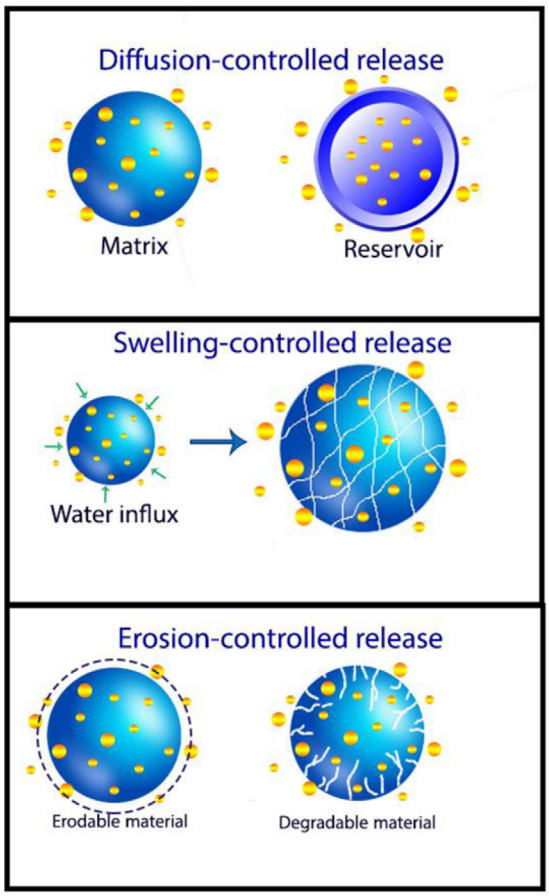


FIGURE 2 A schematic illustration of diffusion-, swelling-, and erosion-controlled release systems

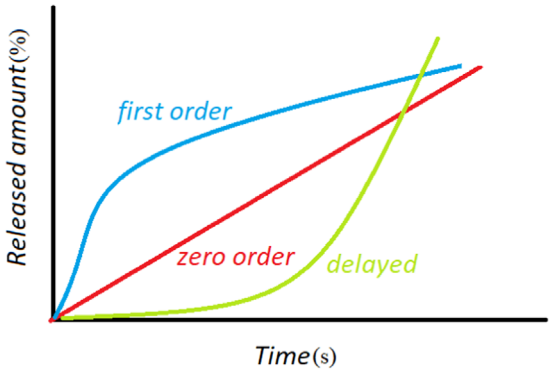


FIGURE 3 Plot of release kinetics for encapsulated materials

4 | EMPIRICAL AND SEMIEMPIRICAL RELEASE MODELS

As it was mentioned in the previous sections, empirical and semiempirical equations do not elucidate the underlying mechanisms in the release process. Also, the quantitative predictions of the effect of process parameters and formulation on the release kinetics are not accurate in such models. These models can be used in order to compare different release profiles (Lokhandwala, Deshpande, & Deshpande, 2013). Semiempirical models are more realistic in some cases and might indicate the underlying mechanisms in the process in certain conditions. Some of the most widely used models in this group are introduced in the following.

4.1 | Zero-order model

The controlled release process could be defined by the rate in which the process continues. The process rate is determined by defining its order. Usually, the controlled release kinetics of encapsulated materials follows zero- or first-order kinetics. However, there are some cases in which there is a rapid initial release, followed by zero- or first-order kinetics (Bruschi, 2015), as shown in Figure 3.

In zero-order kinetics (Table 1), a steady state concentration profile is observed and the release is very slow. In other words, the process rate over time t is independent of the released concentration, and increment or reduction of the concentration does not speed up or slow down the diffusion (Figure 4a). This assumption is based on that the concentration of bioactive agents is always or in most times of the process around or higher than the saturation point during the diffusion process, or the concentration of releasing bioactive agents is infinite (Manca & Rovaglio, 2003; Vasisht, 2014a). It is also assumed that there are no changes in the area and equilibrium conditions. This condition is ideal release kinetics for encapsulated bioactives (e.g., functional food production), because an ideal controlled release system should deliver the bioactive compounds at a controlled rate during a defined duration to ensure efficiency and avoid over/underexposure and variations.

In the case of release modeling of food bioactives in simulated gastrointestinal fluids, the release rate is slower during the gastric phase and it could be estimated by zero-order kinetics. On the other hand, the intestinal phase sometimes follows a first-order release kinetics (Calija et al., 2013; Flores & Kong, 2017; Khan, Ranjha, & Mehmood, 2010).

As mentioned earlier, the zero-order kinetic models explain the prolonged release of the core material or the active agent sufficiently. In the case of food applications, prolonged release of encapsulated flavoring agents or sweeteners in products such as chewing gum is preferred, so the zero-order model could be applied (Anandharamakrishnan, 2015). It should be noted that, unfortunately, the zero-order kinetic results are not always accurate in the release process, and just in the initial period

TABLE 1 A brief review of empirical and semiempirical release models

Model	Equation	Equation no.	Parameter details	Plot	Application	Reference
Zero order	$M_t = M_0 - k_0 t$	15	M_0: the initial concentration of the encapsulated substance M_t: the concentration at time t k_0: the zero-order equation rate constant (concentration per time)	The amount of released bioactive versus time	Describing release kinetics of matrix systems, slabs, low solubility, or coated material, osmotic systems. It is not a common release mechanism in food matrices due to the rapid dissolution of most food materials (Bruschi, 2015; Costa & Lobo, 2001; Vasisht, 2014b).	Bruschi, 2015
First order	$M_t = M_0\, e^{-k_1 t}$	16	k_1: the first-order rate constant (time^{-1})	The decimal logarithm of released bioactive versus time would yield a straight line with a slope of −K/2.303.	This equation best describes the release kinetics of water-soluble material in porous matrices and ionizable oil or water-soluble materials from W/O/W emulsions (Chiang, Fuller, Frankenfeld, & Rhodes, 1978; Costa & Lobo, 2001).	Bruschi, 2015
Higuchi	$f_1 = M_t = K_H \sqrt{t}$	17	K_H: the dissolution constant (concentration per time$^{1/2}$)	Percentage of released bioactive versus square root of time	Best describes the release kinetics of water-soluble and encapsulated materials with a low solubility that are encapsulated in solid or semisolid matrices.	Higuchi, 1962
Hixson–Crowell	$M_0^{1/3} - M_t^{1/3} = K_{HC}\, t$	18	K_{HC}: the model constant incorporating the surface volume relation (concentration per time$^{1/3}$)	The cubic root of remaining bioactive in matrix versus time.	Best describes the release kinetics of planner geometries where dissolution takes place in planes parallel to the bioactive agent surface area (Bruschi, 2015).	Hixson and Crowell, 1931
Korsmeyer–Peppas model	$\frac{M_t}{M_\infty} = kt^n$	19	$\frac{M_t}{M_\infty}$: the released fraction at time t k: the rate constant (which is dependent to structural changes and geometry of the system, also called release velocity constant) n: the release exponent (which is dependent on release mechanism, refer to Table 3)	Log percentage of released bioactive versus log time.	This equation is applicable when the release mechanism is not known or when more than one release mechanism is involved.	Korsmeyer et al., 1983; Ritger and Peppas, 1987

(Continues)

TABLE 1 (Continued)

Model	Equation	Equation no.	Parameter details	Plot	Application	Reference
Baker–Lonsdale	$f_t = \frac{3}{2}\left[1-(1-\frac{M_t}{M_\infty})^{2/3}\right]-\frac{M_t}{M_\infty} = kt$	20	k: the model constant	[d ($Mt/M\infty$)]/dt versus root of time inverse	This model best applies to microspheres or microcapsules.	Baker and Lonsdale, 1974
Weibull	$m = 1-\exp\left[\frac{-(t-T_i)^b}{a}\right]$	21	a: the scale parameter (determines the process time scale) T_i: the location parameter (shows the lag time before the start of the release process [often zero]). B: the shape parameter (Case 1: $b = 1$, an exponential curve; Case 2: $b > 1$, the release curve is S shaped or sigmoid with an upward curvature followed by a turning point; Case 3: $b < 1$, a parabolic curve with a high slope at initial step and then a consistent exponential decay curve)	Log (–ln [1-m]) versus log $(t - T_i)$	This model is suitable for almost all types of release cases and it is applicable for comparing the release profiles of matrix systems.	Langenbucher, 1972; Weibull, 1951
Hopfenberg	$\frac{M_t}{M_\infty} = 1-[1-\frac{k_0 t}{c_0 a_0}]^n$	22	c_0 and a_0: the initial concentration and radius (the radius for sphere or cylinder and half thickness in the case of the slab) of encapsulated material k_0: the constant for erosion rate. The value of n for slab, cylinder, and the sphere is equal to 1, 2, and 3, respectively.	The amount of released bioactive versus time.	This model is suitable for describing the release kinetics of optimized oil spheres using data derived from the composite profile, which essentially displayed site-specific biphasic release kinetics.	Hopfenberg, 1976

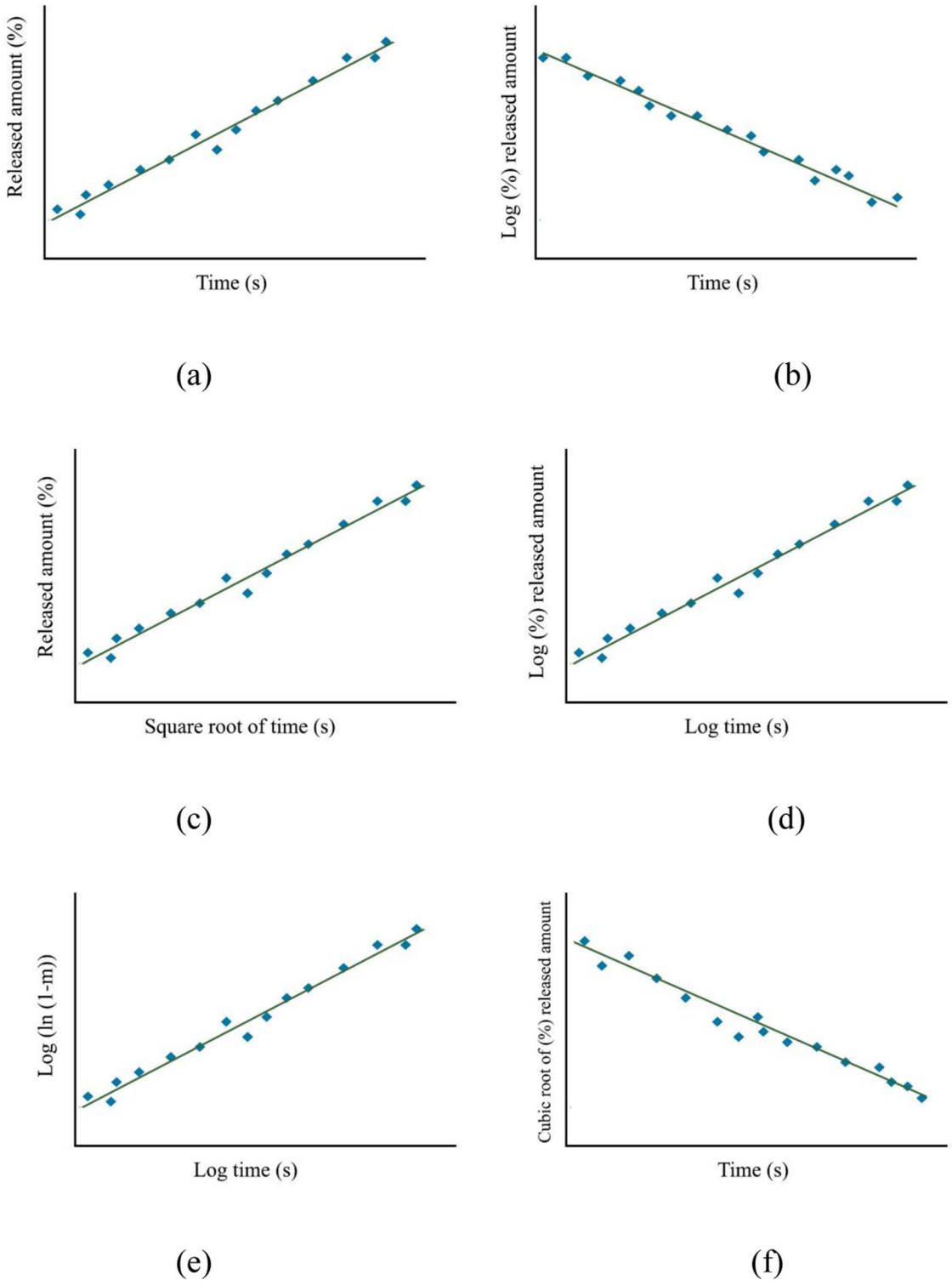


FIGURE 4 Typical release plots for different models: (a) zero order; (b) first order; (c) Higuchi; (d) Korsmeyer–Peppas; (e) Weibull; and (f) Hixon–Crowell

of the release process, the predicted profile is acceptable (Manca & Rovaglio, 2003). Andersson Trojer, Nordstierna, Nordin, Nyden, and Holmberg (2013) reported that only in the case of a monodisperse carrier system (a shell and core) with the steady release, the true zero-order kinetics was achieved. They claimed using the term "zero order" is one of the most frequent mistakes in controlled release literature. Usually, the release kinetics appears to be zero order in a limited period of time, then followed by one of the other release kinetics.

TABLE 2 Comparison between zero-order and first-order models

Parameter	Zero order model	First order model
Unit of rate constant	$(g/m^3)/s$	1/s
Impact of time on the release rate	Rate is constant with time	Rate is changing during the time with concentration changes
Impact of time on release rate constant	Rate constant changes with concentration changes	The rate constant is unchanged with time
Release graphical presentation	The plot of concentration decays over time	The plot of logarithmic concentration decays over time

4.2 | First-order model

First, this model was applied by Gibaldi and Feldman (1967) and then by Wagner (1969) based on Fick's law of diffusion. The rate of a first-order release model (Table 1; Figure 4b) is dependent on the released concentration. In other words, the driving force in such release processes is the difference between the concentration of bioactive inside and outside of the coating of the encapsulated material. The concentration of bioactive agent inside the carrier decays over the process because of releasing through the coating. As it is assumed that such a release is linear, there might be some differences between the actual and predicted release curves in this hypothesis (Manca & Rovaglio, 2003). In this type of release kinetics, the concentration of released material is proportional to the concentration of remaining bioactive in the matrix, and decays as a function of time (Bruschi, 2015). Table 2 represents a comparison between zero-order and first-order models.

4.3 | Higuchi model

One of the most famous and successful mathematical models regularly used in the release kinetic modeling was developed by the father of release modeling, Takeru Higuchi in 1961 (Higuchi, 1961). This equation is based on Fick's first law of diffusion, which was the starting point for quantitative measurements in the controlled release studies. Higuchi model was developed to cover various porous systems and geometries especially for evaluating the release kinetics of water-soluble and encapsulated materials with a low solubility that are encapsulated into solid or semisolid matrices (Costa & Lobo, 2001). There are some assumptions in the extended Higuchi equation (Table 1):

1. The concentration of the releasing material at the beginning of the release process is higher than its solubility.
2. One-dimensional diffusion is assumed.
3. The thickness of the system is more than releasing particles.
4. Dissolution and swelling are neglected.
5. The coefficient of diffusion is constant.
6. Perfect sink conditions are usually established in the release medium.

If the concentration of the bioactive agent is plotted versus $\sqrt{t}$, the plot would be linear as shown in Figure 4c.

The rate constant of the Higuchi equation has a structural similarity with the composite Fickian diffusivity (Flores & Kong, 2017). Release kinetics of many drugs, flavonoids, and organic acids has been modeled using this equation (Argin, Kofinas, & Lo, 2014; Bae et al., 2015; Mesquita, Oliveira, Pedrosa, de Oliveira, & da Silva, 2015; Palma, Garcia, Marquez-Ruiz, Vergara, & Robert, 2014; Peng et al., 2010; Robert, García, Reyes, Chávez, & Santos, 2012). In the case of food systems, for the two-step simulated digestion process, the release of bioactive agents in intestinal conditions could be modeled using the Higuchi model (Khan et al., 2010).

It is worthy to note that the assumptions considered when using the Higuchi model limit the applicability of this model. One of these assumptions was that the initial concentration of the bioactive agent in the matrix should be higher than its solubility in the same matrix. Hydrophobic bioactives can fulfill this assumption, but hydrophilic compounds could not satisfy this condition. In the field of drug delivery, this model is usually used in modeling the release kinetics of a material placed in an infinite solution. One of the most important applications of release modeling in the field of the food industry is the active packaging. Here, various functional ingredients such as antimicrobial and antioxidant agents, coloring agents, flavors, and antibrowning additives are incorporated into packaging films and coatings in order to improve the shelf life, quality, safety, and functional properties of the food. In such systems, the food is assumed to be a finite release medium where the initial concentration of the bioactive in the packaging film is much lower than the drug system; so, the Higuchi model cannot be utilized (Lavoine, Guillard, Desloges, Gontard, & Bras, 2016).

Some studies showed that the results of the Higuchi model are sometimes different than those obtained by

TABLE 3 The n value of Korsmeyer–Peppas model for different geometries

Release mechanism	Geometry	n exponent
Fickian diffusion	Film	0.5
	Cylinder	0.45
	Sphere	0.43
Anomalous transport	Film	$0.5 < n < 1.0$
	Cylinder	$0.45 < n < 0.89$
	sphere	$0.43 < n < 0.85$
Case II transport	Film	1
	Cylinder	0.89
	sphere	0.85
Super case II transport	Film	$n > 1$
	Cylinder	$n > 0.89$
	sphere	$n > 0.85$

direct application of Fick's law in some colloidal systems; this could be due to the different release mechanisms in colloidal matrices. Transforming initial and boundary conditions in Fick's second law solution might result in a square root model similar to the Higuchi equation that can be applied to investigate the release kinetics of microspheres made of dextran, poloxamer gels, and also some other cylindrical matrix systems (Paolino et al., 2019).

4.4 | Korsmeyer–Peppas and Ritger–Peppas model

Korsmeyer, Gurny, Doelker, Buri, and Peppas (1983) and Ritger and Peppas (1987) proposed a simple equation (Table 1) for describing the controlled release of polymeric systems. This model is also known as the "power law model," which is a more general semiempirical relationship in the modeling of the swelling-controlled release (Lao, Peppas, Boey, & Venkatraman, 2011). It is used when the amount of released bioactive is less than 60%. It is stated in this model that there is an exponential proportionality between the amount of released bioactive and time (Figure 4d). The value of n is described in Table 3.

There are three main assumptions considered in this model: first, the general model is best suited for short times where $\frac{M_t}{M_\infty}$ in the release curve is <0.6, which should be used for determination of the exponent n; second, one-dimensional release is considered; finally, the ratio between the system length and thickness should be at least equal to 10.

When the release mechanism is ambiguous or there are several phenomena involved in the release process, the power low model is helpful (Peppas & Narasimhan, 2014).

There are two cases in bioactive release modeling with the power law equation that depends on the value of n. The first one is the Fickian model (Case I) and the second one is the non-Fickian model (case II, Anomalous Case, and Super Case II). In the Fickian diffusion, the controlling mechanism in the process is diffusion. The velocity of the diffusion process is more than polymeric matrix relaxation. At the surface area in contact with the surrounding medium, the equilibrium of absorption is achieved quickly and the kinetics of controlled release is governed by diffusivity. In non-Fickian type, the swelling or polymeric chain or relaxation is the governing mechanism and the release kinetics obeys the zero-order equation.

In slab geometry, when the value of n is between 0.5 and 1, it is called anomalous or non-Fickian transfer. In this case, the mechanism of diffusion is both swelling and diffusion. Polymeric chains rearrange slowly and at the same time, the diffusion process results in the time-dependent anomalous effect. Also, when $n > 1$, Super Case II; is involved, which is an extreme type of transfer. In polymeric matrices where the glass transition temperature (T_g) is lower than the release medium temperature, Fickian diffusion typically occurs. The polymeric chain moves easily in the rubbery state, which leads to enhanced solvent penetration. Sometimes this type of diffusion is observed in polymers with T_g greater than the environment temperature in the case of adding a plasticizer (Bruschi, 2015). When the temperature of release media is less than the T_g (e.g., vitreous polymers), a non-Fickian mechanism is observed. The velocity of solvent penetration is the most important difference between Case II, Anomalous Case, and Super Case II transport non-Fickian mechanisms. In Case II, the velocity of solvent penetration is lower than the polymeric relaxation. In the case of anomalous transfer, the velocity of polymeric relaxation and solvent diffusion is equal. Finally, in Super Case II transport, the solvent penetration velocity is high, which enhances the transportation of the solvent.

Korsmeyer–Peppas equation was then developed in order to consider a latency (or lag) time (l) for the initial period of the release process (El-Arini & Leuenberger, 1998):

$$\frac{M_{(i-l)}}{M_\infty} = k(t-l)^n. \tag{7}$$

Or in a logarithmic form:

$$\log\left(\frac{M_{(i-l)}}{M_\infty}\right) = \log k + n\log(t-l), \tag{8}$$

where M_∞ and M_i are the concentration of released bioactive at equilibrium state and time t, respectively, and l is

the lag time. In the case of a sudden increment of the initial release of bioactives, Equation (9) is proposed in which b represents the burst effect (Kim & Fassihi, 1997):

$$\frac{M_i}{M_\infty} = kt^n + b. \tag{9}$$

4.5 | Peppas and Sahlin model

Peppas and Sahlin (1989) proposed a semiempirical equation by using diffusion and Krosmeyer's "Case II; transport" as following:

$$\frac{M_t}{M_\infty} = k_1 t^m + k_2 t^{2m}, \tag{10}$$

where m, k_1, and k_2 are equation constants. On the right side of the Peppas and Sahlin model, the first term represents the effect of diffusion and the other one identifies "Case II; transport" impacts.

Actually, the basic idea of this model is the assumption of possible calculation of diffusion and relaxation mechanism effects in Anomalous non-Fickian release. The constant m in this model is Fickian's diffusion coefficient that is related to the n exponent of power law equation (Peppas & Sahlin, 1989).

4.6 | Weibull model

An empirical model was developed by Weibull (1951) which defines the drug release fraction as a function of time (Table 1; Figure 4e). There are some criticisms in the literature about this model including:

1. This model has no fundamental kinetic basis and cannot elucidate the release kinetic properties adequately (Bruschi, 2015; Mircioiu et al., 2019).
2. There is not a single parameter that is proportional to the intrinsic dissolution rate of the releasing material (Shaikh, Kshirsagar, & Patil, 2015).
3. Using this equation for defining in vivo or in vitro relationships is limited (Bruschi, 2015).

This equation is helpful in the comparison between the release profiles of matrix systems.

4.7 | Hopfenberg model

Hopfenberg (1976) proposed a semiempirical equation for the heterogeneous erosion-controlled systems with different geometries such as slabs, infinite cylinders, and spheres. In this equation (Table 1), it is assumed that the release behavior follows zero-order kinetics that is combined with dissolution and erosion mechanisms. Dissolution on the particle surface controls the release rate in this model. The release rate in this equation is proportional to the time-dependent surface area. El-Arini and Leuenberger (1998) developed this model by taking into account the lag time (l) in the beginning stage of material release as following. In Equation (11), the erosion of the matrix is the rate-limiting factor of the process.

$$\frac{M_t}{M_\infty} = 1 - [1 - k_1 t\,(t - l)]^n, \tag{11}$$

$$k_1 = k_0 / C_0 a_0. \tag{12}$$

In this model, matrix erosion and time are limiting factors and are dependent on the external and internal diffusing resistances. Another equation was also proposed by Hopfenberg and Frish in order to consider the stress of relaxation and the flux of diffusion:

$$M_t = M_{\infty,F}\left[1 - \frac{6}{\pi^2}\sum_{n=1}^{x}\frac{1}{n^2}\exp\left(-n^2 k_F t\right)\right] + \sum_{i}^{k} M_{\infty,i}[1 - \exp(-k_i t)], \tag{13}$$

where $M_{\infty,F}$ is the absorbed equilibrium amount during relaxing, k_F is the diffusion constant, $M_{\infty,i}$ is the penetrated amount during relaxation, and k_i is the relaxation constant. It is shown that this model takes into account the relaxation and diffusion separately (Sibanda et al., 2004).

4.8 | Cooney model

Cooney (1972) proposed a model for the release of surface eroding spheres and cylinders. In this model, it is assumed that there is only one zero-order kinetics controlling the process. Like the Hopfenberg equation, the release constant is dependent on the time-dependent surface area. This equation for cylinders is as following:

$$f = \frac{(D_0 - 2Kt)^2 + 2(D_0 - 2Kt)(L_0 - 2Kt)}{D_0^2 + 2D_0 L_0}, \tag{14}$$

where L_0 and D_0 are the initial length and diameter of the cylinder, respectively, and K is the rate constant.

4.9 | Baker–Lonsdale model

Baker and Lonsdale (1974) updated the Higuchi model to elucidate controlled release kinetics of spherical matrices, as shown in Table 1.

4.10 | Hixson and Crowell model

In this model (Table 1; Figure 4f), it is assumed that the shrinking particle area is proportional to the cubic root of the volume (Hixson & Crowell, 1931). In this equation, it is assumed that the dissolution rate through the polymer matrix is the limiting factor. There are two conditions to obtain a linear plot for the Hixon–Crowell model: (a) nonequilibrium conditions; (b) diminishing the geometrical shape of the releasing material proportional to the time.

4.11 | Selection of the best model in release studies

There are different statistical approaches to select the best fitted mathematical model. The most frequently utilized index is the correlation coefficient R (or the coefficient of determination, R^2, which is the square of the correlation coefficient). When the model parameters are similar, this method can be helpful. When the number of parameters in the models that are being compared is different, the adjusted coefficient of determination (R^2 adjusted) is used as follows:

$$R^2_{\text{adjusted}} = 1 - \frac{n-1}{n-p}\left(1 - R^2\right), \tag{23}$$

where n is the number of experimental release data and p is the number of model parameters. The best model is that with the highest value of the correlation coefficient.

4.12 | Case studies: Release modeling of bioactives by empirical and semiempirical models

Application of empirical and semiempirical models is more common than mechanistic realistic methods because the latter are difficult to be understood mathematically and they require more experimental data. Also, simpler empirical equations are more stable to experimental data variations; so, their application is preferred to complex ones. For instance, the Higuchi model, which has one parameter, is preferred to Weibull and power law models with two parameters.

In this part, some of the most recent literatures in the modeling of controlled release for encapsulated food bioactives are summarized. It is worth noting that again, the principles used in the release modeling of food materials are gained from the pharmaceutical field to develop food product delivery systems. So, here we also discuss some of the studies in the field of drug active agent release modeling and the application of their results in the field of food release modeling. These findings can help food scientists to design new products and technologies and also enhance the existing ones.

A few studies report the release as a zero-order process. As shown in Tables 4 and 5, the release mechanism of bioactives from the carriers produced by the synthetic or natural polysaccharides (chitosan, starch, inulin, alginate, maltodextrin, etc.) during the simulated conditions is usually a non-Fickian process, which is a combination of diffusion, swelling, and erosion. In contrast, when the bioactive agents are encapsulated into protein matrices (whey protein concentrate, soy protein, zein, casein, etc.), Fickian diffusion is the governing release kinetics.

One of the most important aspects of drug release studies that is very important in the field of food materials is the physical and chemical characteristics of the food or drug active agents and also the carriers used for controlled release purposes. Surface roughness, porosity, molecular weight, particle size, the extent of degradation, and chemical composition are examples of the most critical physicochemical attributes that should be considered in the food and drug release processes and also modeling. Physicochemical attributes of the carrier or the polymeric matrix could be altered using the combination of different polymers. The physicochemical characteristics are also affected by the process parameters used to produce the controlled release system. Freeze drying or lyophilization is one of the most known technologies used to produce controlled release systems. In this process, the solutions in the food or drug are frozen and removed by sublimation under vacuum conditions; so a porous structure is created. This process is applied in the field of pharmaceuticals to produce heat-sensitive drugs and improve the stability of some liable drugs especially injectable drugs in vials. In the field of food, it is used to encapsulate bioactive compounds such as vitamins, anthocyanins, essential oils, and many other functional ingredients. Utilization of this process might alter the release kinetics of food or drug bioactive agents.

Unagolla and Jayasuriya (2018) studied the release kinetics of Vancomycin from chitosan–alginate microcapsules. The first aspect of this study was investigating the physicochemical attributes of the polymeric matrix on release kinetics. They investigated the effect of the polymeric matrix (chitosan, alginate, and their combination) on

TABLE 4 A brief overview of recent release studies regarding empirical/semiempirical modeling of controlled release of food bioactive ingredients

Bioactive ingredient	Encapsulation system	Modeling results	Release mechanism	Remarks	Reference
Flavoring and aroma					
Diacetyl	Whey protein concentrate and alginate	The first-order model described the release kinetics sufficiently.	The exponent of the Korsmeyer–Peppas model: $0.2096 < n < 0.3320$ indicating a diffusion controlled release.	The release mechanism was investigated at simulated mouth conditions.	Zandi, 2014
Limonene	A multilayer microcapsule produced using high methoxyl pectin and soy protein isolate fibrils. About one to six layer emulsion particles were produced and were named as L1 to L6.	Release kinetics of limonene from L1, L2, and L3 microcapsules followed first-order kinetics. This model was appropriate for the description of release through a porous matrix known as burst release. L4, L5, and L6 microcapsules release best described by the Higuchi model.	The exponent in Rigter–Peppas model was $0.43 < n < 0.85$, which showed a non-Fickian mechanism composed of erosion and diffusion phenomena.	–	Ansarifar, Mohebbi, Shahidi, Koocheki, and Ramezanian, 2017
Phenolic compounds					
Curcumin	Liposomes coated with chitosan at different temperatures (23 and 60 °C during 360 min).	At 23 °C release was best described by the Higuchi model, whereas at 60 °C, the Ritger–Peppas equation showed better results.	The exponent in this model was $0.64 < n < 0.81$ indicating a non-Fickian or Anomalous transport where both diffusion and dissolution are considered.	The release was investigated at 23 °C and 60 °C during 360 min	Liu, Liu, Zhu, Gan, and Le, 2015
Gallic acid	Native and acetylated starch and inulin microcapsules by applying a spray drying technique	The release data were fitted to first-order, Higuchi, and Peppas models. All the selected models showed a good agreement between experimental and model data for gallic acid–starch microspheres.	Anomalous diffusion (non-Fickian)	Acetylation of starch did not affect the release profile and no increment in release rate was shown due to increasing the swelling power. The release rate for inulin acetate microspheres was lower than native inulin due to the decrement of hydrophilicity because of acetylation.	Robert et al., 2012

(Continues)

TABLE 4 (Continued)

Bioactive ingredient	Encapsulation system	Modeling results	Release mechanism	Remarks	Reference
Grape seed polyphenols	Uncoated and chitosan-coated primary and secondary liposomes (double coated with chitosan)	The first-order model best fitted the experimental results with a correlation coefficient $R > .99$ for all encapsulated and nonencapsulated liposomes.	As no burst effect was observed in release curves, the main controlling mechanism in this study was diffusion.	The release rates of uncoated liposomes were higher than coated ones	Gibis, Ruedt, and Weiss, 2016
Polyphenols from the strawberry extract	Chitosan	The best model describing the release kinetics of polyphenols was Korsmeyer–Peppas model.	The n exponent in this model suggested that the release at the initial phase is via diffusion and continues by a sustained release. This exponent was different at various pH values and the highest n was seen at pH 7.4, which represented a non-Fickian release.	The release plot showed a burst initial release followed by steady state kinetics that was due to controlling gel formation by chitosan.	Pulicharla, Marques, Das, Rouissi, and Brar, 2016
Curcumin	Zein fibers	First-order and Hixon–Crowell models were the best fitting models.	The governing release mechanism of curcumin from fibers was Fickian (the n exponent <0.43).	The result of kinetic modeling showed that the release mechanism of curcumin was due to diffusion through the swollen fiber matrix and also to some extent due to the porosity of the matrix structure that is filled with water rather than erosion. The first-order model showed that the transfer of curcumin in the matrix was the limiting step.	Wang et al., 2017
Green tea polyphenols	Choline and cholesterol liposomes	Zero-order model best fitted the experimental data.	The release was non-Fickian as the exponent of Korsmeyer–Peppas model was $0.43 < n < 0.89$, which indicated a non-Fickian mechanism composed of diffusion and erosion	Liposomes are an ideal system for the controlled release of bioactive agents that represent a prolonged release.	Prakash Upputuri and Azad Mandal, 2017

(Continues)

TABLE 4 (Continued)

Bioactive ingredient	Encapsulation system	Modeling results	Release mechanism	Remarks	Reference
Curcumin	Various pluronics to enhance the stability of curcumin-loaded liposomes	Peppas model best described the release kinetics	Non-Fickian with the exponent $0.43 < n < 0.89$, and the first order for only one type of liposome.	–	Li et al., 2018
Quercetin	Chitosan and chitosan derivative modified with glucosamine by Maillard reaction	Higuchi equation was not able to predict the results, whereas zero-order, first-order, and Korsmeyer–Peppas equations showed good fitting. The zero-order model best described the release kinetics.	Non-Fickian diffusion mechanism.	–	Vanden Braber et al., 2018
Curcumin	Cress seed mucilage and sodium caseinate	In the simulated gastric condition, Peppas–Sahlin model and intestinal condition Ritger–Peppas model best fitted the release data.	Fickian diffusion in gastric fluids and case-II transport in intestinal fluids was observed.	In simulated gastric conditions, curcumin diffuses out to the media; and in the intestinal condition, the microcapsules immerse in the surrounding media, and relaxation occurs.	Kavousi, Fathi, and Goli, 2018
Hesperetin	Basil seed mucilage–polyvinyl alcohol nanofibers	The Korsmeyer–Peppas best fitted the release data in gastric and intestinal simulated media.	Fickian diffusion in gastric fluids and Fickian dissolution in intestinal fluids were observed.	–	Kurd, Fathi, and Shekarchizadeh, 2019

(Continues)

TABLE 4 (Continued)

Bioactive ingredient	Encapsulation system	Modeling results	Release mechanism	Remarks	Reference
Vitamins					
Vitamin C and B_{12}	Chitosan, modified chitosan, and sodium alginate microcapsules produced by spray drying	Weibull model best fitted the experimental data.	The governing mechanism of release was biopolymer swelling.	–	Estevinho and Rocha, 2017
Vitamin B_{12}	Chitosan microcapsules produced by spray drying	They stated the Weibull equation was useful in comparing the release profile of encapsulated material in the form of a matrix that was produced by the spray drying (in which the bioactive agent is distributed in encapsulating material). The β parameter in this model was <1, which indicated the shape of the release plot had a steep increase.	The release mechanism was usually diffusion controlled and depended on the action of solvents.	The release behavior in simulated gastric conditions was evaluated.	Carlan, Estevinho, and Rocha, 2017
Pantothenic acid (vitamin B_5)	Liposomes and alginate or alginate–pectin microparticles loaded with liposomes	None of the systems followed zero-order kinetics. For alginate– pectin microparticles loaded with liposomes and single liposomes, the first-order model best fitted the release data that shows the dependency of release rate to concentration. Release kinetics from pure alginate microparticles followed the Higuchi model.	Diffusion	–	Ota et al., 2018

(Continues)

TABLE 4 (Continued)

Bioactive ingredient	Encapsulation system	Modeling results	Release mechanism	Remarks	Reference
Essential oils					
Coriander essential oil	Chitosan/alginate/inulin	The release kinetics at pH 2.5 and 37 °C for chitosan microcapsules showed two individual parts: the first part showed a burst release followed by a slow release rate. The burst effect is due to swelling and high oil concentration on the surface of microcapsules where water passes through the microcapsule wall and polymer changes from a glassy state (inside) to a rubbery state (outside). Both first-order and Peppas equations fitted the experimental data at mentioned pH values properly. For alginate and inulin microcapsules, the release was directly proportional to time and best described by the Higuchi equation. At elevated pH values, the first-order kinetics fitted the release data more properly.	pH 2.5 and 37 °C → the n exponent of 0.4032 for chitosan microcapsules was an indicator of Fickian mechanism, whereas the other microcapsules represented a non-Fickian behavior ($0.43 < n < 0.85$). At high pH, the n exponent for chitosan and chitosan–alginate microcapsules indicated a diffusion-controlled mechanism because of low swelling degree and for the others showed a non-Fickian transport mechanism.	Different pH values (2.5 and 6.5) and temperatures (37 and 65 °C) to simulate gastrointestinal and food processing conditions were tested. Different temperatures did not have any effect on the release mechanism.	Dima, Pătraşcu, Cantaragiu, Alexe, and Dima, 2016

(Continues)

TABLE 4 (Continued)

Bioactive ingredient	Encapsulation system	Modeling results	Release mechanism	Remarks	Reference
Thymol and carvacrol	Maltodextrin and soy protein matrices produced by oil in water emulsions	Weibull model fitted better to the experimental data.	Fickian release	The release rate was a function of the type of encapsulating substance and concentration.	Ulloa, Guarda, Valenzuela, Rubilar, and Galotto, 2017
Mentha longifolia L. essential oil	Balangu seed gum	The release kinetics fitted best to the Peppas–Sahlin model.	Fickian diffusion	The release was evaluated in different food simulants including acidic, alcoholic, aqueous, alkali, and oily systems.	Rezaeinia, Ghorani, Emadzadeh, and Tucker, 2019
Carvacrol	A commercial biodegradable polymer, Mater-Bi®	Korsmeyer–Peppas model fitted the experimental data.	Fickian release	A small contribution of swelling was observed in foam containing 5% carvacrol compared to foams contacting 10% and 20% carvacrol.	Lopresti et al., 2019
Lavender oil	Different mixtures of coating materials (gum Arabic [GA], sodium caseinate [SC], gelatin [GE], chitosan [CS], β cyclodextrin [β-CD], and polyvinyl alcohol [PVA])	Korsmeyer–Peppas model best fitted the release data of GA, GA–SC, GA–PVA, GA–β-CD, GA–SC–CS, and GA–SC–GE. Higuchi and first-order models were more suitable for GA–CS and GA–SC–PVA systems, which demonstrates Fickian diffusion and first-order release.	The exponent of Korsmeyer–Peppas model GA–PVA and GA–SC–PVA was $0.43 < n < 0.85$, which indicated the diffusion and swelling release mechanism (non- Fickian). The exponents for the other wall materials were $n < 0.43$, which demonstrates a Fickian diffusion.	Burst release and diffusion was observed.	Zhang, Huang, Xiong, Qian, and Ji, 2020

TABLE 5 A brief overview of recent release studies regarding empirical/semiempirical modeling of food bioactives from different nanocarriers

Bioactive ingredient	Encapsulation system	Modeling results	Release mechanism	Remarks	Reference
Caffeic acid	Chitosan, alginate, and pectin as coating material through layer by layer coating	Reciprocal powered time and Rigter–Peppas were the best; the poorest one was the zero-order model. Higuchi model was also not suitable for polymer-coated nanoparticles because of the swelling nature of biopolymers and the weakness of the Higuchi model for swelling-controlled release modeling.	Fickian diffusion ($n < 0.43$ in Rigter–Peppas model)	The values of a_w in the Weibull model were <1.0, which represents a parabolic release curve that the slope in the initial section of the curve is higher followed by a steady exponential release. The carbohydrate coating declined the burst release, but still, the initial release period was seen.	Fathi, Mirlohi, Varshosaz, and Madani, 2013
Hesperetin	Solid lipid nanoparticles and nanostructured lipid carriers	The best and the worst models were Rigter–Peppas and zero-order models, respectively.	Both diffusion and dissolution ($0.45 < n < 0.89$ in Rigter–Peppas model)	–	Fathi, Varshosaz, Mohebbi, and Shahidi, 2013
Lippia sidoide essential oil	Alginate/cashew gum nanoparticles by spray-drying technique	Korsmeyer–Peppas and Higuchi fitted the results best.	The n exponent was below the power law limit, so the power law equation had some inefficiencies in elucidating release mechanisms.	–	de Oliveira, Paula, and de Paula, 2014
Eucalyptus staigeriana essential oil	Cashew gum by spray drying	Korsmeyer–Peppas and Higuchi fitted the results best.	The n exponent of the Korsmeyer–Peppas model was outside the stated limits for some nanoparticles indicating the limitation of the power law equation.	–	Herculano, de Paula, de Figueiredo, Dias, and Pereira, 2015
Curcumin	Kafirin (sorghum prolamin) nanoparticles	Korsmeyer–Peppas fitted the results best.	Fickian diffusion release ($0.17 < n < 0.19$ in Korsmeyer–Peppas model)	–	Xiao, Nian, and Huang, 2015
Ethylvanillin	Ethylcellulose	Ritger–Peppas fitted the results best.	Non-Fickian diffusion mechanism ($0.43 < n < 0.85$ in Korsmeyer–Peppas model)	–	Eltayeb, Stride, and Edirisinghe, 2015

(Continues)

TABLE 5 (Continued)

Bioactive ingredient	Encapsulation system	Modeling results	Release mechanism	Remarks	Reference
Curcumin	Chitosan and gum Arabic nanoparticles	The lowest correlation coefficient was seen in the first-order model, whereas the Ritger–Peppas model had the highest R^2 value.	The n value in this model showed that the release profile of curcumin from nanoparticles was controlled by both swelling and diffusion (Anomalous transport), whereas the release of curcumin from the emulsion was case II; transport (swelling controlled).	Such behavior might be due to the swelling of the polymer matrix in the acidic medium because of the protonation of chitosan amine groups.	Tan, Xie, Zhang, Cai, and Xia, 2016
Crocin (main bioactive agent of saffron)	Double nanoemulsions (W/O/W) constructed with Angum gum, Arabic gum, and whey protein	Rigter–Peppas was the best and zero order was the worst model.	Diffusion controlled release mechanism	–	Mehrnia et al., 2017
Folic acid	Pectin–whey protein double W/O/W emulsions by spray drying	The best model fitting for folic acid release data was observed for single-layer WPC (whey protein concentrate)Encapsulated powders with the highest R^2	Diffusion and dissolution mechanisms	–	Assadpour, Jafari, and Maghsoudlou, 2017
Onion peel quercetin	Chitosan–cellulose hydrogel with green zinc oxide nanoparticles	Korsmeyer–Peppas model best fitted the release data for both pure chitosan cellulose and nanohybrid hydrogels.	Fickian diffusion was the controlling mechanism	–	George, Maheswari, and Begum, 2019

(Continues)

TABLE 5 (Continued)

Bioactive ingredient	Encapsulation system	Modeling results	Release mechanism	Remarks	Reference
Green tea polyphenols	Casein nanoparticles	The best model describing the experimental data was zero-order model, which is an ideal model for the release of drugs from nanoparticulate sustained release formulations.	The n exponent was 0.43, indicating a Fickian release.	Casein nanoparticles could be applied as an ideal carrier for the bioactives, for a prolonged or a sustained release system.	Ravi and Mandal, 2019
β-Carotene	Citric acid native and modified banana starch nanoparticles	Korsmeyer–Peppas equation explained the release kinetics well.	The n exponent of Korsmeyer– Peppas model and the ratio of the ($k1/k2$) in Peppas–Sahlin model (Equation 10), which was >1, indicated a Fickian diffusion mechanism.	Cross-linked nanoparticles indicate a more controlled release in the simulated intestinal condition. It means that they are suitable vehicles for intestine-specific delivery.	Santoyo-Aleman, Sanchez, and Villa, 2019
Origanum vulgare and *Thymus vulgaris* essential oils	Zein nanocapsules	Korsmeyer–Peppas equation explained the release kinetics.	The oregano essential oil nanocapsules presented an Anomalous diffusion ($n = 0.52$) and the thyme essential oil-loaded nanoparticles showed a Fickian release ($n = 0.39$).	The nanoparticles followed a slow release without any burst effects in the first 8 hr. This behavior is considered as a characteristic of the nanoprecipitation method.	Gonçalves da Rosa et al., 2020

release kinetics and consequently the best model that fits the release data. The capsules containing just chitosan showed the lowest release rate (according to k constant in models related to diffusion phenomena) because of strong cross-linking of the polymer matrix that prevents the active agent to be released at the desired time. The alginate capsules indicated the highest release rate with a burst effect not suitable for controlled release systems. The combination of chitosan and 1% alginate resulted in moderate release rates that were due to decrement of the voidage in polymeric structure, thus reducing the swelling and preventing the burst effect. Increasing the amount of alginate did not increase the release rate in the studied system. They also investigated the effect of the drying process (air drying and lyophilization) on release kinetics. Ritger–Peppas, Higuchi, zero-order, first-order, and Peppas–Sahlin models were used to fit the experimental data. The models were only acceptable for the first 60% of the release process. Among the mentioned models, the Peppas–Sahlin model showed the best fit meaning that both Fickian diffusion and Case II relaxation are involved in drug release. The values of n exponent of the Ritger–Peppas model in all microcapsules except the lyophilized ones were around 0.3 indicating a Fickian diffusion in polydisperse spherical systems. In the lyophilized microcapsules, the value of n was around 0.5, which reveals a non-Fickian or anomalous transport. So, it was concluded that the porosity of the microcapsules, which was the result of using different drying methods, plays a critical role in drug transport phenomena. Heterogeneous distribution of the active agent is created in the drying process as a result of the migration of bioactive agents that causes the burst effect. Also, cracks might form on the surface of the microspheres that increase the burst effect and facilitates surface erosion. This study confirmed that the physicochemical characteristics of the microcapsules have a critical effect on the transport mechanisms and the rate of the released drug. These results are important in the field of food materials because the burst effect is usually not desired in the controlled release of food bioactive agents. For example, in the case of active packaging, the antimicrobial or antioxidant compounds should be provided to the food material during the shelf life and the burst release might cause problems. Different drying processes are also used in the food encapsulation depending on the type of materials and many other factors such as economic issues that have a direct impact on the release kinetics. So, the selection of the polymeric matrix composition and also the type of drying process should be performed carefully to prevent negative side effects.

One of the other most important attributes affecting the controlled release kinetics is the shape of the encapsulated release system. In the case of drugs, they may be provided in the shape of different size cylinders, spheres, slabs, and so on. In the case of encapsulated food, various geometries also might be produced. For example, one of the frequently used methods to produce food controlled release systems is hot melt extrusion. This method is used to form amorphous matrices to entrap aromas or flavoring agents or mask off flavors of vitamins or minerals incorporated into the food system. In such systems, desired shapes of food material including rods, ropes, and pellets could be produced. The controlled release of the active agent from these systems is proportional to their geometry. To elucidate the behavior of polymer erosion, different kinetic models were fitted to the experimental mass loss data of photo-cross-linkable polyanhydrides tablet surface erosion. MATLAB software was used to fit the data and the model with the highest R^2 and lowest RMSE (Root-mean-square deviation) was selected as the most suitable one. The results showed that Hixon–Crowell and Hopfenberg models best fitted the experimental release data of cylindrical tablets, whereas Hixon–Crowell and Weibull models best fitted for cubic tablets. This study demonstrated that the shape of the samples has a direct impact on mass loss profiles (Geraili & Mequanint, 2020). So, the effect of the geometry of the controlled release profile of different food systems should always be considered as an important factor in release studies.

In a recent study (Bastos, de Sá Costa, Siqueira, & Garcia-Rojas, 2020), modeling the release kinetics of microencapsulated black pepper essential oil using β-lactoglobulin/sodium alginate was studied. Various food models including alcoholic, acidic, alkali, and oily systems were prepared to study the release kinetics. The highest R^2 value was reported for the Ritger–Peppas model. The value of n exponent in this model for all food simulants was <0.43, which showed the main release mechanism is Fickian diffusion (Case I transport) in spherical particles. It has been stated that the main release mechanism for flavoring agents (e.g., essential oils)—which are extensively applied as the antimicrobial and antioxidant agents in food packaging and various other applications—is Fickian diffusion. The main reason is the low swellability of the essential oils and also the existence of oil droplets at the exterior layer of the capsules or their surface. In the diffusion process, the active food ingredients transfer into the surrounding medium. The structure of the capsules may change (dissolution, fragmentation, or erosion) or remain intact during this process; it is highly dependent on the relative solubility and the diffusion coefficient of the active agents in the encapsulation matrix and the surrounding media. These authors reported that although using food simulant is a suitable approach to study the release kinetics, applying real food systems is also necessary that can provide more accurate data.

In some release cases, a significant difference is observed between the slope of release curves in the initial and final stages of the process, indicating a transient state in the release that can be explained using a two-stage model. In a recent study, Fazli-Abukheyli, Rahimi, and Ghaedi (2019) investigated the release process of indole-3-acetic acid from nanoporous anodic alumina as a drug delivery system by a two-stage model. In the first stage of the release process, the initial concentration of the drug inside the porous medium was higher than the solubility, and because of quick water penetration to the pores, a saturated drug solution was generated. As drug dissolution inside the pores is faster than the diffusion through the nanofiber film, the concentration of the drug remains constant in the pores. A zero-order kinetics was used to describe this stage. At the beginning of the second stage, the solid active agent is exhausted inside the porous medium. As the released drug is not replaced by the excess dissolved drug, its concentration decreased with time during the process. So, a first-order model can describe this stage sufficiently. A very good fit was reported between the new proposed model and experimental data in this study. This behavior might be observed in some encapsulated food systems. Peng et al. (2010) reported a similar two-stage behavior for releasing resveratrol (a natural polyphenol in many food sources) from chitosan microspheres cross-linked using vanillin. They claimed in the first release stage, a burst release was observed due to the rapid diffusion of the active agent onto the outer layer of microspheres because of swelling the polymeric chain. This stage was followed by a slow controlled release. This behavior is helpful in designing controlled release nutraceutical functional foods and also in the case of active packaging. In the first stage, the burst release helps to reach the effective concentration of the bioactive agent in the plasma or food packages. In the second stage, this effective concentration remains constant that is useful for prolonged release purposes.

Some of the recent studies regarding release modeling are summarized in Table 4. Also, some other studies have focused on the release modeling of nanocarriers, which are currently an interesting subject in the food systems. A brief overview of the literature regarding nanocarriers is tabulated in Table 5.

Sometimes the release behavior of various delivery systems cannot be predicted adequately by the common release kinetics models. Thermosensitive liposomes are one of these systems that are receiving extensive attention because of exposing triggered release behavior. They can release the active agent rapidly in the heated area, whereas the release rate in the nonheated parts of the body is low. So, the release kinetics cannot be predicted by common mathematical models. Lu and ten Hagen (2020) established a new model to describe the release behavior of such systems while fitting the release data to different commonly used mathematical models in the literature. The novel model considered the Laplace pressure as a driving force for the release process in liposomes with a size <100 nm. They reported only the Weibull and Korsmeyer–Peppas models to show acceptable fitting results. The novel kinetic model showed a better fit within all temperature ranges and can be used for nanosized stimuli-responsive systems. Thermosensitive liposomes are currently used to deliver drugs to the specific sites of actions in body organs or cancer cells. They have the advantage of increased efficiency and decreased side effects. The knowledge behind pharmaceutical studies of thermosensitive liposomes could be applied in the field of food technology to produce carriers in thermal unit operations including bakeries, for example, the release of flavoring agents incorporated into ready-to-eat products by an increment in the temperature of cooking.

Sometimes the empirical and semiempirical approaches might result in poor and inaccurate results at various stages of the release process. The comparison between these models and other approaches is not done in the literature. Polyák, Bartha, and Pukánszky (2020) proposed a novel approach for modeling the drug release based on Fick's second law for cylindrical geometry without involving any simplification or introducing empirical constants. The model was solved numerically using computer software. They also compared the results with the empirical model results in different stages of the release process. It was shown that this novel method can exactly predict the dissolution of the active agent from poly (3-hydroxybutyrate) fibers over the entire release time in fibrous matrices. The Higuchi and square root models were less accurate in the first and final stages of the release process. There are a few studies regarding the utilization of numerical computational methods in the field of food bioactive encapsulation.

A new model was developed by Romero et al. (2018) for progesterone release from the polymeric matrix of poly-3-hydroxybutyric acid based on the second-order kinetics. This model lumped the important stages in the release process together and unlike the power law model, it encompassed the entire release time. The model contained only two parameters and was validated using the experimental release data; it was also compared to six empirical and semiempirical known models. Based on the Akaike information criterion, the developed model fitted the experimental data better than other models. The equilibrium distribution constant and the external mass transfer coefficient was determined by the model accurately. Application of such modeling in the field of food is limited and this approach can be transferred to model the entire release time of the prolonged release

kinetics of food instead of using frequently used power law model.

The release profile of the drugs and active agents from nano-, micro-, or supramolecular carriers depends on different mechanisms (such as diffusion, swelling, and erosion), the composition of the coating material, and technological aspects such as loading rate, geometry, size, and shape that affect the selection of appropriate release model. In a recent study, Paolino et al. (2019) evaluated the suitability of different modeling approaches (such as linear, Noyes–Whitney, Higuchi, Peppas, and Weibull) for modeling the release kinetics of fluorescein from monoglyceride colloidal liquid crystals with and without taking the lag time into account. The diffusion equation was solved in different boundary and initial conditions using Laplace and Fourier functions to study the release from an infinite reservoir system in a semi-infinite medium. The differences among the results of mathematical models were evaluated by statistical methods (Akaike and Schwarz criteria, Imbimbo criterion, and Fisher [F] test). The phenomenological models came out with better results than empirical and semiempirical models. The square root equation was selected as the most suitable model to describe the release kinetics of hydrophilic compounds from the mentioned colloidal systems. Information obtained from the square root equation could be improved by Weibull and Peppas models (Paolino et al., 2019). Liquid crystals are suitable vehicles for drug delivery systems. They can contain equal amounts of nonpolar and polar ingredients being hydrophobic or hydrophilic. They also have the advantage of protecting the core active material through the digestion system until reaching the targeted site of action. These advantages are used in the field of food to produce smart foods. Besides the mentioned benefits, lyotropic liquid crystal phases are applied in some food products to control textural and rheological properties. One of the challenges in the application of such systems in the food industry is the optimization of their release in different processing stages (Lagerwall & Scalia, 2012). The result of these carriers in the field of the pharmaceutical can be applied to food liquid crystal release modeling.

As various factors affect the release process of bioactives in food systems and also GIT (human digestion system), modern modeling techniques such as intelligent modeling approaches can yield interesting results in this field (Jafari, Ganje, Dehnad, & Ghanbari, 2016). Some research is conducted in order to evaluate the effectiveness of neurofuzzy modeling of food release (e.g., β-carotene release from NaCMC/carrageenan matrix; Hezaveh, Muhamad, Noshadi, Shu Fen, & Ngadi, 2012) or artificial neural network modeling of pharmaceutical products release (Barmpalexis, Kachrimanis, & Georgarakis, 2011). The basic principle of the fuzzy logic approach is the fuzzy sets theory. A novel fuzzy logic approach was used by Ganje et al. (2019) along with mathematical modeling using empirical and semiempirical models for release modeling. They used the Mamdani method in MATLAB software for fuzzy modeling. The inputs were the concentration of amylose and limonene and sonication time and the outputs were the residence time of the produced nanoparticles. The amount of released limonene at the times of 1 to 6 hr was categorized into different groups. Among the fitted models, the Peppas model had the highest coefficient of determination (0.98), whereas the fuzzy logic approached yielded the coefficient of determination of 0.99 in order to model the release of limonene from amylose nanocarriers.

There are other studies considering the kinetic models to investigate the release behavior of food in GIT conditions. Release kinetics of magnesium and calcium ions from egg white was modeled in simulated stomach conditions. Korsmeyer and Peppas model was successfully applied to the release data of nutrients from the egg white system and it was concluded that the release followed a Fickian diffusion. In order to investigate the contributions of diffusion and erosion mechanisms in the system, Peppas and Sahlin model was fitted to the experimental data. The authors stated that although this model can describe successfully the release process of bioactive agents in the pharmaceutical field, it is not widely used in food applications yet (Tomczynska-Mleko, 2015; Tomczyńska-Mleko et al., 2016).

The Weibull model is also one of the frequently used models to predict the bioactive release in the field of pharmaceutical applications. This model can be applied successfully in modeling the release kinetics of solids from food in GIT conditions. In a study, this model was applied to determine the release kinetics of carrots during in vitro simulated GIT conditions (Kong & Singh, 2011).

5 | MECHANISTIC REALISTIC RELEASE MODELS

5.1 | Mechanistic theories

This type of modeling is called mathematical, analytical, realistic, intrinsic, or other names. A lot of findings have been achieved in medicine, biology, engineering, and many other branches of science using this type of modeling. It is not necessary for these models to have explicit mathematical correlations and they might be only conceptualizations (Rescigno & Thakur, 2012). In mechanistic modeling, the theoretical or fundamental knowledge of the variables and their interactions is used in order to define the desired variable. Mechanistic or theoretical

modeling is therefore identical. In the mechanistic modeling approach, the mathematical relationships are applied to define the interactions of the most important phenomena taking place in the system. In other words, the relationship between several parameters and variables of the system is summarized in this type of modeling. Physical laws, experimental data, and sometimes, physical models are used in mechanistic modeling. This approach is usually complicated and the theoretical equations need to be simplified or generalized (e.g., the geometry, initial, and boundary conditions) and finally an approximation of system dynamics is represented (Carranza, 2009).

Mechanistic modeling of controlled release is performed based on the conservation laws of mass and energy that are in the form of partial differential equations (PDEs). The solution of these PDEs is either *numerical* or *analytical* based on the complexity of the system. In the case of simpler sets of equations, analytical solutions are preferred, in which the release rate is calculated as a function of the system-specific parameters. There are two different solutions, *explicit* and *implicit*. In the explicit method, the release rate or the amount of released bioactive could be separated from other parameters and variables on one side of the equation. In this method, the impact of processing parameters can be elucidated. In the implicit method, the release rate or the amount of released bioactive could not be separated from other parameters and variables on the other side of the equation and the effect of processing parameters is less directly observed. Numerical modeling is performed when the equations are sophisticated and the analytical approach cannot be solved easily. In this method, approximations and simplifications are made. Nowadays, using advanced computer programs facilitates the application and solution of numerical methods (Siepmann & Siepmann, 2008).

Mechanistic modeling is generally categorized into two types: *deterministic* and *stochastic*. In the first type, the mathematical equations are solved and make definite predictions while no randomness in the variable distributions is considered. On the other hand, in the stochastic modeling, the mathematical equations are solved considering some randomness in the predictor or target variable distribution. So this method does not yield a single prediction of the target variable. It results in a probability distribution of estimates derived from several simulations that reflect the random distributions in the target and predictor variables. Usually, no modeling approach is purely deterministic or stochastic (Carranza, 2009).

Performing mechanistic modeling might be time-consuming and expensive. High computational power might be required to solve these complex mathematical models. It should be noted that the quality and accuracy of the selected model depend on the target of modeling, and in some cases, simplifications are included using empirical equations. One of the most important issues in mechanistic modeling is the determination of the model complexity based on the rate-limiting processes in the system.

In the case of controlled release systems, the most important mechanism is the diffusion, and the application of quantitative and mechanistic realistic models in this process is extremely helpful. Some other systems are more complex and a combination of mechanistic realistic sets of equations, which consider the diffusion of water into the polymeric matrix, swelling of the matrix, matrix degradation, and so on, should be applied to quantify the underlying release mechanism (Siepmann & Göpferich, 2001; Siepmann & Siepmann, 2008; Siepmann & Siepmann, 2012). Three important insights of mechanistic realistic modeling of the controlled release process are summarized in Figure 5.

5.2 | Mechanistic modeling based on the diffusion

As it was noted before, the phenomenon of diffusion has a vital role in several processes in nature and human organs. In a three-dimensional system (x, y, and z) where the coefficient of diffusion varies with time, position, and the concentration of the solute, Fick's law of diffusion changes to

$$\frac{\partial c}{\partial t} = \frac{\partial}{\partial x}\left(D\frac{\partial c}{\partial x}\right) + \frac{\partial}{\partial y}\left(D\frac{\partial c}{\partial y}\right) + \frac{\partial}{\partial z}\left(D\frac{\partial c}{\partial z}\right). \quad (24)$$

In the case of independency of the diffusion coefficient from time, position, and concentration, it becomes

$$\frac{\partial c}{\partial t} = -D\frac{\partial^2 c}{\partial x^2}. \quad (25)$$

Such equations could be solved analytically when the initial and boundary conditions are specified. The initial condition is the concentration of the bioactive agent in the beginning point of the release process and the boundary condition is the concentration of the bioactive agent at the surface of the system. The analytical solution can calculate the bioactive release as a function of time. The analytical solution of Fick's second law of diffusion for various initial and boundary conditions and different geometries is provided by (Crank, 1979). The analogous heat transfer equation solution might be applied using the book of Jaeger and Carslaw (1959) when the analytical solution for a specific case is not found in Crank's book. If the coefficient of diffusion is dependent on time, space, and concentration and the systems with complex geometries, no analytical solution of Fick's law is present and the numerical methods should be used.

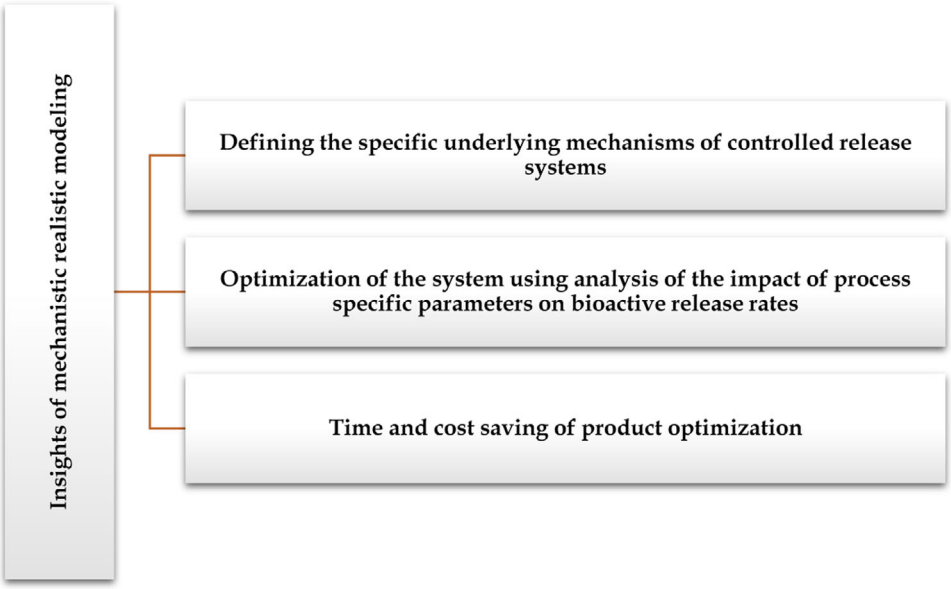


FIGURE 5 Three important insights of mechanistic realistic modeling in controlled release process

According to Arifin, Lee, and Wang (2006), there are three main categories assumed for the boundary condition:

1. In the first case, the surface mass transfer resistance can be neglected while the release environment is infinite. This condition is called "perfect sink condition" in which the concentration on the surface of the release system (C_s) is a constant as a function of bioactive concentration in the surrounding environment (C_b) with a partition coefficient between these two concentrations (K), $C_s = KC_b$.
2. In the second case, there is a limited mass transfer resistance at the surface of the system, but the perfect sink condition exists in the surrounding medium. In this system, the surface concentration is defined using the convective mass transfer coefficient (h) and the bioactive concentration in the surrounding medium is constant:

$$\left(-D\left(\frac{\partial c}{\partial r}\right)_{r=R} = h\left(C|_{r=R} - KC_b\right)\right). \quad (26)$$

3. In the last case, the volume of the surrounding medium is limited and its concentration alters during the release process. The mass transfer resistance at the surface is either limited or not.

The diffusion-controlled systems are classified into two different categories: reservoir and matrix systems. In the first system, a polymeric shell surrounds the bioactive core. In the second system, the bioactive agent is dissolved or dispersed in a polymeric matrix.

Aguilar-Rabiela, Hernández-Cooper, Otero, and Vergara-Porras (2020) proposed a physical model considering analogous heat and mass transfer. The mass balance model was solved based on the diffusion equation in this work. As the total mass balance showed some nonlinearities, a semi-analytical method was applied based on the heat balance method. The results of curcumin release from the polyhydroxybutyrate delivery system were used to validate the model and it was shown that the model had a more accurate prediction of the experimental values. The release profile of progesterone from poly (lactic-co-glycolic acid) microspheres with different sizes was studied using a newly developed mathematical model. The model took dissolution, diffusion, and polymeric degradation of the drug system into account. It consisted of two modules including a degradation module and a release module (based on diffusion equation) with some hypotheses. The model was solved using MATLAB software and showed a very good agreement with the experimental data. The authors suggested that the proposed model could be used to select the suitable particle size or molecular weight of polymeric matrix to yield a desired drug delivery profile (Busatto, Pesoa, Helbling, Luna, & Estenoz, 2018).

As noted earlier, modeling the release of nutraceutical food agents is one of the most important applications of release modeling in the field of food science. Two critical phenomena that govern the release of food bioactive agents are diffusive mass transport from food to GIT fluids, and surface erosion of food as a result of mechanical

force in the stomach. The diffusion process is composed of liquid (acid and enzyme) diffusion from GIT fluid to the food as a consequence of concentration gradient and diffusion of food solutes (vitamins, fibers, oils, minerals, etc.) to GIT medium. It is worth noting that many previous studies in the field of food science showed that Fick's second law of diffusion could be considered as theoretical support to model the diffusion of gastrointestinal juice into different food systems (Mennah-Govela & Bornhorst, 2016; Somaratne et al., 2020).

The diffusion coefficient of gastric fluids in different food matrices such as sweet potato, carrots, and rice has been investigated (Kong & Singh, 2011; Mennah-Govela & Bornhorst, 2016; Mennah-Govela, Bornhorst, & Singh, 2015). Understanding the relationship between the rate of diffusion of GIT fluids and microstructural changes of food that leads to the release process of nutrients is beneficial in designing functional food products with enhanced benefits. Besides the diffusion of gastric juice in food, the mechanism of nutrient release from solid food structure as a result of the food matrix structure breakdown is very important in designing controlled delivery systems. Mathematical models of solid breakdown (especially fragmentation and erosion) should be coupled with mass transfer models in order to elucidate underlying mechanisms.

5.2.1 | Reservoir systems

In reservoir (core–shell) systems, the bioactive agent is either dispersed or dissolved in a reservoir that is coated with an inert membrane (wall material) that limits the mass transfer rate. These two parts are physically distinct. In fact, such membranes offer a better controlled release profile. Zero-order release in which the release rate is constant during time is achievable in reservoir systems where an excess amount of the bioactive is presented. According to the literature, the release rate from the food reservoir systems is dependent on the thickness, the surface area, and the permeability of the barrier (Mastromatteo et al., 2010). Some of the common examples of reservoir systems in food applications are bakery leavening agents, microemulsion systems produced to enhance the solubility of lipophilic nutraceuticals, and so on.

The reservoir systems might have a constant or nonconstant activity source. In nonconstant activity source systems, the bioactive concentration is less than its solubility, so its concentration declines during the release process. In the constant activity source systems, the bioactive concentration is higher than its solubility, so the released bioactive molecules are replaced instantly. In these systems, the concentration of bioactive agent remains constant during the release until it falls below its solubility. As the reservoir systems come in contact with water, the bioactive molecules diffuse through the coating material due to the concentration gradient across it. Three main transport phenomena taken place in this process are the diffusion of water, dissolution of bioactive, and its diffusion. The last transport phenomenon is the rate controlling process because it has the slowest rate. In such systems, a simplification can be made that is solving the diffusion equation. It is helpful in defining the release profile and characteristics.

For reservoir systems, Fick's first law of diffusion (Equation 5) could be used in order to describe the controlled release of bioactives through the membrane. It should be noted that if the coefficient of diffusion is dependent on time and position due to matrix degradation, matrix swelling, or erosion, no analytical solution is applicable for Fick's law and only the numerical methods should be used (Perale et al., 2009).

The initial and boundary conditions for different systems and situations are not the same. The initial distribution of diffusing species could be explained using the initial condition in the system. The mathematical solution is straightforward if this distribution is homogenous. The boundary condition denotes the diffusion at release system boundaries. If the system dimension is constant with time, the boundaries are stationary. In contrast, if the dimension is proportional to time, the moving boundary condition is considered. In the case of swelling, the boundaries move in an outward direction, and in the case of erosion or dissolution, the boundaries move inward. Sometimes, the perfect sink condition is assumed, which means the concentration of bioactive agents in the surrounding media is negligible.

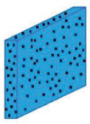
In this part (diffusion controlled release), the mathematical models that would be discussed in the following sections are derived based on the assumptions that (a) the diffusion is the mass transfer limiting process in the system; (b) the coefficient of diffusion is constant; (c) perfect sink condition is provided; (d) no swelling (or rapid swelling) or erosion takes place; and finally, (e) the resistance due to unstirred boundary layers of liquid on the surface is negligible.

Three important aspects should be considered before selecting an appropriate mathematical model for controlled release systems: (a) the distinction between reservoir and matrix system, (b) the initial concentration of bioactive agent (higher or lower than its solubility), and (c) the geometry of system (slab, sphere, or cylinder; other geometries are much more complex and not included in this study). A brief review of mathematical models used in the literature is tabulated in Table 6.

Nonconstant activity sources

As explained, bioactive concentration in nonconstant activity source reservoir systems is less than its solubility,

TABLE 6 A brief review of mathematical models used in release literature

Type of the system	Geometry	Schematic illustration	Amount/rate of the released bioactive agent	Equation No.
Non-constant activity source reservoir systems	Slab		$\frac{M_t}{M_\infty} = 1 - \exp\left(-\frac{ADKt}{VL}\right)$	(27)
	Cylinder		$\frac{M_t}{M_\infty} = 1 - \exp\left(-\frac{(R_iH + R_0H + 2R_iR_0)DKt}{R_i^2h(R_0 - R_i)}\right)$	(28)
	Sphere		$\frac{M_t}{M_\infty} = 1 - \exp\left(-\frac{3R_0DKt}{R_i^2R_0 - R_i^3}\right)$	(29)
Constant activity source reservoir systems	Slab		$M_t = \frac{ADKC_s}{L}t$ $\quad \frac{dM_t}{dt} = \frac{ADKC_s}{L}$	(30, 31)
	Cylinder		$M_t = \frac{2\pi HDKC_s}{Ln\left(\frac{R_0}{R_i}\right)}t$ $\quad \frac{dM_t}{dt} = \frac{2\pi HDKC_s}{Ln\left(\frac{R_0}{R_i}\right)}$	(32,33)
	Sphere		$M_t = \frac{4\pi DKC_sR_0R_i}{R_0 - R_i}t$ $\quad \frac{dM_t}{dt} = \frac{4\pi DKC_sR_0R_i}{R_0 - R_i}$	(34,35)
Monolithic solutions	Slab		Early time approximation $\frac{M_t}{M_\infty} = 4\left(\frac{Dt}{\pi L^2}\right)^{1/2}$	(36, 37,38)
			$\frac{M_t}{M_\infty} = 1 - \frac{8}{\pi^2}\sum_{n=0}^{\infty}\frac{\exp\left[-D(2n+1)^2\pi^2t\right]}{(2n+1)^2}$ Late time approximation $\frac{M_t}{M_\infty} = 1 - \frac{8}{\pi^2}\exp\left(-\frac{\pi^2Dt}{L^2}\right)$	
	Cylinder		$\frac{M_t}{M_\infty} = 1 - \frac{32}{\pi^2}\sum_{n=1}^{\infty}\frac{1}{(q_n)^2}\exp\left(\frac{q_n^2}{R^2}Dt\right).\sum_{p=0}^{\infty}\frac{1}{(2p+1)^2}\exp\left(\frac{(2p+1)^2\pi^2}{H^2}Dt\right).$ Early time approximation $\frac{M_t}{M_\infty} = 4\left(\frac{Dt}{\pi R^2}\right)^{1/2} - \frac{Dt}{R^2}$ Late time approximation $\frac{M_t}{M_\infty} = 1 - \frac{4}{(\pi)^2}\exp\left(-\frac{(\pi)^2Dt}{R^2}\right)$	(39,40,41)
	Sphere		$\frac{M_t}{M_\infty} = 1 - \frac{6}{\pi^2}\sum_{n=1}^{\infty}\frac{\exp\left[-Dn^2\pi^2t/R^2\right]}{n^2}$ Early time approximation $\frac{M_t}{M_\infty} = 6\left(\frac{Dt}{\pi R^2}\right)^{1/2} - \frac{3Dt}{R^2}$ Late time approximation $\frac{M_t}{M_\infty} = 1 - \frac{6}{(\pi)^2}\exp\left(-\frac{(\pi)^2Dt}{R^2}\right)$	(42,43, 44)
Monolithic dispersions	Slab		$M_t = A\sqrt{Dc_s(2c_0 - c_s)}.t$	(45)
	Cylinder		$\frac{M_t}{M_\infty} + \left(1 - \frac{M_t}{M_\infty}\right)\ln\left[1 - \frac{M_t}{M_\infty}\right] = \frac{4D}{R^2}\frac{c_s}{c_0}.t$	(46)
	Sphere		$\frac{M_t}{M_\infty} - \frac{3}{2}\left[1 - \left(1 - \frac{M_t}{M_\infty}\right)^{2/3}\right] = -\frac{3D}{R^2}\frac{c_s}{c_0}.t$	(47)

so it declines over the release time. It is assumed that the perfect sink condition exists in the surrounding medium (meaning that the surrounding fluid is infinite and the bioactive concentration is negligible[1]). In Table 6, in the case of a very thin membrane, the film approximation was used according to Fick's law of diffusion. Here, we assume K is similar inside and outside of the membrane and independent of the bioactive concentration (Siepmann & Siepmann, 2012). Other equations for cylindrical and spherical geometries are also presented in Table 6. These equations are helpful in predicting the effects of formulation parameters (e.g., thickness of the coating material and system size) and also coating formulation on the release process.

Constant activity sources

It has been mentioned that, if an excessive amount of dissolved bioactive agent is present, in perfect sink condition, the released molecules are replaced with the excess amount rapidly. If it is assumed that the composition and dimension of the coating membrane do not alter during the release process, the concentration gradient of bioactive agents inside the coating is constant and a constant release rate can be considered (i.e., zero-order kinetics). Table 6 shows the related equations that can be used for a thin film (slab), spherical, and cylindrical geometries.

5.2.2 | Matrix systems

In monolithic or matrix systems, the bioactive agent is either uniformly dispersed or dissolved inside a nonbiodegradable polymeric matrix. These types of systems can be classified according to the initial bioactive concentration in dissolved and dispersed matrix systems. There is no rate-limiting shell in such systems, so the release rate is not constant during the process and it declines with time. In a dissolved matrix system, the initial loading of the bioactive agent is less than its solubility inside the matrix ($C_0 < C_s$), whereas this condition is contrariwise in dispersed systems ($C_0 > C_s$). In the field of food applications, such microparticles can be produced by spray chilling or extrusion in which the bioactive agent is dispersed in carbohydrate, fat, or other matrices uniformly. These matrices might be swellable or nonswellable. Diffusion from small voids is the governing release mechanism in such systems. The main types of matrices used in food technology for the purpose of controlled release are microspheres and films. In food packaging technology, films are used to create a physical barrier to preserve the freshness, keep flavor and aroma, and also prevent water loss. Also, it inhibits oxygen transfer and thus retards oxidation reactions. The films can serve as antimicrobial-loaded vehicles too. Microspheres are used to deliver functional components into food.

Monolithic solutions

In the dissolved matrices, the bioactive agent is dissolved uniformly in the matrix. Fick's second law of diffusion is solved for the slab, spherical, and cylindrical geometries in perfect sink condition of monolithic solutions. The fractions of the released bioactive agent M_t/M_∞ at time t for the slab, spherical, and cylindrical geometries are presented in Table 6. There are some simple but precise approximations that can be used in the early and end stages of the release process. These approximations for short and long release times (first and last 60% for slabs and first and last 40% for cylinders and spheres) are also presented in Table 6. These equations are valid for very thin slabs where the release through the slab edges is negligible and for cylinders where the release in the radial direction is dominant and the release through the ends is negligible. In these models, it is assumed that no changes in the physical properties and dimensions take place (no degradation or loss).

Methods such as fluorescence correlation spectroscopy or nuclear magnetic resonance could be applied in order to define the diffusivity. These equations have been successfully applied in the prediction of the diffusion coefficient of entrapped functional proteins in the peptide hydrogel matrix, asthma drug in polyacrylic acid–polyethylene glycol hydrogels, and many other cases (Koutsopoulos, Unsworth, Nagai, & Zhang, 2009; Serra, Domenech, & Peppas, 2006). In the cases of nonhomogenous geometry (e.g., if the system is composed of various materials or layers) or ionic species and moving boundary conditions or when the diffusion is not Fickian, considering a constant diffusion coefficient leads to deviation from actual results (Parmar & Sharma, 2018).

One of the most interesting applications of mathematical modeling in the field of the food industry is the antimicrobial food packaging systems. In recent decades, mathematical modeling and simulations have been utilized by the researchers to develop deterministic migration models based on Fick's laws. The Food and Drug Administration and the European Union in Commission Regulation No. 10/2011 have adopted modeling as supplementary tools for the determination of the exposure of the customer to packaging migrants and helping in making regulations. The coefficient of diffusion and partition coefficient are two important parameters that are commonly used to describe the release of the active agent from food packaging material to food or simulated food conditions. In fact, diffusivity determines the speed of active agent transport in the packaging film and the partition coefficient determines the amount of active agent released from the packaging film to

[1] Mathematical solution for nonsink condition is more complex and the reader should refer to Crank (1979)

food at equilibrium conditions (Chen, Chen, Xu, & Yam, 2019).

Generally, there are some assumptions that are common in almost all release modeling literature related to food packaging systems (Chen et al., 2019): (a) the rate controlling process is the diffusion of the bioactive agent in a polymeric film; (b) the structure of the packaging film does not change during the release process; (c) the bioactive agent would be desorbed from the packaging film promptly into the food product; (d) the initial distribution of the bioactive agent is homogenous in the film; (e) the concentration of the bioactive agent in the food system is zero; (f) there is no concentration gradient of the bioactive in the food system; (g) at a specific temperature, the coefficient of diffusion and the partition coefficient is constant; (h) there is no interaction between the food and the packaging film; and (i) the bioactive compound does not degrade.

An important point during the utilization of such type of modeling for food systems is model validation before accepting it. If the release kinetics does not obey a Fickian diffusion mechanism or some of the assumptions mentioned in the previous paragraph are not violated, the model would not fit the data. An example is biopolymeric films that undergo swelling when they are in contact with food liquids or food simulants. In this case, the bioactive agent will transfer at a faster rate and the Fickian behavior is not observed. In such cases, assumption number 8 is not achieved and interaction occurs between the food and the packaging film, which caused swelling. If this deviation from the Fick's law is small, it could be accepted. Otherwise, the non-Fickian models considering the effect of polymer swelling should be utilized.

Although modeling using Fick's second law of diffusion is helpful in prediction of the release profiles, its application in real food systems is also limited because of the considered assumptions; many studies conducted the release process in food simulants such as ethanol in a stirred medium to fulfill the assumption numbers 3 and 6 that stated that the bioactive agent should be promptly desorbed from the packaging to the food and no concentration gradient should be existed, respectively.

The balance between the kinetics of microbial growth and the release of the antimicrobial bioactive from the packaging material determines the effectiveness of these types of systems and ensures the optimum shelf life of the perishable foods. It should be considered that antimicrobial activity is directly proportional to the diffusion of the antimicrobial material used in the system. So, various mass transport experiments should be done using simulated food media under different conditions in order to assess the accurate performance of the packaging system. In fact, the release rate should be sufficient in order to be equal or higher than the minimum inhabitation concentration of the specific microorganisms presented in the food media. The structure of the polymeric network, packaging film thickness, and the initial dosage and composition of the bioactive agent are the critical controlling factors involving in the transport phenomena. The important challenge in the mass transfer analysis of the packaging systems is the slow rate of these processes; so, accordingly, their experimental determination might be very costly and laborious. Sometimes performing such types of analysis is impractical due to analytical or technical issues or lack of suitable analytical methods. In these cases, mathematical models could be applied as a valuable tool to study the physicochemical processes taking place in the active packaging systems instead of experimental analysis (Cerisuelo et al., 2012).

Rubilar, Cruz, Zuñiga, Khmelinskii, and Vieira (2017) studied the mathematical modeling of controlled release in an antimicrobial food packaging system. They determined mass transfer parameters using different models in order to find out if the active agent from the polymeric packaging matrix is released at a certain rate during a prespecified period required to increase the product's shelf life (Table 7). So, the modeling could be employed to optimize the design of the active package to ensure that the required dosage of bioactive agents is presented in the headspace to prevent the growth of foodborne pathogenic or spoiling microorganisms. In another study, Cerisuelo et al. (2012) used mathematical modeling to describe the controlled release of an antimicrobial bioactive (carvacrol) from an ethylene–vinyl alcohol copolymer (EVOH) coating on a polypropylene (PP) film. The release was studied in a commercial ready-to-eat salad product. The release kinetics of carvacrol within the packaging system was determined in different relative humidities. Then, a novel finite element-based mathematical model was developed to estimate the efficiency of carvacrol release. Chemical Transport of Diluted Species physics interface, which is a part of the Chemical Reaction Engineering module of the COMSOL Multiphysics software, was used for developing and solving the model. A three-dimensional system consisted of four layers including environment, PP, EVOH-29, and package headspace was considered as the modeling geometry (Figure 6). In this system, the environment was considered to be independent of the packaging system, so the concentration of all substances in this layer was assumed to be constant; also, the geometry was considered as a multilayer infinite sheet with only three domains (PP, EVOH-29, and headspace) for the sake of simplicity. This model could describe two interconnected independent variables (carvacrol and water concentrations) at different positions of PP, EVOH-29, and headspace domains in the packaging system at various release times. The experimental and modeling data were compared and it was concluded that

TABLE 7 A brief overview of the recent release studies regarding the mechanistic modeling of diffusion controlled release of food bioactives

Bioactive ingredient	Encapsulation system	Release system type	Modeling procedure	Modeling results	Reference
Cardamom	Alginate–whey protein microcapsules	Nonconstant activity source reservoir	The diffusion coefficient was obtained using the unsteady diffusion equation.	Higher temperature and shear force increased the diffusion coefficient, whereas other investigated factors had no significant effect.	Zandi, Dardmeh, Pirsa, and Almasi, 2017
Caffeine	Cellulose nanofiber films (active food packaging)	Monolithic solutions	The second law of diffusion was used for slab geometry taking both partition coefficient (k) and diffusivity (d) into account in the release mechanism. The initial and boundary conditions were as following: $T = 0, 0 < x < +\mathrm{l}, c = c_0$, $t > 0,\ x = 0,\ \frac{\partial c}{\partial x} = 0$, $t > 0,\ x = +L,\ -D\frac{\partial c}{\partial x} = \frac{V^L}{A^P}\frac{\partial C}{\partial t}$, V^L is the volume of the solution and A^P is the material area. $\frac{M_t}{M_\infty} = 1 - \sum_{n=1}^{\infty}\frac{2\alpha(1+\alpha)}{1+\alpha+\alpha^2 q_n^2}\exp(\frac{q_n^2 D t}{L^2})$, where $\alpha = \frac{V^L}{kV^p}$, where V^p is the volume of the sample films and k is the partition coefficient between the sample and the solution. q_n is the positive root of $\tan q_n = -\alpha q_n$.	The equation was solved using Matlab software. They reported that the mathematical model was valid for caffeine release. The release was not totally diffusion controlled. They successfully designed an active food packaging film based on the modeling and minimum inhibitory concentration experimental results.	Lavoine et al., 2016
Gallic acid	Antimicrobial and antioxidant chitosan packaging films incorporated with carvacrol and grape seed extract	Monolithic solutions	Fick's second law and Equation (37) that is driven from Fick's second law under specific conditions and simplified for short-time release in slab geometry were solved to calculate the effective diffusion coefficient.	They reported that simplification of the Fickian model can successfully fit the experimental data and there was no distinction between the results of the simplified and original model for calculation of the diffusion coefficient.	Rubilar et al., 2017

(Continues)

TABLE 7 (Continued)

Bioactive ingredient	Encapsulation system	Release system type	Modeling procedure	Modeling results	Reference
Limonene	Microcapsules produced based on high methoxyl pectin and soy protein isolate	Monolithic solutions	The unsteady state diffusion equation of monolithic solutions in spherical geometry for early release (Equation 42) was used for calculating the diffusion coefficient of limonene from the encapsulated matrix as a function of time under different shear forces.	The results showed that the diffusion coefficient declined with an increment of microcapsule wall layers leading to a reduction of the limonene release rate.	Ansarifar et al., 2017
Carvacrol	Electrospun poly-(ε-caprolactone) nanofibers	Monolithic solutions	Equation (36) was solved using the solver tool (Microsoft Excel) in order to calculate the coefficient of diffusion. Peleg's (1988) model was also used to determine the equilibrium concentration and the release rate of carvacrol release in different simulants. The Korsmeyer–Peppas model was used to define the controlling mechanism of release.	Peleg's equation determined the slowest and fastest release rate in different food simulants. It was shown that the less polarity of the solvent, the more release of the active agent. A Fickian diffusion, according to the n exponent, takes place in less polar simulants, whereas anomalous transport is observed in aqueous media. The D values calculated using Fick's law were also highly dependent on the polarity of release media.	Tampau, González-Martínez, and Chiralt, 2018
Cinnamaldehyde	Corn starch-based polymeric films as food packaging material	Monolithic solutions	Fick's second law in a food simulant system was evaluated. They divided the diffusion process into short-term ($\frac{M_t}{M_\infty} < 0.6$) and long-term diffusion. Equations regarding slab geometry in Table 6 were used for modeling.	For short-term diffusion, the diffusivity increased with the increment of temperature. For long-term diffusion, diffusivity values declined by 10^5 to 10^6 times in relation to short-term diffusion, and the partition coefficient declined with the increment of temperature.	Ke et al., 2019

(Continues)

TABLE 7 (Continued)

Bioactive ingredient	Encapsulation system	Release system type	Modeling procedure	Modeling results	Reference
Nisin	Composite packaging films made of polyvinyl alcohol–*Alyssum homolocarpum*seed gum	Monolithic solutions	The power law model was used to investigate if the release is Fickian or non-Fickian. The coefficient of diffusion was calculated using Equation (37). Also, the partition coefficient was calculated as the ratio of the released agent in the simulated food model to the released agent in the polymeric film. Weibull model was also used to determine the release kinetics. MATLAB software was utilized for model calculations.	The *n* exponent showed the release was Fickian. The results of Fick's law showed that the coefficient of diffusion increased with nisin concentration due to enhanced hydrophilicity of the composite packaging film. The partition coefficient was <1.0 except in one case that indicated a better affinity of nisin for the polymer than the release solution. The release kinetics was also predicted suitably using the Weibull model.	Marvdashti, Yavarmanesh, and Koocheki, 2019
Zinc	Polylactic acid based nanocomposites	Monolithic solutions	Release kinetics of zinc from the packaging film into food simulants (10%, 20%, and 95% ethanol) was studied. Equation (36) was solved using MATLAB software to calculate the coefficient of zinc diffusion. The power law model was also fitted to the experimental data in order to determine the release mechanism.	Except for two cases, in all of the other conditions a pseudo- Fickian release was observed. The values of the coefficient of diffusion increased with increasing storage temperature. Diffusion in 95% ethanol was also faster than two other simulants. The results of calculating the partition coefficient also showed that the affinity of zinc for the studied polymer was higher than food simulants.	Heydari-Majd et al., 2019
Vanillin	Thermoplastic starch and chitosan nano films	Monolithic solutions	Equations (37) and (38) were solved for early and long-term diffusion in order to investigate the migration of the vanillin from packaging films. The first-order and Korsmeyer–Peppas models were also used to fit the data.	The diffusion process followed the Fick's second law.	Mlalila, Hilonga, Kaale, and Swai, 2020

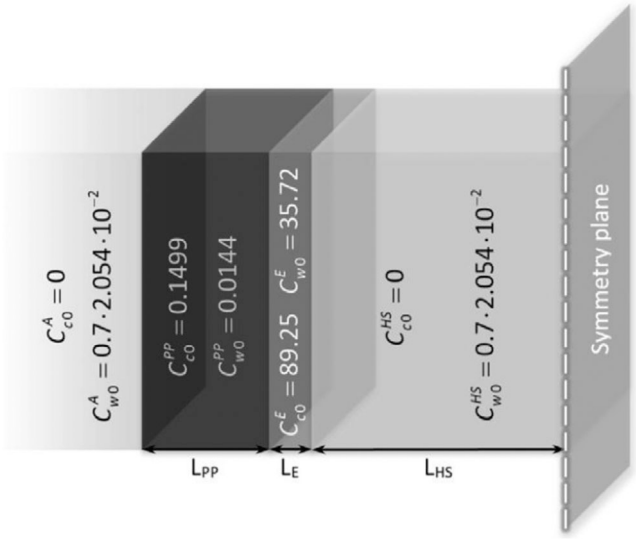


FIGURE 6 Scheme of the simplified system used to model the mass transport processes occurring in an active packaging system, and the corresponding initial concentrations for water and carvacrol in each material layer (kg/m^3); reprinted with permission from Cerisuelo et al. (2012)

the model could be utilized to optimize the active packages in order to maintain a certain concentration of the active agent in the headspace. The same modeling approach was used by these authors to describe the release of carvacrol from an active PP/EVOH/PP package for salmon (Cerisuelo et al., 2013).

Ramos, Beltrán, Peltzer, Valente, and Garrigós (2014) studied the migration process of carvacrol and thymol from active packaging films prepared by PP using the diffusion coefficient. They considered the packaging film and the food to be finite and the migration occurs from the packaging film with a limited volume into a homogenous limited volume of food material. Four different food systems were used to obtain a deep knowledge of antioxidant migration from packaging films. The release was studied during 15 days. Fick's second law was solved to determine the diffusion coefficient of the antioxidant agents. The results showed that the type of antioxidant does not affect the diffusion coefficient because carvacrol and thymol have similar polarity and molecular weights. In the case of different food simulants, the diffusion coefficient of antioxidants in isooctane was four to six times higher than ethanol (100 mL/L), acetic acid, and ethanol (950 mL/L). This might be due to the sorption of this simulant by the PP packaging films and the formation of void spaces that favors the transport of phenolic compounds.

Cozzolino et al. (2013) used the Fick's second law for a slab geometry assuming constant boundary conditions to model release kinetics of lysozyme from cellulose nanofiber films in food simulants as following:

$$\frac{M_t}{M_\infty} = 1 - \frac{8}{\pi^2} \sum_{n=0}^{n=\infty} \frac{1}{(2n+1)^2} \exp\left[-\frac{D_{LYS}}{l^2}(2n+1)^2 \pi^2 t\right], \quad (48)$$

where M_t is the released amount at time t and M_∞ is the released amount at infinite time, D_{LYS} is the apparent diffusion coefficient of lysozyme (cm^2/s), and l is the film thickness. In Equation (48), it was assumed that the release is taking place in an infinite solution, so the partition coefficient was neglected. Lavoine et al. (2016) confirmed that the partition coefficient is very important in describing the release kinetics in real cases such as food packaging, in which the volume of the material in contact is finite. So, they took both the partition coefficient and diffusivity into account to solve the diffusion equation for the packaging system (Table 7). These authors reported that within the food active packaging framework and the experimental condition they studied, the value of the diffusion coefficient was not determining in the selection of the material configuration, and the main parameter was the partition coefficient. The latter determines the amount of released bioactives in the medium. Some other authors also used the same approach for modeling the food packaging systems (Imran, Klouj, Revol-Junelles, & Desobry, 2014; Mascheroni, Guillard, Nalin, Mora, & Piergiovanni, 2010; Otero-Pazos et al., 2014; Torres, Romero, Macan, Guarda, & Galotto, 2014). Applying this strategy can help in the prediction of the antimicrobial agent release in food accurately.

Another application of release modeling in the food industry is the controlled delivery of vitamins, essential oils, and polyphenols in functional foods. In a recent study, Whitehead, Paramita, Teimouri, Young, and Kasapis (2019) investigated the release kinetics of swellable polymeric networks (genipin-crosslinked gelatin) with a moving boundary in order to enhance the prediction of bioavailability and absorption of the active agents (ascorbic acid). Swellable food-based polymer matrices should be modeled under moving boundary conditions to understand the dynamic behavior of polymer swelling and the relationship between diffusion of the food bioactive agent from food. The swelling and diffusion kinetics were studied in order to understand the behavior of this sophisticated delivery system. The classical Higuchi equation was used to model the initial stages of swelling. A linear relationship was observed in the early stages of swelling that indicated a Fickian mechanism, where diffusion is slower than the polymer chain relaxation. In order to estimate the coefficient of water diffusion, Equation (36) was used and it was observed that in higher concentrations of genipin, the values of the coefficient of diffusion were lower. In the latter stages of swelling, Case I Fickian kinetics was not

observed and the power law model could better linearize the data. Quantification of the swelling kinetics was used to discuss the release of ascorbic acid. In release modeling, the perfect sink condition was assumed whereby the bioactive concentration in the surrounding medium is negligible. The stirring of the system also minimizes the effect of resistance to the mass transfer in the boundary layer. As for polymer swelling, the diffusion of ascorbic acid generated two fractional diffusion datasets that were modeled using the power law equation. The n exponent value in early stages was 0.5, which indicates a Fickian diffusion meaning that the polymeric relaxation is not the limiting factor for the release process in the gelatin–genipin matrix. Again, Equation (36) was used to calculate the diffusion coefficient of ascorbic acid. The authors stated that these values were an order of magnitude higher than those of water molecules. These findings prove the diffusion of water is the rate limiting process in the studied system. In the latter stages of the release, the n exponent was <0.5, which indicates the process is becoming less Fickian. The reason might be molecular rearrangements that gradually are bringing the system to thermodynamic equilibrium.

In a recent study, the release of arbutin from inulin/polyvinyl alcohol biomaterial was investigated. The release kinetics were studied in solutions with different pH values and in artificial skin system in order to examine the efficiency of drug release in transdermal delivery systems. Fickian and empirical models were used to study the release mechanism (Equation 36 describing diffusion on a thin slab and the empirical Korsmeyer–Peppas model). The results showed that the Fickian model can explain the release properties more adequately than the empirical models in buffer solutions. However, the empirical model determined the release kinetics more satisfactory than the diffusion model in artificial skin system. The n exponent of the Korsmeyer–Peppas model was >0.5, which indicated a non-Fickian mechanism in slab geometry (Kim et al., 2020). Such modeling techniques can be transferred to food active packaging systems.

In some studies, kinetic models considering both Fickian diffusion and Case II transport have been applied. This model is called the linear superimposition model that is occasionally suitable for hydrophilic matrices (Azevedo, Bourbon, Vicente, & Cerqueira, 2014; Pinheiro, Ana, António, & Mafalda, 2013; Rivera, Pinheiro, Bourbon, Cerqueira, & Vicente, 2015).

$$M_t = M_{t,F} + M_{t,R}, \tag{49}$$

where M_t was the overall released bioactive from the polymeric matrix and $M_{t,F}$ and $M_{t,R}$ were related to the Fickian and relaxation processes at time t, respectively. After applying some assumptions and simplification of the original equations, the superimposition model was applied to fit the experimental data at two different pH values (7.4 and 2) as follows:

$$\frac{M_t}{M_\infty} = X\left[1 - \frac{6}{\pi^2}\exp -K_F t)\right] + (1-X)\left[1 - \exp -K_R t\right], \tag{50}$$

where X is the fraction of the compound released by Fickian transport. Bourbon, Cerqueira, and Vicente (2016) used this model to investigate the release kinetics of curcumin and caffeine from lactoferrin–glycomacropeptide nanohydrogels. This model could successfully describe the release mechanism of the nanohydrogels because it was proven that the release mechanism in hydrogels was both Fickian and Case II transport in which the main polymer relaxation is observed. Also, the release was pH dependent.

Monolithic dispersions

Dispersed matrix systems are composed of two regions: the core where the concentration of undissolved solute is C_0 and the dissolved region, in which the dissolved solute exists and diffusion takes place. It should be noted that the mathematical models of this case are only valid when $C_0 > C_s$. In this type of matrix, shrinkage of the core is probable during the release of the bioactive agent; so moving boundary conditions should be considered that increases the complexity of analytical solving for governing equations. Higuchi (1963) solved the mathematical model of dispersed drug system for a planner sheet geometry by Equation (51):

$$M_t = A\sqrt{Dc_s\left(2c_0 - c_s\right).t}, \tag{51}$$

where C_0 is the initial concentration of the bioactive agent and C_s is its solubility.

There are some conditions in which the Higuchi equation is applicable: (a) the initial concentration of bioactive agent should be much higher than its solubility; (b) the perfect sink condition should be maintained; (c) edge effects should be negligible because of the thin thickness of the slab; (d) the releasing material particles should be smaller than the slab thickness; (e) dissolution and swelling could be neglected; and (f) the diffusion coefficient of the bioactive agent in the matrix should be constant. The error in using the Higuchi equation is around 13%, so a modification has been proposed that declines this error to <0.5% (Bunge, 1998):

$$\frac{M_t}{M_\infty} = 2\sqrt{\left(2 - 0.727\frac{c_S}{c_0}\right)\left(\frac{c_S}{c_0}\right)\left(\frac{Dt}{L^2}\right)}. \tag{52}$$

Higuchi equation has been updated for spherical and cylindrical geometries when $c_s/c_0 \ll 1$as it is presented in Table 6.

Charalambopoulou, Kikkinides, Papadokostaki, Stubos, and Papaioannou (2001) modeled the release behavior of a spherical dispersed matrix system. The dispersed solute release was studied from both the single and laminated matrices. Also, the effect of resistance in the boundary layer and the accumulation of solute in the release medium was considered. They focused on the special case of supersaturated monolithic dispersions with a constant effective diffusivity and multilayer matrices with a constant thickness of each layer. Two mathematical models were used to describe the controlled release process, and the first one assumed fast solvent penetration happens. They also assumed that the excess amount of solute exists in the form of finely dispersed molecules that does not change the transport characteristic of the matrix and equilibrium is maintained during the release process in the dissolved solute. In this model, a moving boundary layer was considered, which induced a more complex solution to the problem. The second model was a more general approach that considered the liquid solvent uptake by the polymeric chain and the release of the loaded solute. The results of numerical simulations for both models were indistinguishable and they were in a very good agreement with the experimental data of release rate measured using a model disperse dye in single and laminated matrices.

Some of the recent literatures regarding the mechanistic modeling of diffusion-controlled bioactive release are tabulated in Table 7.

5.3 | Mechanistic modeling based on swelling

Swellable polymers are used to enhance the controlled release of bioactives. In these systems, the diffusivity of the bioactive agent is very low, so it cannot diffuse out of the polymeric matrix. When it comes in contact with water, the water is absorbed into the hydrophilic polymer (e.g., hydroxyl propyl methyl cellulose [HPMC]) and disentangles the matrix (relaxation) causing the concentration to decrease and also cause swelling. This swelling leads to creating a rubbery state in the polymer in which the diffusion and mobility of the bioactive and also its volume increase. The Fickian model does not work properly in this system because the involving phenomena are not just diffusion, but dissolution and matrix disentanglement are also happening. One of the most important swelling-controlled release systems are hydrogels based on HPMC. This system is a hydrophilic three-dimensional structure in a glassy state. When the hydrogel comes in contact with water, HPMC absorbs water and reaches to a glass transient temperature. At this point, the phase transition takes place from glassy to rubbery state, which leads to the continuous release of the bioactive agent.

As it has been mentioned, two important phenomena happen during the contact of water with the polymer. First, water diffusion, and second, polymeric chain relaxation. The rate-limiting process between these two mentioned processes is the slower process. If water diffusion is slow, polymer chain relaxation is rapid and increment in polymer volume is negligible. In the other case, water diffusion is rapid, which leads to enhanced volume and mobility.

Oztop and McCarthy (2011) performed mechanistic modeling of the swelling process in whey protein gels with high moisture content. Fickian diffusion and kinetic models were used to model the mass transfer. They conducted their experiments in cylindrical coordinates and assumed that the diffusivity (D) is constant. Equation (53) was used for modeling:

$$\frac{\partial C}{\partial t} = D\left[\frac{\partial^2 C}{\partial z^2} + \frac{1}{r}\frac{\partial C}{\partial r} + \frac{\partial^2 C}{\partial r^2}\right], \tag{53}$$

where z and r are the axial and radial dimensions, respectively. The initial and boundary conditions for the mass transfer equation were as follows:

$$\text{IC}: \ t = 0;\ C = C_0, \tag{54}$$

$$\text{BC}: \ z = \pm L_0/2; C = C_1, \tag{55}$$

$$\text{BC}: \ r = 0;\ \frac{\partial C}{\partial r} = 0;\ r = R_0;\ C = C_1, \tag{56}$$

where C_0 and C_1 are initial moisture fractions in the sample and surface concentration, respectively. R_0 and L_0 are the radius and the length of the cylinder, respectively. Multiplying the infinite slab and infinite cylinder geometries results in (Y), a dimensionless solution for moisture fraction:

$$Y = Y_{\text{inf}-\text{cyl}}Y_{\text{inf}-\text{slab}} = \frac{C_1 - C}{C_1 - C_0} = \sum_{m=1}\sum_{n=1}\frac{4(-1)^{m+1}}{\lambda_m \beta_n J_1(\beta_n)} J_0\left(\beta_n \frac{r}{R}\right)\cos\left[\frac{\lambda_m z}{\left(\frac{L}{2}\right)}\right]\exp\left[-\left(\frac{{\lambda_m}^2}{\left(\frac{L}{2}\right)^2} + \frac{{\beta_n}^2}{R^2}\right)Dt\right], \tag{57}$$

and roots for the infinite slab are

$$\lambda_m = \frac{(2m-1)\pi}{2}. \tag{58}$$

The roots for an infinite cylinder can be determined by using the Bessel function of the first kind:

$$J_0\ (\beta_n) = 0. \tag{59}$$

Integration of Equation (40) yields average concentration, C_{ave}:

$$\frac{M_t}{M_\infty} = 1 - \frac{C_1 - C_{\text{ave}}}{C_1 - C_0} = 1 - 8\sum_{n=1}^{\infty}\sum_{m=1}^{\infty}\frac{1}{{\lambda_m}^2{\beta_n}^2}\exp\left[-\left(\frac{4{\lambda_m}^2}{(L)^2} + \frac{{\beta_n}^2}{R^2}\right)Dt\right], \tag{60}$$

The n exponent of the Peppas equation could be determined between 0.35 and 0.43 using the values obtained by Equation (57) for the finite cylinder geometry.

Dimension changes take place according to swelling, so the mentioned boundary conditions would change to time-dependent values of $R = f(t)$ and length $L = f(t)$:

$$L = f\,(t)\,, \tag{61}$$

$$\text{BC}:\ z = \pm\, L(t)/2; C = C_1, \tag{62}$$

$$\text{BC}:\ r = 0;\ \frac{\partial C}{\partial r} = 0;\ r = R\,(t)\,;\ C = C_1. \tag{63}$$

The coefficient of diffusion of whey protein hydrogels was successfully predicted using this modeling approach. Also, axial and radial dimensions of gel during the swelling process were determined and it was concluded that mass uptake is totally dependent on the surface area. The results of modeling in this study showed the Fickian diffusion with moving boundaries was the most realistic model describing the release behavior.

5.4 | Mechanistic modeling based on erosion/degradation

Erodible systems are one of the most important classifications of controlled release carriers. In such systems, the encapsulated material erodes and disappears over time. Erosion might happen at the surface or bulk. In surface erosion, surface degradation of the encapsulated material is faster than liquid uptake, so degradation is mainly observed on outer layers. In bulk erosion, degradation happens in the whole system and it is not limited to the outer layers. Mechanistic models that describe the erosion-controlled release are classified into two categories: (a) cellular automata models that assume erosion to be a random process and use Monte Carlo simulations and (b) reaction–diffusion models that assume the erosion as a combination of transport phenomena and chemical reactions and would be solved using deterministic equations (Lao et al., 2011). Cellular automata models are not capable of taking into account the autocatalysis and cannot be used in size-dependent bulk erosion.

Siepmann, Faisant, and Benoit (2002) solved Fickian diffusion analytically for poly(lactic-co-glycolic acid) microspheres in perfect sink condition. They considered a finite mass transfer coefficient at the microsphere surface and also the effective diffusivity to be constant. These authors determined the mass transfer coefficient and effective diffusivity for various particle sizes using curve fitting. The effective diffusivity was strongly proportional to the microsphere size. Solving the Fickian equation with constant effective diffusivity led to deviation from the experimental data. Their results showed that autocatalytic effects should be incorporated into bulk erosion-controlled system modeling.

In another study, a model representing both bulk and surface erosion was developed by Rothstein, Federspiel, and Little (2009). Diffusion equations were combined with pore formation and dissolution equations to determine the bioactive release in the system. The degree of polymer hydration was expressed using Equation (64):

$$\frac{\partial C_{\text{w}}}{\partial t} = \nabla\,(D_{\text{w}}\nabla C_{\text{w}}) - kC_{\text{w}}M_{\text{w}}, \tag{64}$$

where C_{w} is water concentration at time t, D_{w} is water diffusivity within the polymeric matrix, K is the rate constant for degradation, and M_{w} is the molecular weight of the polymer. Equation (65) defines the breakdown of polymer bonds due to hydration. In this equation, it is considered that the diffusion of polymer components before starting the erosion is not important:

$$\frac{\partial M_w}{\partial t} = -kC_wM_w. \tag{65}$$

A second-order equation can model the dissolution of the bioactive agent. The changes in solvent concentration during the release time is considered in this equation as follows:

$$\frac{\partial C_s}{\partial t} = -K_{\text{dis}}C_{\text{Sn}}C_{\text{An}}C_{\text{wn}}, \tag{66}$$

where K_{dis} is the dissolution rate constant, C_{sn} is the normalized solid-phase bioactive concentration in the

polymeric matrix, C_{An} is the difference between the limit of solubility and aqueous agent concentration, and C_{Wn} is the normalized concentration of water. Equation (67) represents the bioactive concentration as a function of time and position:

$$\frac{\partial C_s}{\partial t} = \nabla (D_{eff} \nabla C_A) + K_{dis} C_{Sn} C_{An} C_{wn}. \quad (67)$$

In this equation, D_{eff} is the effective diffusivity that is dependent on polymeric matrix porosity and diffusivity of the bioactive agent through the matrix; D_A ($D_{eff} = D_A \varepsilon$). The cumulative fraction of remaining bioactive agent in the polymeric matrix at time t is calculated using the integration of the normalized bioactive concentration in the matrix over the space:

$$P\ (t) = V^{-1} \int \frac{C_s + C_A}{C_{s0}} dV. \quad (68)$$

So, the fraction of released bioactive during time is

$$R_t = 1 - P_t. \quad (69)$$

The porosity of the polymeric matrix is also calculated by Equation (70):

$$\varepsilon = 1 - \frac{1}{2}\left(\text{erf}\left(\frac{M_w - M_{w,r}}{\sqrt{2\sigma^2}}\right) + 1\right), \quad (70)$$

where, $M_{w,r}$ is the molecular weight of polymer during delivery and σ^2 is the variance (Gopferich & Tessmar, 2002; Kamaly, Yameen, Wu, & Farokhzad, 2016; Shah, Cha, & Pitt, 1992).

6 | CONCLUDING REMARKS

Mathematical modeling of bioactive release from encapsulated materials in food matrices is an emerging topic, especially in the field of active packaging and nutraceutical delivery. There are different types of mathematical modeling including empirical, semiempirical, and mechanistic models. Empirical and semiempirical models are simple and practical but the underlying release mechanisms are not elucidated, whereas the mechanistic models define the mechanisms occurring in the release process. When adequate reliable information is available, using mechanistic models is the best modeling approach. Anyway, the best model for any process is the simplest model that could give detailed information about the release mechanism and highlight the factors influencing it.

Currently, one of the most important shortcomings of mathematical modeling of controlled release is performing the studies on simulated food systems. As real food products are complicated systems, the actual underlying mechanism in real systems is not well defined. The mathematical modeling of release from different food-grade polymers can help selecting suitable carriers with appropriate release rate that could be practical for use in industrial food products.

One of the other critical points in the mathematical release modeling of food components is the breakdown of food structure in different stages. These current models are on the basis of many assumptions that consider food material as an ideal medium (e.g., spherical shapes). So, the development of customized models that requires fewer simplifications and assumptions for prediction of the impact of food matrix microstructure, chemical composition, behavior under different conditions, and structure breakdown should be considered. It could be a new goal in modeling controlled release in the field of food.

Also, information about the underlying release kinetics can aid in reducing the dosage of some bioactive food ingredients (e.g., natural antimicrobials and antioxidants) that may cause an off-odor or off-flavor in food products when used in high amounts. It is predicted that in future researches, the main issue would be the bioavailability of the released bioactive agents (i.e., within the human body) and utilization of novel computational techniques to solve sophisticated release models.

AUTHOR CONTRIBUTIONS

Narjes Malekjani wrote the first draft and compiled the manuscript. Seid Mahdi Jafari designed the framework and contents of the text, finalized the manuscript, and took the responsibility of submissions and publishing stages.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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