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A Review of Encapsulation of Bioactive Peptides with Antimicrobial and Antioxidant Activity

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Abstract: *Encapsulation is referred to as the technology of packaging active ingredients in remarkably small coverages that release their contents at a controlled rate over time. Encapsulation is divided into three categories based on the particle size: nanoencapsulation (particle size less than 1 micron), microencapsulation (particle size between 1 to 1000 microns), and macroencapsulation (particle size higher than 1000 microns). In recent years, the application of this technology has increased significantly in the food and pharmaceutical industries. Peptides are protein derivatives with many biological properties in foods as bioactive compounds because of their amino acids' composition and sequence. Bioactive peptides with antioxidant and antimicrobial activity are among the most critical peptides in the food and nutrition industries. Bioactive peptides are sensitive compounds that, in the case of being exposed to other substances and availability of conditions, are probably to combine with them, leading to reduced biological activity, neutralization, and even toxicity. Different encapsulation methods can be used in connection with this problem. In order to encapsulate bioactive peptides, the properties of the nucleus (peptide) and the encapsulant material must be considered. Several factors must be considered, including the transmission system components' edibility and the no threat to consumer health to design transmission systems in encapsulation. After placing the capsule in certain circumstances, the encapsulated compound can be extracted by diffusion, fragmentation, erosion, and swelling methods.*

Keywords— antioxidant; antimicrobial; bioactive; encapsulation

1. INTRODUCTION

Encapsulation is a technology for placing various materials such as liquids, solids, and gases in a homogeneous or heterogeneous coverage by placing it in continuous base material to protect, stabilize, and slow the release of nuclear compounds down [1]. Microencapsulation technology started in the 1950s and has been extensively developed and applied in industries such as pharmaceuticals, chemical, and food industries [2]. Substances such as oils and fats, odor-forming compounds, oleoresins, vitamins, minerals، and enzymes have been microencapsulated in food products. The beginning of the application of this technology on a commercial scale returns to 1954 [3]. In this technology, capsules can release their contents in a controlled manner. The technology prevents the formation of unpleasant odors and tastes and the loss of nutritional and metabolic value by protecting the material from oxidation during production and storage [4]. Encapsulation is divided into three categories based on the particle size: nanoencapsulation (particle size less than 1 micron), microencapsulation (particle size between 1 to 1000 microns), and macroencapsulation (particle size higher than 1000 microns). The use of different encapsulation methods in the food industry possess its advantages and disadvantages.

The protection of sensitive substances against environmental conditions and prevention of volatility during warehousing, resistance to destructive reactions such as oxidation, dehydration, improvement of process capability (improvement of solubility, flowability, dispersibility), preservation of flavor, the smooth and safe examination of toxic substances, stabilization of enzymes and microorganisms, transferring liquid materials as solids, controlled and targeted release of active compounds, easy application and tissue strength of the product during and after production are some of the advantages of encapsulation method. The disadvantages or challenges facing the use of encapsulation technology in the food industry include the consumer's unfavorable feeling about the presence of capsules in food products, increased cost and complexity of production, instability of capsules in processing, and warehousing of food products [5,6].

In general, an encapsulated compound's structure consists of two main parts, the central core and the wall covering and a sub-part called the emulsifier. The core is any compound or active substance that is encapsulated by a wall. Vitamins, enzymes, antioxidants, food preservatives, flavorings, and probiotics are compounds transported by the encapsulation method. A structural wall is protection against environmental factors that preserves its core content against oxidative damage, light, moisture, and the effects of other compounds or agents. This structure also protects the control of volatile compounds in the proper manner and their release at the right place and time. Waxes and fats (beeswax, Carnauba wax, Glyceryl distearate, natural and modified fats), carbohydrates (starch, maltodextrin, chitosan, sucrose, glucose, ethyl ester, cellulose acetate, alginate, carrageenan), proteins (gelatin, whey protein, zein, soy protein, and gluten), industrial polymers (polypropylene, polyvinyl acetate, polystyrene, polybutadiene) are among the wall constituents. It is noteworthy that carbohydrates are the best choice for microencapsulation applications due to their desirable physicochemical properties such as solubility and melting, different sizes, and low price [7].

possess nutritional values in some cases. Bioactive compounds that include vitamins, minerals, active lipids, probiotics, amino acids, peptides and proteins, phytosterols, and antioxidants play an essential role in society's health and safety due to their proven role in human development and also reducing the risk of disease.

Table 1: Properties of the core, encapsulant material, and microcapsule of importance in the design of encapsulated bioactive [8]

Component	Properties
Core	1. Bioactivity of the material 2. Solubility (hydrophilicity/lipophilicity) 3. Stability to environmental conditions (e.g., moisture, heat, pH, salts, light, enzymes) 4. Taste 5. Propensity to interact with other food components
Encapsulant material	1. Solubility 2. Viscosity 3. Stability to pH, salts, temperature, shear, enzyme 4. degradation 5. Film forming and emulsification properties 6. Regulatory status for food application
Microcapsule	1. Format for delivery (i.e., liquid or powder) 2. Storage stability 3. Stability to different process conditions 4. Release properties 5. Particle size 6. Payload (bioactive core loading) 7. Cost of production

2. ENCAPSULATION OF BIOACTIVE COMPOUNDS

The application of encapsulation techniques has increased significantly in recent years. Bioactive compounds are among the compounds that can be protected by a variety of encapsulation methods. Bioactive food compounds are natural compounds that have biological activity and also

Adding bioactive compounds to foods that are commonly consumed in people's diet in society can improve and strengthen consumers' health [9-11]. For instance, consuming bioactive compounds in fruits and vegetables helps fight heart disease, cancer, obesity, diabetes, and gastrointestinal disorders. The most critical plant-derived bioactive substances with health-giving properties in the diet include glucosinolates, sulfur-containing compounds in the garlic family, terpenoids (carotenoids, monoterpenes, and phytosterols), and various groups of polyphenols (anthocyanins, flavones, isoflavones, ellagic acid, etc.).

Table 2: Selected examples of active ingredients that need to be encapsulated for use in the food industry [15]

Name	Examples	Potential advantages of encapsulation
Flavors	Citrus oils	1. Allow incorporation in an aqueous medium 2. Facilitate storage and utilization 3. Retard chemical degradation 4. Control flavor release profile
Antimicrobials	Essential oils	1. Improve matrix compatibility 2. Facilitate storage and utilization 3. Retard chemical degradation 4. Mask off-flavors 5. Increase potency
Antioxidants	Carotenoids	1. Allow incorporation in an aqueous medium 2. Facilitate storage and utilization 3. Retard chemical degradation 4. Increase the efficacy
Bioactive peptides	Cholecystokinin	1. Retard degradation in the stomach 2. Reduce bitterness and astringency 3. Control release profile and bioactivity
Oligosaccharides and fibers	Chitosan	1. Avoid adverse ingredient interactions 2. Improved product texture 3. Control delivery in GI tract
Minerals	Iron	1. Avoid undesirable oxidative reactions 2. Prevent precipitation 3. Enhance bioavailability 4. Reduce off flavors and astringency
Vitamins	Vitamin D	1. Allow incorporation in an aqueous medium 2. Improve ease of utilization 3. Prevent chemical degradation 4. Increase bioavailability
Bioactive lipids	ω-3 fatty acids	1. Allow incorporation in an aqueous medium 2. Improve ease of utilization 3. Avoid chemical degradation (oxidation) 4. Controlled delivery in GI tract 5. Increase bioavailability
Probiotics	Lactic-acid bacteria	1. Avoid degradation in the stomach 2. Improve cell viability in product

In addition to plants, bioactive compounds are also present in animal sources and microorganisms. The examples include essential fatty acids, glucose amines, chitosan in sea sources, probiotics, and enzymes extracted from some microorganisms. Due to the high value of bioactive compounds and their extensive use and most of the bioactive compounds are prone to spoilage, their preservation seems to be necessary [12-14].

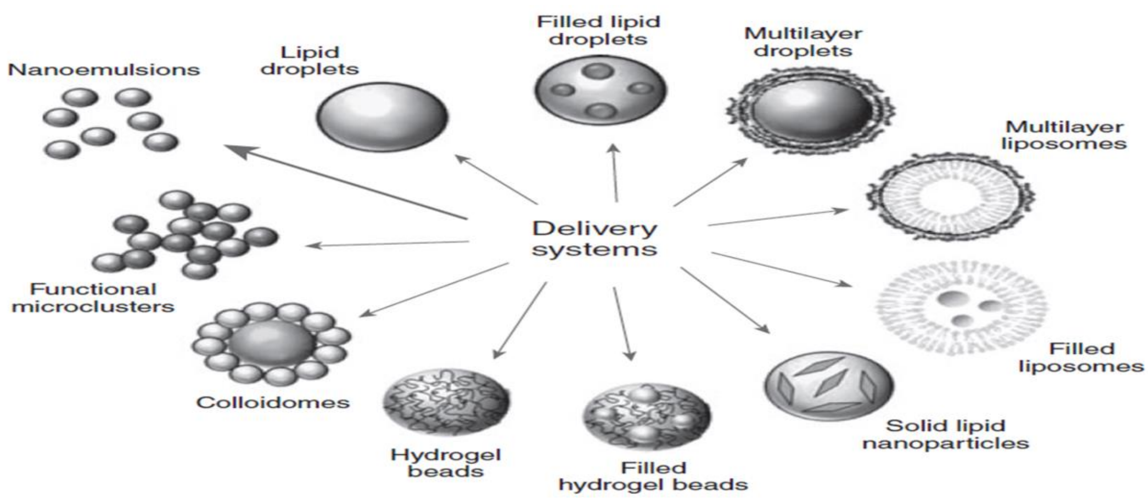
3. BIOACTIVE PEPTIDES

In recent years, a great deal of interest has been attracted to bioactive peptides. Bioactive peptides are defined as peptide sequences within proteins capable of applying beneficial effects on body function and/or positively affect human health beyond their known nutritional value. Bioactive peptides can be prepared by proteolytic hydrolysis or during food processing such as cooking or fermentation. Sequences of different amino acids cause the formation of proteins. The peptide is formed by the breakdown of this sequence through the process of fermentation or proteolytic hydrolysis. Bioactive peptides typically contain 3 to 20 amino acids that the biological activity of these amino acids is determined by the combination and sequence strength of them [16,17]. Preventing damage to these peptides in the gastrointestinal tract is one of the main challenges in consuming these bioactive compounds. Bioactive peptides in the gastrointestinal tract are damaged by proteases and peptidase enzymes and acidic environments [18,19].

Bioactive peptides with antioxidant and antimicrobial activities have received more attention in recent years. Many studies have shown that antioxidants positively affect human health because they can protect the human body against deterioration with free radicals and reactive oxygen species (ROS), including singlet oxygen, hydrogen peroxide, superoxide anion, and hydroxyl radicals. Reactive oxygen species and free radicals attack macromolecules such as DNA, proteins, and lipids and cause many health disorders such as inflammatory diseases, aging, diabetes, cardiovascular diseases, and cancer [20,21]. [21,22]. Therefore, much attention has been paid to bioactive peptides with antioxidant activity to be applied as an alternative to synthetic antioxidants. Antimicrobial activity is another feature of bioactive peptides that have attracted the interest of the food industry. In these peptides, the placement of polar heads of phospholipids on the cell membrane and electric charge distribution in the peptides are vital factors in the peptide reaction with the membrane. In prokaryotic cells (bacterial cells), hydrophilic antimicrobial peptides recognize the anionic lipids on the bacterial membrane's outer surface. In eukaryotic cells, these anionic lipids are placed on the cytoplasmic side of the membrane that this structural feature is the reason for the relatively high cell-killing activity of antimicrobial peptides compared to bacterial cells against eukaryotic cells. Three processes of binding the antimicrobial peptides to the bacterial membrane, their accumulation in the membrane, and the formation of pores for cell perforation and cell death lead to a bacterium's death due to the formation of pores in the bacterial membrane [21, 23-25].

4. DELIVERY SYSTEMES FOR ENCAPSULATED COMPOUNDS

Fig. 1. *Examples of different kinds of delivery systems that can be created from grade ingredients [15]*



Free radicals outside the body also affect foods. Synthetic antioxidants are commonly used to prevent the damaging effects of these radicals in food. Many synthetic antioxidants such as butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), tert-butyl hydroquinone (TBHQ), and propyl gallate (PG) have been employed to delay peroxidation in foods. However, the use of these antioxidants is controversial in terms of toxicity and food safety; as well as the adverse effects of synthetic antioxidants that have toxic effects and subsequently lead to a variety of cancers have been proven, and their usage is being limited in the world

Various substances such as lipids, surfactants, proteins, carbohydrates, minerals, and water can be used to construct delivery systems for the components to be encapsulated. Food grade (transmission system must be entirely composed of food), economic production (production of transmission system must be cost-effective), food matrix compatibility (transmission system should not have any adverse effect on the encapsulated component), protection against chemical degradation (transmission system should protect the encapsulated component from various destructive factors), loading capacity and retention (the transmission system must

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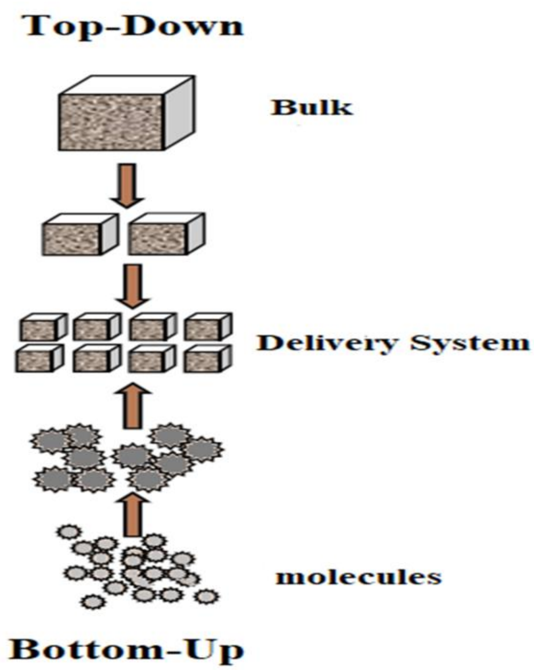
be capable of encapsulating a large amount of the desired component and preserve the encapsulated component for a specified period of time), the delivery mechanism (the transmission system must be able to release the encapsulated component under certain circumstances), and bioavailability (transmission system should lead to the increased bioavailability of the encapsulated component) are the important points to consider when selecting a transmission system [15].

In order to transfer active components, various delivery systems have been designed and tested; however, in practice, only some of them have been employed because of the high cost of using some transmission systems.

Fig. 2. *General view of top-down and Bottom-up approaches(with a few changes from [26])*



5. RELEASE M COMPONE

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their surrounding
mechanisms. In general, four methods can be considered for this release [15].

5.1 Diffusion

The active components can be released from the surrounding matrix by the diffusion method. The rate of release of active components in this technique depends on the size, shape,

The top-down and bottom-up approaches or a combination of both methods are applied to construct transmission systems. In the top-down method, the bulk material breaks into smaller particles to form a transmission system, while in the bottom-up approach, the molecules or colloidal particles convert to particulate structures and form the transmission system [15, 26].

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types: facilitated diffusion and simple diffusion. The facilitated diffusion is the mechanism by which substances are transported to other sides of membranes of living cells through protein transport. One example of simple diffusion is the diffusion mechanism of releasing the active components surrounded by the matrix.

5.2 Fragmentation

The matrix's active components can be released if the matrix is physically damaged and disintegrated by applying shear forces. In these circumstances, the release rate depends on the particle's fracture properties, such as the size and shape of the fragments formed and the applied stress when the fracture occurs. Although diffusion can be effective in this mechanism, the release rate is higher than diffusion, with the matrix disintegrating because of increased surface area and reduced diffusion path [15].

5.3 Erosion

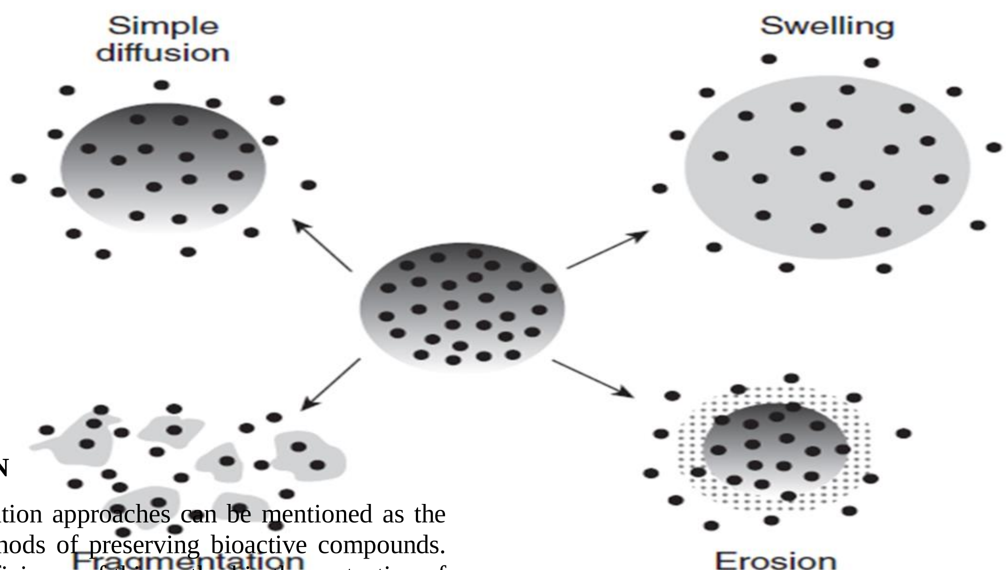
In this mechanism, the active components are released by physical, chemical, or enzymatic degradation by the erosion of the matrix's outer layers.

The release rate also depends on the rate at which erosion occurs that depends on the composition and structure of the matrix's outer layers and the magnitude and duration of the factor responsible for erosion, which includes shear force, acid strength, and enzyme type and concentration [15].

5.4 Swelling

In this mechanism, the matrix releases the active components inside the matrix by absorbing the solvent and swelling. The diffusion is also effective in this mechanism, so that swelling occurs, and the active components are released by diffusion by absorbing solvent molecules by matrix particles [15].

Fig. 3. *A delivery system may release an encapsulated component through various mechanisms [15]*



6. CONCLUSION

Different encapsulation approaches can be mentioned as the most effective methods of preserving bioactive compounds. Despite the high efficiency of this method in the protection of bioactive compounds, these approaches have not been extensively commercialized due to the high cost of the technology. However, there is hope that new advances in encapsulation technology in the future to cause extensive use of this technology in the food industry and cause some changes in people's diets.

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