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# Release of Encapsulated Bioactive Compounds from Active Packaging/Coating Materials and Its Modeling: A Systematic Review

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**Abstract:** The issue of achieving controlled or targeted release of bioactive compounds with specific functional properties is a complex task that requires addressing several factors, including the type of bioactive, the nature of the delivery system, and the environmental conditions during transportation and storage. This paper deals with extensive reporting for the identification of original articles using Scopus and Google Scholar based on active packaging as a novel packaging technology that controls the release of antimicrobial agents encapsulated into carriers in the food packaging systems. For evidence-based search, the studies were extracted from 2015 to 2020 and screened using the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Following the review and screening of publications, 32 peer-reviewed articles were subjected to systematic analysis. The preliminary search indicated that the encapsulation of bioactives enhances their bioavailability and stability. From a theoretical viewpoint, mathematical models play an important role in understanding and predicting the release behavior of bioactives during transportation and storage, thus facilitating the development of new packaging material by a systematic approach. However, only a few studies could formulate parameters for mathematical models in order to achieve the specific release mechanism regulated for the quality and safety of foods. Therefore, this paper will cover all encapsulation approaches, active packaging, and mathematical modeling in the food industry into structural form and analyze the challenges faced by the complex nature of active packaging in real food systems.

**Keywords:** active packaging; bioactive compounds; controlled release; encapsulation; mathematical modeling

## 1. Introduction

The main characteristics of food items depend on several factors, such as texture, flavor, and major compositions. Nowadays, consumers prefer minimally processed products with advantages such as longer shelf lives, nutritional value, and unique flavors. However, novel encapsulation techniques can help in the stability of bioactive compounds (bioactives) and reduce their reactivity with minimal losses. The encapsulation strategies of bioactives (essential oils, plant extracts, etc.) allow them to be protected against external factors and degradation [1]. Additionally, environmental and ecological safety concerns over non-biodegradable packaging materials have also raised issues that require considering an alternative approach.

Active packaging (AP) is described as a method for food preservation, ensuring quality, safety, and integrity with a longer shelf life of food products. As defined by European Regulation (EC) No. 450 (2009), active packaging comprises packaging systems that interact with the food in such a way as to deliberately incorporate components that would release or absorb substances into or from the packaged food or the environment surrounding the food. AP is the extended version of conventional packaging, considering the high quality of the food items and protection from moisture and oxygen to avoid deterioration [2]. Based on movement, AP has two divisions: non-migratory and migratory AP. In non-migratory AP, the package induces a response without the migration of bioactives into the food. Oxygen absorbers fall into this category, and they are based on the oxidation of ascorbic acid, catechol, or enzymatic catalysis. Some of the examples are self-adhesive materials, sachets, or materials incorporated into the layering of packaging material. On the other hand, migratory AP permits a regulated migration of non-volatile agents or an emission of volatile compounds into the atmosphere surrounding the packaged food [3].

The unique property of AP is obtained from the direct incorporation of certain bioactives, for example, antimicrobial compounds. In a similar way, packaging based on bioactives maintains the intrinsic properties of compounds and focuses on positive interactions between the bioactives and packaging material in an eco-friendly way [3,4]. Bioactives enhance the ability of the coating material to maintain the physicochemical properties of food and increase long-term preservation and transportation. Recently, antimicrobial (AM) packaging has emerged as an active form of AP that enables the food industry to combine the preservative functions of AM compounds with the characteristics of functional foods [5]. The release of compounds from AM materials is based on types of surface materials such as semi-solids or pure solid surfaces, and the release takes place either through direct contact between the AP material and the food using non-migratory AP systems or through indirect contact utilizing volatile AP releasing systems. For example, natural bio-based films use direct contact to release cinnamon essential oils (EOs), and chitosan particles can promote the antimicrobial properties of the packaging material. Some of the other AP films use compounds coated with oxygen-sensitive materials or compounds coated with antioxidative materials or use carriers for packaging materials [6,7].

Encapsulation of bioactives in AP protects or maintains the controlled release of bioactives to uphold the rapid migration that leads to loss of packaging efficiency and microbial inhibition during the storage of food products [8]. It also maintains the nutritional properties and vitamins, flavors, sweeteners, minerals, amino acids, antioxidants, colorants, EOs, enzymes, etc., that are only protected from physical (such as crystallization, precipitation, and evaporation), chemical (oxidation), and abiotic (such as bacteria growth) damage. The preservatives used in traditional synthetic food products are not safe and compromise the nutritional availability of compounds [9]. Most of the marketed items contain synthetic preservatives in food, which could harm human health and hamper the environment.

These problems have accentuated the interest of researchers to find the best bioactives for encapsulation, such as antimicrobial EOs with preservative properties, and reduce the facile spoilage of food during processing and manufacturing [10].

Some of the nanotechnology approaches can be applied for the delivery of bioactives in different food products [4]. The encapsulation of bioactives in food packaging is based on two important release mechanisms: sustained and controlled release based on delivery and the targeted site of action. One of the emerging applications of controlled release is designing an antimicrobial material in which the migration rate is equivalent to the growth of microorganisms for long-term effectiveness. In cases where the concentration of AP material is dependent on the AM agent, the migration rate of the AM agent has to be faster than the rate of microbial growth; otherwise, the antibacterial activity of the packaging material will be lost, leading to contamination [11,12].

The legal status and requirements of nanotechnology in food packaging vary, depending on the country and jurisdiction. In general, the use of nanomaterials in food packaging is subject to regulatory scrutiny due to concerns about their potential impact on human health and the environment. Several countries, including the United States, the European Union, Canada, and Australia, have established regulatory frameworks for the use of nanomaterials in food packaging. These frameworks typically require manufacturers to conduct safety assessments and provide evidence that the nanomaterials used in their products do not pose a risk to human health or the environment. In the United States, for example, the Food and Drug Administration (FDA) has issued guidance on the use of nanotechnology in food and food contact materials, including packaging. Manufacturers are required to provide information on the composition, structure, and properties of nanomaterials used in their products and demonstrate their safety through toxicological and environmental risk assessments. Similarly, the European Union has established regulations that require manufacturers to submit a safety assessment and obtain approval before using nanomaterials in food packaging. The regulations also require the labeling of products containing nanomaterials. Overall, the use of nanotechnology in food packaging is subject to strict regulatory oversight to ensure the safety of consumers and the environment. Manufacturers must comply with these regulations to legally use nanomaterials in their products [13].

A model is based on a mathematical equation with different parameters, such as the kinetics of the release process. Many modeling approaches are used in drug delivery systems and have recently been adopted in the nutraceutical industry due to their wide applicability. Modeling of the release data is performed using three main methods, such as empirical, semi-empirical, and mechanistic modeling [14,15]. The mathematical modeling in the process of encapsulation with bioactives is based on mathematical theories of drug release in pharmaceutical dosage, and the following points must be considered:

(1) The design of novel packaging material with a controlled release mechanism.
(2) For better experimental results in mathematical modeling and in vitro release testing, it is important to predict the release rate and the profile of the nanocarriers or polymers used as encapsulation materials.
(3) In active packaging systems, mathematical modeling helps optimize the release process.
(4) The release rate is affected by the physical attributes of packaging material such as morphology (shape, size, and composition), porosity, thickness, etc.

In this review, we have conducted a systematic review of different encapsulation processes in AP with underlying release mechanisms and the science of mathematical modeling of controlled release to understand the release kinetics designed to modify the data of encapsulated bioactives in packaging systems. In addition, the advantages and limitations of each process are also discussed. Some of the most popular mathematical models are introduced, and the most recent food-related literature from 2015–2020 is discussed in terms of how pharmaceutical principles can be used to design and improve cutting-edge technologies, such as AP and targeted nutraceutical delivery systems, in food products and overcome the challenges of packaging systems for future studies.

## 2. Materials and Methods

### *2.1. Study Evaluation*

The study was adopted with the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement based on the hierarchical methodology for systematic reviews [16]. The literature search was performed using Scopus and Google Scholar databases, and the results were analyzed considering two factors: (a) combining descriptors for subject-based headings on biological-based domains, and (b) combining Boolean precedence (AND, OR, NOT) to meet literature search requirements for a clear and unambiguous search and avoiding all stop words for the search. The documents included titles, abstracts, and keywords using two different sections to narrow down the search. The first one includes [(active AND packaging) OR "bioactive compounds AND release mechanism")] and the second one is [(mathematical modeling AND active packaging) OR "mathematical models AND release mechanism"] "limited to 2015–2020", respectively. Additionally, secondary documents in the Scopus database were considered for the literature analysis. Following this, each section is described in a detailed manner.

The study search of the Scopus database was performed based on the terms [("active packaging") OR ("bioactive compounds release mechanism")]. The study search in Google Scholar was performed based on similar terminologies used for the Scopus database. The data was limited to 2015–2020 and sorted by relevance with 'release of bioactive compounds, active packaging, and mathematical modeling' anywhere in the title and text of the articles. The content includes articles of any type, including review and research articles, and then sorted based on titles and abstracts in the Microsoft Excel database. For further assessments, duplicates were analyzed in the excel file from both Google Scholar and Scopus databases.

### *2.2. Inclusion and Exclusion Criteria*

These criteria include original research articles as well as review literature for understanding the perspectives of different authors and are limited to the publication year from 2015 to 2020. The articles were extracted from the past 6 years, and submitted thoroughly in English, with the mechanism, principles of release among different places, and mechanism of plant probiotic bacteria through their bioactives. The study is limited to "Agricultural and Biological sciences" for nutraceutical-related studies. Most studies included the nutraceutical-based industry for the release of bioactives and its mathematical modeling. The study excluded reports that mentioned the use of AP in the pharmaceutical industry with no review or conference papers.

## 3. Results and Discussion

The search protocol generated 700 articles by combining two main databases. Almost 100 duplicates were eliminated in the Microsoft Excel database when all databases were combined. A total of 300 publications were evaluated based on their title and abstract content, and 252 of them were discarded since they did not meet the inclusion criteria. A total of 48 articles were analyzed. Two articles were classified as additional literature from other sources. A total of 50 papers were finalized for the study (Figure 1).

The literature was analyzed considering inclusion and exclusion criteria based on the search protocol, and the diverse literature can be categorized into five sub-sections. The first one contains the process of encapsulation of bioactives. The second section focuses on understanding the mechanism behind the release of bioactives. The third and fourth sections involve mathematical-based modeling, including mechanistic and empirical. The fifth one attempts to explain the limitations and challenges of the application of release modeling in food AP.

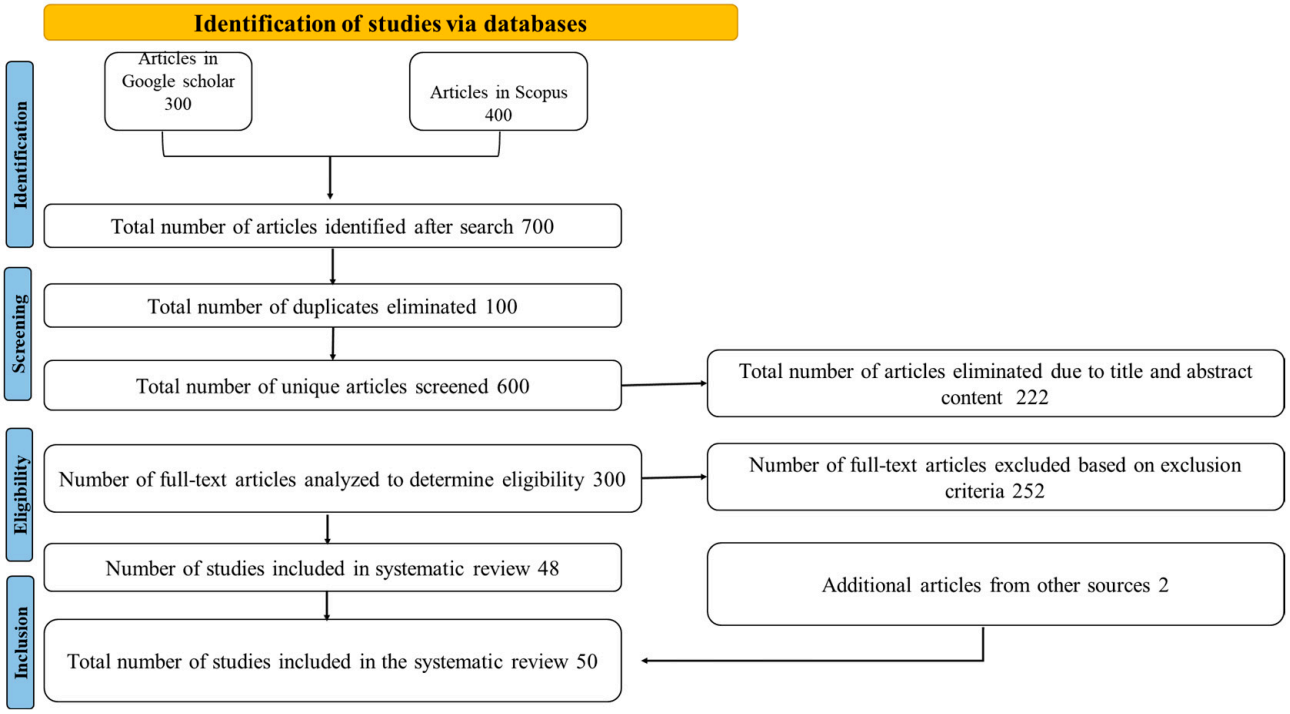


**Figure 1.** PRISMA framework: Flowchart representing the search protocol used for the systematic review [16].

## 4. Encapsulation of Bioactives in Food Coating/Packaging Material

Many substances are used for encapsulating solids, liquids, or gases of different properties. The compounds used for drug encapsulation have not been permitted for the food industry because these are not considered "generally as safe" (GRAS) materials. So, it should meet the FDA protocols for designing an encapsulating material [17]. Encapsulation is an emerging approach due to its versatility, which is dependent upon the entrapment and enhancement of bioactives, and results in the release of their content at controlled rates over an extended period of time in regulated conditions [18]. There is a broad range of carriers developed lately to encapsulate bioactives for protection and preservation in food technology; for example, emulsions serve as carriers for bioactive substances such as flavor, antioxidant, or nutrient and consist of two immiscible liquids; these colloidal systems can be used for the encapsulation of bioactives. There are three types of emulsions [19]:

(1) Oil-in-water emulsions for lipophilic compounds;
(2) Water in oil emulsions for hydrophilic compounds;
(3) Multiple emulsions such as oil-in-water-in-oil (O/W/O) or water-in-oil-in-water (W/O/W).

CDs are other types of carriers from the family of cyclic oligomers of α-D-glucopyranose linked by α-1,4 glycosidic bonds. These natural CDs are obtained from the biotransformation of polysaccharides by certain bacteria, such as *Bacillus macerans*. They are found as truncated conical cylinders with an inner non-polar cavity and a polar outer cavity with encapsulated hydrophobic substances [20]. In the last few years, CDs have evolved as an encapsulation method in antimicrobial packaging incorporated with advanced materials such as electrospun nanofibers. These electrospinning techniques are effective and low-cost, with improved thermal stability and higher solubility of natural compounds such as cinnamon [21].

Liposomes are microscopic vesicles with a spherical shape composed of a phospholipid bilayer with a hydrophilic part facing inwards and a hydrophobic part facing outwards, similar to a micelle. These structures are further engineered for the packaging material for food applications with controlled release. For example, the incorporation of cinnamon

EO-loaded nanoliposomes in gelatin films with a controlled antimicrobial release rate has been reported [22,23].

There are several types of carriers for protecting bioactives from degradation in food packaging to maintain their antioxidant and antibacterial properties [24]. Two major types of encapsulations in which bioactives are encapsulated into other substance particles are known as nanoencapsulation and microencapsulation, respectively. Nanocapsules, or nanofibers, are tiny carriers composed of structures with bioactives located at the core with polymeric walls [4]. The delivery of bioactive compounds of a particular size becomes more efficient via nanocapsules that enhance the prolonged bioavailability and improve the release rate with a precise targeting system [25]. The polymers in nanocarriers are obtained from biopolymers such as starch, cellulose, cellulose acetate, chitin, chitosan, and proteins (gelatin, zein, and silk) [26], or bio-engineered polymers such as polyhydroxyalkanoates (PHA), polyglutamic acids obtained from microorganisms and plants [27].

Most of the nanocarrier food systems use chitosan, which is derived from the deacetylation of chitin, due to its abundance after cellulose and exceptional compatibility and degradability with biomolecules. It has a long shelf life as a coating and packaging material. It is also environment-friendly and obtained from sustainable sources for future use [28]. One example is chitosan films incorporated with polyphenols obtained from strawberry extract, which had antimicrobial activity against food-borne microorganisms [29]. Most of the time, the in vitro experiments showed positive results with antimicrobial potential; however, the application on an industrial scale is still a challenge since bioactives such as EOs have limitations of low solubility, low thermal stability, and organoleptic taste [30,31]. In recent years, there have been extensive studies, and some examples of encapsulation are listed in Table 1.

**Table 1.** Selected studies on the encapsulation of bioactive compounds in the last 5 years.

| Type of Bioactive Compounds | Encapsulation Materials | Encapsulation Method | Encapsulation Conditions/Parameters | Key Findings | References |
|---|---|---|---|---|---|
| Thymol and carvacrol (antimicrobials) | Maltodextrin and soy protein matrices | Microencapsulation | Microcapsules were prepared by O/W emulsions at different concentrations (10, 20% for MD and 2, 5% for SP) | Microencapsulation of AM agents (thymol and carvacrol) can be used in packaging materials | [32] |
| Carvacrol | Commercial biodegradable polymeric foams | Disc diffusion | Morphological analysis, mechanical tests, and measurements of CRV release kinetics in food samples | Carvacrol concentration promotes antibacterial activity in food items | [33] |
| Green tea polyphenols (GTP) | Casein nanoparticles | Spray drying | EE = 76.9% at 5 mg/mL GTP concentration | GTP nanoparticles are best for the prolonged release of bioactives | [34] |
| Hesperetin (HSP) | Basil seed mucilage (BSM)-polyvinyl alcohol (PVA) nanofibres | Electrospinning | EE and physicochemical properties were assessed | HSP and BSM have high EE and physical stability as packaging materials | [35] |
| Limonene | Microcapsule with methoxy pectin and soy protein isolate (SPI) fibrils | Layer adsorption | Size, uniformity, zeta potential, morphology, functional groups, modeling, and release kinetics were considered | Limonene microcapsules could be used as edible raw materials with vegetable-based protein sources when used as packaging materials | [36] |
| Cardamom | Whey protein concentrate (WPC) with alginate | Emulsification/internal gelation | Storage, stew processing, and simulated mouth situations | Can be used to design agent-based models for flavor release in food packaging | [30] |
| Curcumin | Liposomes coated with chitosan | Ethanol injection | The release rate is faster with temperature increase while chitosan decreases the release rate | Curcumin is protected from damage and leaks in food packaging | [23] |
| Curcumin (CUR) | Zein (zein-CUR) electrospun fibers | Electrospinning | EE is approximately 100%, and the encapsulated CUR still retained its antioxidant capacity | Zein-CUR fibers as antimicrobial applications to inhibit bacterial growth and propagation in food AP | [37] |
| Curcumin | Cress seed mucilage and sodium caseinate microparticles | Spray and freeze-drying methods | EE, load, and morphology, FTIR and release kinetics | These carriers had a high potential for encapsulation and controlled release of hydrophobic food bioactives | [38] |

**Table 1.** *Cont.*

| Type of Bioactive Compounds | Encapsulation Materials | Encapsulation Method | Encapsulation Conditions/Parameters | Key Findings | References |
|---|---|---|---|---|---|
| Hesperetin | Basil seed mucilage (BSM)/PVA nanofibers | Electrospinning | EE = 96, 93, and 89%, and loading capacity values of 10, 14, and 18% were obtained for 10, 15, and 20% (*w*/*w*) HSP-loaded nanofibers | Encapsulation of bioactives in the food industry | [35] |
| Pantothenic acid ($B_3$) | Liposomes and alginate or alginate-pectin microparticles loaded with liposomes | Proliposome | EE = 0.75 was achieved, and for alginate microparticles, 0.60 | $B_3$ release was mainly driven by a diffusion-controlled mechanism in food products | [22] |
| *Mentha longifolia* L. EOs | Balangu seed gum nano-capsules | Electrospinning | EOs emulsions with Balangu seed gum (0.25 and 0.5% *w*/*w*) and various PVA levels (0.5, 1, and 2%) combined with Tween-20 (0.06, 0.08, and 0.1%) were electrosprayed | Nano-capsules were a good choice for fast-flavor release systems | [39] |
| Lavender oil (LO) | Different mixtures of coating materials (GA, sodium caseinate [SC], gelatin [GE], CS, β cyclodextrin [β-CD], and PVA) | Spray drying | Encapsulating efficiency (EE), loading capacity, mean particle size, and morphology | Proper encapsulating coating materials can help in the controlled release of LO microcapsules | [40] |
| Ethylvanillin | Ethylcellulose | Electro-hydrodynamic process | Particle size varied between 45 and 85 nm, and polydispersity index (PDI) was between 16 and 34%, loading capacity 67 and 81%, and EE between 71 and 84% | Modified nanoparticles for the encapsulation and controlled release of specific bioactives to engineer the functional characteristics of food products | [41] |

Natural polysaccharides are sugar units linked with glycosidic bonds with antimicrobial and immunological properties, and the mechanism works by damaging the cell wall by inhibiting biological functions. The polysaccharides are obtained from plants (gums or cellulose), algae (agar or alginate), animals (chitin or hyaluronic acid), bacteria (dextran or xanthan), or fungi (yeast glucans) [42]. For example, gelatin and chitosan were used to prepare antibacterial nanofiber films to maintain food quality and shelf life [43]. EOs are also used to produce active films or coatings to improve the quality of food for long-term preservation. EOs obtained from clove (*Syzygium aromaticum*), peppermint (*Origanum vulgare*), tea tree (*Malaleuca alternifolia*), cinnamon (*Cinnamomum zeylanicum*), lemongrass (*Cymbopogon citratus*), and many others are used in foods and pharmaceuticals industries for their solubility, bioactivity, fragrance masking, and to improve the taste. Interestingly, they can be used with biopolymers to entrap the functional properties of EOs, and advantageously, these food-grade biopolymers are safer, compatible, environment-friendly, and biodegradable with antioxidant properties and are non-reactogenic [8,24].

## 5. Mechanism Underlying the Release of Bioactives

Based on the encapsulation methods discussed, mathematical models are used to formulate the possible release mechanisms of bioactives from packaging materials. The requirement for the release profile exists in knowing the most accurate and precise process of the release mechanism and being quantitatively able to predict release kinetics. This section deals with the different mechanisms resulting in the release of bioactives into the membranes of food items, considering prolonged and immediate release processes.

### *5.1. Release Mechanisms from Different Packaging Materials*

To design AP material for long-term preservation and efficient digestion, it is crucial to understand the release mechanism of encapsulated bioactives, which is controlled by the chemical composition and characteristics of the carrier wall and the quality of the material used to make bioactives (Figure 2). Apart from that, physical properties, for instance size, shape, and morphological characteristics of the carriers, should be considered very carefully [19,44,45]. Additionally, the atmosphere, such as relative humidity and temperatures, has a significant influence on the design of packaging materials such as triggered release systems where the moisture content of AP films is regulated. Thus, it is important to customize and optimize the properties of packaging material for the desired and extended shelf life of the food and to control microbial growth [5,46].

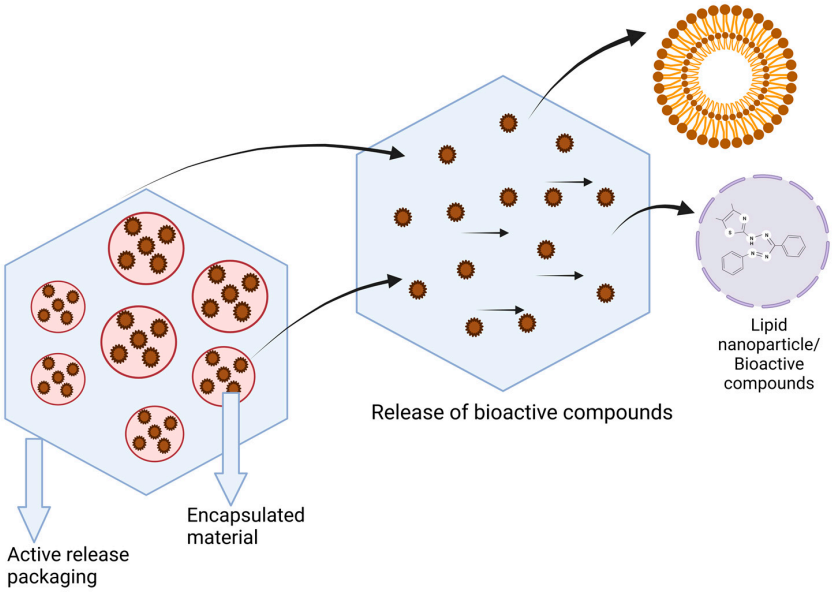


**Figure 2.** Illustration of the release of bioactive compounds from active packaging material (BioRender.com).

### *5.2. Controlled Release*

The controlled release strategy is recently being applied in food delivery systems and is considered a characteristic that assists the release mechanism of the encapsulated bioactives to the target site while maintaining the biological and functional characteristics. Additionally, it works on the mechanism of a pre-designed release rate in the defined time intervals. In delivery systems, the release of compounds at the site often results in the accumulation of bioactives, resulting in side effects and insufficient delivery of bioactives. On a contrary, with the help of a controlled release mechanism, this problem is resolved with targeted delivery, food protection from source to sink with encapsulation, and transferring bioactives, controlling to the targeted site [12]. This strategy is used to maintain the functional properties of bioactives in the nutraceutical delivery and preservation process. The food ingredients, such as flavorings, sweeteners, enzymes, antimicrobial compounds (antibacterial and antioxidant), and food preservatives are sensitive to moisture, heat, infection with microbes, or any other issues while packaging [47,48]. For better action, bioactives can be encapsulated using carbohydrates, gums, lipids, or proteins with prespecified delivery behavior and a regulated release time and site of action [49].

The most popular application of controlled release is to design antimicrobial food packaging in the form of AP, which was discussed earlier [6,12]. On the contrary, the real challenge is balancing the migration rate of bioactives and microbial growth. The release mechanisms are divided into two processes: the first is a delayed release, which helps to protect bioactives from degradation, such as probiotic bacteria in the human gastrointestinal tract, and delivers them to the site of action in the colon. The second mechanism is sustained release, which is mostly used in food products when there is a need to maintain the release rate, such as aroma, flavor, antioxidant, or antimicrobial compounds. However, the limitations are thermal and acidic processes, which could decrease the bioactivity of additives and ingredients compared to chemical additives [50]. The sensorial and toxicological issues are observed due to very high or very low concentrations of bioactives in the delivery system [51].

The mechanisms of controlled release are dependent upon the following factors [14]:

- Types of bioactives;
- Dose of bioactives;
- Conditions for the release of media;
- Geometry and size of bioactives.

There are a few known release mechanisms based on different phases such as dissolution, diffusion, swelling, and erosion that are explained and tabulated below, and can be applied to packaging materials as well. These mechanisms are very important in understanding the release kinetics of encapsulated material in AP systems (Figure 3). The first mechanism of dissolution is defined as a process when two phases are mixed together to form a new phase in such a way that two different solutes are dissolved to form a new solvent [52–54]. In the case of encapsulated material, bioactives are dissolved in the release media. The theory behind this process is that the ions or molecules of bioactives are transferred to the surrounding environment [45,55]. The second is diffusion, which is defined as the total transport of molecules from a higher concentration to a lower concentration field. The driving force for diffusion is the spatial concentration gradient of the existing species. Fick's first and second laws of diffusion proposed equations based on mass transfer phenomena [15,56].

The third mechanism is swelling, the phenomenon in which hydrophilic molecules interact with water molecules and together form a macromolecule. The dissolution of the polymer occurs during swelling and might be affected by pH, the temperature of nutrients, and the composition of the compounds. Biodegradable delivery systems are highly recommended in the pharmaceutical and nutraceutical industries, and the swelling mechanism is particularly used for therapy involving injections for retrieval after the medication has completely been released. The controlled release enables targeted distribution and will treat toxicity-related problems in the damage [14]. The fourth is erosion, which

is responsible for the passive function of polymers that show erosion behavior in active packaging delivery systems controlled by the surroundings. The erosion process is divided into surface heterogeneous, homogeneous, or bulk. These erosion processes are dependent on the rate of polymeric matrices and invasion by a water molecule. Surface erosion occurs when the release rate of system hydrolysis is higher than the invasion by a water molecule in the polymeric systems. In other cases of the erosion rate of the system, hydrolysis is lower than the water invasion [57]. Table 2 defines the release mechanisms of different bioactives along with the factors affecting the whole process of encapsulation.

**Table 2.** Release mechanisms of bioactives from encapsulated materials.

| Encapsulation System | Release Mechanisms | Factors Influencing the Releases | Key Findings | References |
|---|---|---|---|---|
| Cardamom-coated alginate-whey protein | First-order and Korsmeyer-Peppas models indicate Fickian diffusion | Release media temperature, pH, and shear force | An agent-based model for flavor release could be easily designed | [30] |
| Limonene-coated SPI fibrils and high methoxyl pectin | Rigter-Peppas model indicates non-Fickian diffusion | Size, uniformity, zeta potential, morphology, functional groups, modeling, and the release kinetics | Encapsulation method can be used for vegetarians since the material is plant-based | [36] |
| Curcumin coated liposome | Non-Fickian diffusion | Temperature and fluidity | Curcumin release was controlled by both diffusion and dissolution | [23] |
| Grape seed polyphenols coated liposomes | Diffusion-based release mechanism | Total phenolic content | The release rate of uncoated liposomes was higher than that of coated ones | [58] |
| Strawberry polyphenols coated chitosan | Diffusion-controlled non-Fickian | pH, particle size | pH 1.4–7.4 is perfect for the application of controlled release, either orally or externally on the skin | [29] |
| Curcumin-coated zein fibers | Fickian diffusion | morphology and size | Zein-CUR fibers were a promising material for antimicrobial applications to inhibit bacterial growth and propagation in food AP | [37] |
| Green tea polyphenols, coated choline, and cholesterol liposomes | Non-Fickian diffusion and erosion | pH, temperature, and release rate | Radical scavenging activity is observed | [34] |
| Curcumin-loaded pluronics, modifiedliposomes | Non-Fickian diffusion | pH, thermal stability, particle size, and PDI | Pluronics modification could improve absorption in the GIT tract | [59] |
| Quercetin coated microcapsules | Non-Fickian diffusion | Size and stability | Possess antioxidant functions | [60] |
| Curcumin-coated cress seed mucilage | Fickian diffusion | pH, morphology, release kinetics | Potential for the controlled release of hydrophobic food bioactives | [38] |
| Hesperetin-coated basil seed mucilage-PVA nanofibers | Fickian diffusion | EE and physical stability | Best carrier for encapsulation | [35] |
| Vitamin $B_{12}$ coated chitosan microcapsules | Diffusion controlled mechanism | pH, temperature, release kinetics | Very stable microcapsule | [61] |
| Pantothenic acid-coated liposomes and hydrogel microcapsule | Diffusion controlled mechanism | pH, temperature, morphology, release kinetics | Production of a pantothenic acid capsules is possible | [22] |
| Coriander oil loaded chitosan/alginate/inulin microcapsules | Chitosan microcapsule-Fickian diffusion<br>Other microcapsules, non-Fickian diffusion | pH, temperature, morphology, moisture, wettability, solubility, flowability, swelling, and release mechanisms | Chitosan, alginate, chitosan/alginate, and chitosan/inulin as wall materials, are resistant to pH and temperature variations | [62] |

**Table 2.** *Cont.*

| Encapsulation System | Release Mechanisms | Factors Influencing the Releases | Key Findings | References |
|---|---|---|---|---|
| Thymol and carvacrol-coated maltodextrin and soy protein | Fickian diffusion | EE, release rate | The release rate is dependent on the encapsulating substance and concentrations | [32] |
| Green tea polyphenol-coated casein nanoparticles | Fickian diffusion | pH, temperature, morphology, release kinetics | Ideal for a sustained release system | [63] |
| *Origanum vulgare* and *Thymus vulgaris* oil-coated zein nanocapsules | Fickian diffusion | - | The nanoprecipitation method was effective for slow release without bursting | [64] |
| Beta-carotene coated citric acid and banana starch nanoparticles | Fickian diffusion | - | Nanoparticles with cross-linkage showed sustained release | [65] |

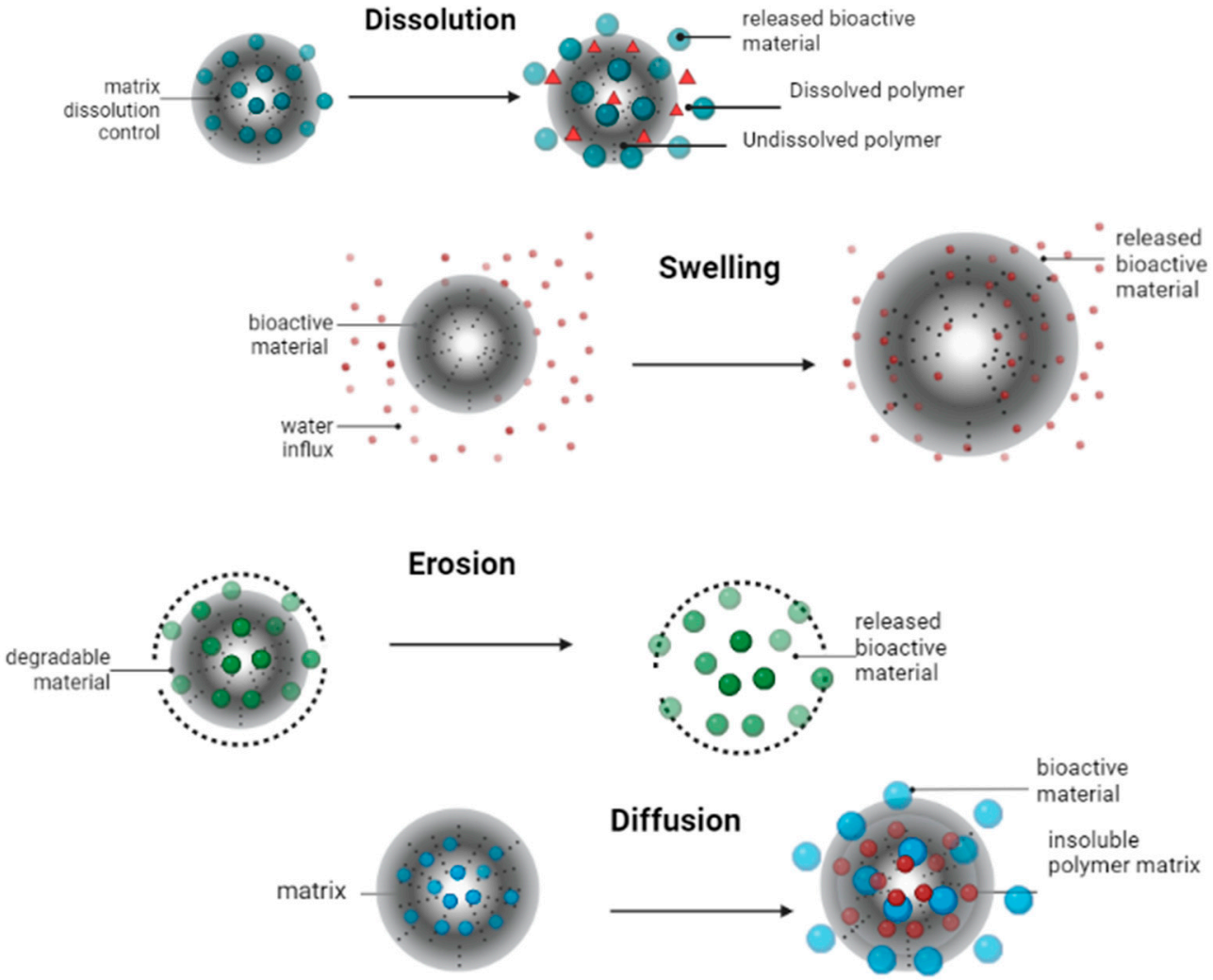


**Figure 3.** Schematic release mechanism of bioactives from packaging material [15,66].

## 6. Empirical Release Models

Empirical models (Table 3) can be helpful in providing advice in industries or taking precautionary measures to regulate the release of bioactives, but they cannot be used in experimental tests due to high variability. For example, the empirical models based on response surface methodology were used to predict the migration of bisphenol (bioactive) in can processing by adjusting variables and the coefficient of determination. In conclusion, they can be used by food industries to control processing in order to ensure the conformity of canned products [67]. However, empirical models do not accurately explain the information behind the detailed mechanism of the compound, which is considered a disadvantage since the modeling is not based on physicochemical or biological phenomena. Additionally, this type of model cannot make better predictions based on dimensions, geometry, formulations, or process conditions in bioactives. In contrast to that, the mathematical analysis in empirical models is more dependent upon two or more release profiles using a predefined release rate constant for the experimental design [14]. According to previous studies, these models can assist in the comparison of different release models and profiles [68].

**Table 3.** Empirical release models.

| Model Type | Kinetics Equations | Variables |
| --- | --- | --- |
| Zero-order Model | $\frac{dM}{dt} = \frac{DS}{l}(C_s - C)$ | $M$ is the mass of solute dissolved during the time $t$, $dM/dt$ is the velocity of mass dissolved (mass/time), $D$ is the diffusion coefficient of the solute in solution, $S$ is the solute area exposed, $l$ is the thickness of the diffusion layer, $C_s$ is the solid solubility, and $C$ is the solute concentration in the solution on time $t$ |
| First-order Model | $\frac{dC}{dt} = -KC$ | $C$ is the concentration in the drug molecule, and $k$ is the first-order release constant |
| Higuchi Model | $Q = \sqrt{D(2C - C_s)}C_s t$ | $Q$ is the amount of drug released on time $t$ by area unit, $C$ is the initial amount of drug contained in dosage form, $C_s$ is the solubility of bioactives in the matrix medium, and $D$ is the diffusion coefficient in matrix medium |
| Korsmeyer-Peppas Model | $F = (M_t/M) = K_m t^n$ | $F$ is the fraction of drug releases at time $t$, $M_t$ is the amount of drug releases at time $t$, $M$ is total amount of the drug in dosage form, $K_m$ is the kinetic constant, $n$ is the diffusion or release exponent, and $t$ is time in hours |
| Hixson-Crowell Model | $\sqrt[3]{W_0} = \sqrt[3]{W_i} + K_{HC}t$ | $W_0$ is the initial amount of the drug in the system, $W_i$ is the amount remaining in the system on time $t$, and $K_{HC}$ is the constant of incorporation, which relates surface and volume |
| Weibull Model | $m = 1 - exp\left[\frac{-(t-T_i)b}{a}\right]$ | The drug fraction accumulated ($m$) in the solution at time $t$, and the scale parameter ($a$) defines the timescale of the process. The localization parameter ($Ti$) represents the latency time of the release process, often being zero |
| Hopfenberg Model | $\frac{M_1}{M_\infty} = 1 - \left[1 - \frac{k_0 t}{C_0 a_0}\right]\log n$ | $\frac{M_1}{M_\infty}$ is the fraction of the drug dissolved, $k_0$ is the erosion grade constant, $C_0$ is the initial concentration of drug in the matrix, and $a_0$ is the initial radius of the sphere or cylinder, or a half part of the thickness of the film |
| Baker-Lonsdale Model | $f_t = \frac{3}{2}\left[1 - \left(1 + \frac{M_1}{M_\infty}\right)^{2/3}\right] - \frac{M_t}{M_\infty}$ | $M_t$ is the amount of the drug released at the time $t$, and $M_\infty$ is the amount released at the infinite time |

In order to design an AP material, four critical aspects must be carefully considered in the mathematical modeling of controlled release [49].

(a) There should be a balance between the simplicity of models and computational efforts for better prediction results and an understanding of the control mechanisms.
(b) There must be comparative studies between theoretical and experimental data. In the first case, optimization of model parameters is performed to obtain the minimum difference between theoretical and experimental data. Thus, despite the model possibly not being efficient, it would frequently result in a good fit between experiment and theory. In this instance, not just one step in the process but the entire release profile should be described. In the second case, which defines the applicability of the concept as designed. Multiple sets of experimental data would be used to identify system-specific characteristics, and then the impact of various conditions on release kinetics would be assessed [15,69,70].
(c) None of the mathematical models can be utilized for all types of systems.
(d) Finally, despite strong correlations between diverse experimental and theoretical findings, some experimental evidence does not always coincide with model results [55].

## 7. Mechanistic Release Models

Mathematical relationships are used in the mechanistic modeling technique to define the interactions of the most significant phenomena occurring in the system. This component has been utilized in AP to deal with a theoretical or foundational understanding of the variables and the interactions between them. This type of modeling summarizes the link between a number of system characteristics and variables. This method is typically complex since the theoretical equations (such as the geometry, starting, and boundary conditions) need to be generalized before being represented as an approximation of system

dynamics. Mechanistic models are similar to theoretical modeling. This type of modeling is extensively used in different fields of medicine, biology, engineering, and many other branches of science [71]. Mechanistic modeling is based on the conservation laws of mass and energy that follow partial differential equations (PDEs). The solution of these PDEs is either numerical or analytical, based on the complexity of the system. Studies that use multiresponse kinetics modeling are dependent upon the mechanistic approach for packaging systems to quantify the release rate and rate of degradation, such as the ground mustard seeds used to describe the ally isothiocyanates (AITC) formation from enzymatic sinigrin hydrolysis. Based on release rates, there are simpler sets of equations to understand system-specific parameters to manipulate the design of packaging material [46].

The optimization m is either explicit or implicit. In the explicit method, the release rate, or the amount of released bioactives, is differentiated from other parameters and variables on one side of the equation, and the impact of processing parameters can be defined. While in the implicit method, the amount of released bioactives cannot be differentiated from the other parameters and variables, and the impact is seldom observed. Numerical modeling is performed instead when the equations are sophisticated, and advanced computer programs are very useful for applying and solving the numerical methods [49].

There are two types: deterministic and stochastic. In the first type, the mathematical equations are solved and definite predictions are made, while no randomness is observed. While stochastic modeling is dependent on mathematical equations considering some randomness in the target variable [71].

The drawbacks include high-throughput computational expertise, being time-consuming and expensive, and having quality and accuracy depend upon the target of the modeling. The determination of the model complexity based on rate-limiting processes in the system is an important factor.

### *7.1. Mass Transport and Parameters*

In the case of mass transport, the coefficient of diffusion varies with time and the concentration of the solute, and Fick's law of diffusion gets modified to

$$\frac{\partial c}{\partial t} = -D\frac{\partial^2 c}{\partial x^2} \quad (1)$$

The equations could be solved analytically when the initial and boundary conditions are specified. There are three main categories for boundary conditions:

| | | | |
|---|---|---|---|
| First condition | Perfect sink condition | $C_s$ = K $C_b$ | Concentration on the surface of the release system ($C_s$) is constant as a function of bioactive concentration in the surrounding environment ($C_b$) with the partition coefficient between two concentrations (K) |
| Second condition | Perfect sink condition with limited mass transfer resistance at the surface of the system | $\left(-D\left(\frac{\partial c}{\partial r}\right)_{r=R} = h(C\vert_{r=R} - KC_b)\right)$ | In this system, surface concentration is defined using the convective mass transfer coefficient ($h$), and the bioactive concentration in the surrounding medium is constant |
| Third condition | The volume of the surrounding medium is limited | | Mass transfer resistance at the surface is either limited or not limited |

### *7.2. Systems of Mechanistic Models*

A reservoir and/or matrix consists of a polymeric shell surrounding the bioactive core, while the matrix has the bioactives dissolved or dispersed in a polymeric matrix [15]. One of the most significant uses of release modeling in the field of food science is the modeling

of the release of bioactives. Food surface erosion caused by the mechanical action of the stomach and diffusive mass transit from food to GIT fluids are two important phenomena that control the release of bioactives. As a result of a concentration gradient, liquids (acids and enzymes) diffuse from the GIT fluid to the food, while food solutes (vitamins, fibers, oils, minerals, etc.) diffuse to the GIT medium. It is important to note that numerous prior investigations in the field of food science have shown that Fick's second rule of diffusion may be used as a theoretical foundation to simulate the diffusion of GIT juice into various food systems [72]. The reservoir system limits the mass transfer rate as the core material is either dispersed or dissolved in a reservoir that is coated with an inert membrane. Some of the common examples of reservoir systems in food applications are bakery leavening agents and microemulsion systems produced to enhance the solubility of lipophilic nutraceuticals. It might have a constant or non-constant activity source [55]. The bioactives are either evenly spread or dissolved inside the non-biodegradable polymeric matrix in matrix systems. Consideration of a constant diffusion coefficient causes findings to deviate from those expected in situations including non-homogeneous geometry, the presence of shifting boundary conditions, the presence of several materials in the system, or non-Fickian diffusion [57]. The advantages/disadvantages of the mechanistic release models in AP systems are described in Table 4.

**Table 4.** Advantages and disadvantages of the mechanistic models applied in food packaging systems.

| Mechanistic Models | Advantage | Disadvantage |
|---|---|---|
| Reservoir system | Widely used in lipophilic nutraceuticals | Not suitable for all types of bioactives |
| Matrix system | Used in antimicrobial food packaging systems | No concentration gradient of bioactives is observed in the food systems |
| Swelling based | Widely used for hydrogels | The Fickian model does not work for this phenomenon |

## 8. Challenges for the Application of Release Modeling in Food Packaging Systems

In food packaging systems, there are a few hypothetical conditions that are considered while applying the release modeling (Figure 4), such as diffusion is the rate-controlling process, the structure of packaging film does not change the release process, desorption of packaging film is spontaneous, homogeneity, zero concentration gradient, no interactions follow, and bioactive materials do not degrade [73]. Therefore, if the release kinetics follow all these conditions, the model would fit with the data. However, there are problems when the model does not follow these conditions., For instance, in a study, the release kinetics of encapsulated black pepper EOs indicates Fickian diffusion as the primary release mechanism, but with low swellability of the EOs and the presence of oil droplets on the surface or outer layer of the capsules [74]. This process changes the structure of the encapsulated material in controlled lab conditions. Although release profiles can easily be determined using Fickian diffusion, the problem is these types of studies do not show promising results in real food systems. Another major challenge is microbial growth since the growth is faster than the release of bioactives in perishable foods. It should be considered that antimicrobial activity is directly proportional to the diffusion rate of material used in the system for better performance of the packaging system. Sometimes performing mass transfer analysis of packaging systems is not possible due to slow procedures, some technical issues, or a lack of accurate analytical methods.

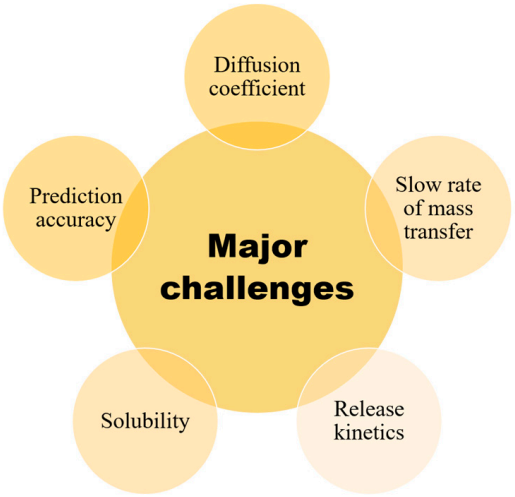


**Figure 4.** Major challenges in packaging systems.

## 9. Conclusions and Future Remarks

Based on the systematic review of the literature, it can be concluded that the release kinetics of bioactive compounds from active packaging and coating materials are complex and can be influenced by encapsulation technique or polymer matrix. In addition, the controlled release of bioactive compounds from active packaging and coating materials can improve the shelf life and safety of food items. Mathematical modeling can be used to predict the release kinetics of bioactive compounds from active packaging and coating materials. Moreover, there are more standardized methods for characterizing and testing the release of bioactive compounds from active packaging and coating materials in order to better compare and evaluate their performance.

This systematic review revealed a lack of real-time modeling techniques used for designing and testing the encapsulated bioactives in packaging systems. The reports indicate that one of the best models is explained as the simplest model that could easily be understood and give detailed information about the release mechanism and factors involved in it. All the models have their own advantages and disadvantages, and different statistical methods are used to find the best model among them. According to this study, one of the most important barriers to mathematical modeling of controlled release is performing studies on simulated food systems in controlled or lab conditions. Since the original food items are complex systems and the actual release mechanisms are way too far from the simulated food systems. The color, odor, texture, and other properties of the original food system are complicated to understand in simulated food systems and make the model less efficient. However, the mathematical modeling of release from different food-grade polymers can help select suitable carriers with appropriate release rates that could be practical for use in AP systems with multiple trials.

Another critical point in the mathematical release modeling of bioactives is the breakdown of food structure into different stages based on shapes. The tested models are mostly based on the parameters that consider an ideal food medium, for example, food structures in spherical shapes. Therefore, there is a dire need for the development of customized models that are less based on simulations and assumptions for testing the apprehensive impact of food matrix microstructure, chemical composition, and behavior under different conditions. Additionally, understanding the underlying release kinetics can definitely assist in reducing the dosage of some bioactives during the release, such as natural antimicrobials or antioxidants that may cause odorless or flavorless food products when used in high amounts. Future research could be based on the issues of the bioavailability and assimilation of the released bioactives within the human body. Another important consideration is the utilization of novel computational techniques to simulate and design the realistic food matrix using precise details from mathematical modeling.

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