Chapter 7

β-Cyclodextrins as Encapsulating Agents of Essential Oils

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.73568

Abstract

Many scientific studies have made advances in the ability to encapsulate natural extracts by cyclodextrins. These studies have addressed the physical and chemical conditions of the encapsulation reactions, employed several types of essential oils and characterized the microcapsules as to their ability to release encapsulated active principles. The essential oils studies with cyclodextrin encapsulation processes have been highly varied. However, the most studied are the essential oils with antimicrobial and antioxidant capacities. The essential antimicrobial and antioxidant oils are easily degraded. In the presence of oxygen, they are oxidized, and at low temperatures, they are volatilized and decomposed. Thus, cyclodextrins are coatings capable of protecting these essential oils from environmental conditions and agents capable of promoting oil degradation, in addition to controlling their release. In this chapter of the book, we review scientific papers that examine the encapsulation of antimicrobial essential oils and antioxidant essential oils with β-cyclodextrins.

Keywords: β-cyclodextrin, essential oil, microencapsulation techniques, inclusion complex, protection

1. Introduction

Essential oils are complex and multicomponent mixtures produced from plant secondary metabolites and it can be extracted from different parts of the plants. Its composition depends

on factors such as harvest season, part of the plant where the oil was extracted, geographic origin, and extraction method. They are used in the most diverse areas such as pharmaceuticals, cosmetics, agriculture, food, and textiles, among others.

Essential oils' antimicrobial activity has been extensively studied, succeeding both against Gram-positive bacteria and Gram-negative bacteria, as well against fungi. They also exhibit antiparasitic, antiviral, and antioxidant properties. However, its use is conditioned to processes and/or products that do not undergo thermal processing, as these essential oils are largely volatile, oxidizable, and thermosensitive.

Thus, the encapsulation techniques present themselves as an effective alternative in the protection of essential oils, releasing them at the desired time and place. There are several encapsulation techniques, among which we can highlight spray drying, spray cooling, extrusion, solvent evaporation, coacervation, and the use of supercritical fluids. What differs them from each other are the equipment used and the process conditions, the encapsulation efficiency, the particle size obtained, and the cost.

One of the key factors to be considered in the encapsulation process is the coating material. This determines the particles stability, the efficiency, and the degree of the core protection. Examples of coating materials are synthetic and biodegradable polymers, inorganic materials such as clays and silicates, proteins such as gelatin and casein, polysaccharides, and sugars, with emphasis on cyclodextrins. These are widely used in the industry due to properties such as inertia and toxicity.

The encapsulation process can form macroparticles, microparticles, and nanoparticles, and obtaining them is dependent on the choice of techniques and parameters involved in the process. In general, the compound to be encapsulated is suspended in a solution, and then the coating material is dissolved and precipitated by overlaying the core.

Therefore, encapsulating an essential oil ensures that it maintains its properties of interest while being protected from external factors such as mechanical stress, temperature, and oxidation. In the case of thermal protection, this is an extremely important advantage in which the inclusion complex can be used in processes and/or products that make use of thermal sources.

2. Essential oils

The use of plants in daily life has been a constant throughout all stages of evolution. They have been used as an unlimited source of food for humans and animals, fibers for clothing, and as useful medicines. Among the compounds obtained from vegetal material, the essential oils stand out and deserve particular attention due to their peculiar characteristics [1, 2].

2.1. Definitions

Essential oils are oily aromatic liquid compounds containing complex mixtures of volatile compounds, which are the secondary metabolites of plants and play an important role in their

defense. They are extracted from the vegetal material (flowers, shoots, seeds, leaves, branches, peels, fruits, and roots) of a large number of plants, usually representing only a small fraction of the plant composition (less than 5% of dry material) [2–5].

These bioactive compounds have promising potential to maintain and promote health and to prevent microbial growth, and have been applied in diverse areas, such as in pharmaceuticals, food, textiles, biomedical applications, cosmetics, and agriculture industries. They usually possess low solubility and absorption and are chemically unstable and susceptible to oxidative deterioration and loss of volatile compounds, especially when exposed to oxygen, light, moisture, and heat, resulting in decreased bioavailability and efficacy [6–8].

The essential oil constituents are a family of organic compounds with a low molecular weight, and they can be divided into four groups according to their chemical structures: terpenes, terpenoids, phenylpropenes, and "others." Terpenes are hydrocarbons produced from the combination of several isoprene units (C_5H_8), and they are synthesized in the cytoplasm of vegetal cells. The main representatives of this group are the monoterpenes ($C_{10}H_{16}$) and sesquiterpenes ($C_{15}H_{24}$), but longer chains, such as diterpenes ($C_{20}H_{32}$) and triterpenes ($C_{30}H_{40}$), are also part of this group. Limonene is a classic example of a terpene. Terpenoids are terpenes that undergo biochemical modifications through enzymes that add oxygen molecules and move or remove methyl groups. Terpenoids can be subdivided into alcohols, esters, aldehydes, ketones, ethers, phenols, and epoxides. Examples of terpenoids are thymol, carvacrol, linalool, menthol, and geraniol [4, 9]. Phenylpropenes constitute a subfamily among the various groups of organic compounds called phenylpropanoids that are synthesized in plants from the amino acid precursor phenylalanine. Phenylpropenes constitute a relatively small part of essential oils, and those that have been more carefully studied are eugenol, vanillin, and cinnamaldehyde [4].

The proportion of these constituents is different in each essential oil and is a function of several factors, including the species, the part of the plant from which the oil was extracted, the harvesting season, geographical origin, and the method of extraction. All these factors directly influence the oil composition and, consequently, the bioactive properties, conferring different biological functionalities to them [10–18].

2.2. Antimicrobial activity and mechanism of action

Antimicrobial activity can be considered the most investigated activity of essential oils, especially when associated with food preservation and the consequent increase in shelf life, because these bioactive compounds have the capacity to slow down growth and even eliminate contaminating pathogens from food products. Therefore, essential oils meet the current requirements of more concerned and demanding consumers who prefer to consume food without synthetic preservatives, expanding their application in this segment of the population [19].

In addition, foodborne illness is a growing public health problem throughout the world; only in the United States, 31 species of pathogens are estimated to cause 9.4 million cases of foodborne illness per year [20]. This demands new strategies and more effective control and has

motivated several studies with essential oils. Another characteristic of these compounds is the safety of their use in food. Many essential oils are considered by the Food and Drug Administration (FDA) as Generally Recognized as Safe (GRAS), meaning that they can be used in food products without the need for approval via technical analysis [21].

Some investigations have confirmed the antimicrobial activity of several essential oils. Teixeira et al. [22] studied the antimicrobial activity of 17 different essential oils against 7 different types of bacterial strains. All essential oils inhibited the growth of at least four of the bacteria tested. Pesavento et al. [23] tested the antimicrobial activity of the essential oils of oregano, rosemary, and thymol against *Staphylococcus aureus* and *Listeria monocytogenes* bacteria in meat, verifying that the insertion of essential oil decreased the microbial growth but altered the flavor of the food. Piletti et al. [19] evaluated the antimicrobial activity of eugenol against *Staphylococcus aureus* and *Escherichia coli* bacteria. The authors observed that eugenol has greater inhibitory activity toward *Staphylococcus aureus*, because they are Gram-positive bacteria and, therefore, are more susceptible to essential oils compared with Gram-negative bacteria, such as *Escherichia coli*.

According to studies presented by Affonso et al. [24], clove oil presents pronounced antimicrobial activity when tested against *S. aureus*, *E. coli*, *Campylobacter jejuni*, *Salmonella enteritidis*, and *Listeria monocytogenes*, significantly decreasing the growth rate, because it is effective against Gram-negative and Gram-positive bacteria except for *Pseudomonas aeruginosa*.

Knezevic et al. [25] confirmed the antimicrobial activity of essential oils of *Eucalyptus camaldulensis* against *Acinetobacter baumannii* bacteria, demonstrating the possibility of using this oil together with conventional antibiotics and confirming synergistic interactions between the two compounds in order to develop new strategies for infection treatment and reduce the dose of antibiotics used.

The antimicrobial activity of essential oils is related to their hydrophobicity, a characteristic that favors interaction with the lipids of the cell membranes and with the mitochondria of the microbial cells. These interactions generally alter the permeability of bacterial cells, causing disturbances in the structures and resulting in coarse fractures that cause ion, molecule, and cellular content leakage, leading to microorganism death or inhibition of their growth [3].

In general, essential oils act to inhibit bacterial cell growth and the production of toxic bacterial metabolites. Most essential oils have a more pronounced effect on Gram-positive bacteria than on Gram-negative species, and this effect is likely due to differences in the cell wall composition of these bacteria [9, 26, 27].

According to Muñoz-Bonilla and Fernández-García [28], Gram-positive bacteria have only one outer layer, which facilitates penetration of external molecules, promoting interaction with the cytoplasmic membrane and making them more fragile compared with Gram-negative bacteria. Gram-negative bacteria have an additional membrane with a phospholipid bilayer structure responsible for protection of the inner cytoplasmic membrane, which confers greater resistance to this class of bacteria. The hydrophilic wall hinders the penetration of hydrophobic compounds, for example, essential oils, into the cell [29, 30].

Mechanisms that explain the action of essential oils on bacterial cells have been studied, but it is still not possible to say with certainty how the essential oils act on a microbial cell. These bioactive compounds have many components, and the antimicrobial action cannot be confirmed by the action of only a single component or by the activity on a single cell site [31].

The typical hydrophobic characteristic of essential oils is responsible for the breakdown of bacterial structures, which leads to increased permeability due to the inability of separation between the essential oils and the bacterial cell membrane. This fact alters cellular functions, making it difficult to maintain the energetic state, altering solute transport, promoting cellular component leakage, and deregulating cellular metabolism [9]. Furthermore, because they contain phenolic compounds, the essential oils can disturb the cell membrane and inhibit the cell functional properties and are even capable of spilling cellular materials. The chemical composition of essential oils and/or their volatile compounds has a major impact on their antimicrobial mechanism, because phenolic compounds contain hydroxyl groups, which operate effectively against foodborne pathogenic bacteria [31].

2.3. Miscellaneous properties

Essential oils or their components not only have antibacterial properties [22, 23, 25, 32, 33] but also have antiparasitic [34, 35], antiviral [36, 37], antifungal [38–40], and antioxidant properties [32, 41, 42].

Alves-Silva et al. [43] determined the chemical composition and antimicrobial, antifungal, and antioxidant activities through four different antioxidant tests of three aromatic herb essential oils, coriander (*Coriandrum sativum*), celery (*Apium graveolens*), and bush-basil (*Ocimum minimum*), widely used in Portugal. The results showed that the essential oils of coriander, bush-basil, and celery obtained from plants grown in Portugal have significant antioxidant and antimicrobial activity, and the high antimicrobial activity is due to the high percentage of the main constituents or synergy between the different oil components that provide a biocidal effect against bacteria.

Even with so many well-researched studies, the application of essential oils still has some limitations. When used as a food preservative, the problem of essential oil constituents is that they often cause negative organoleptic changes if added in amounts sufficient to provide an antimicrobial effect, which generally requires high concentrations [44]. Additionally, in many foods, the hydrophobicity of essential oil constituents is detrimental due to interactions with fat-containing foods [4].

There is also another aggravating factor which makes impossible for these compounds to be used in other products that wish to make use of its main characteristic. The compounds that promote antimicrobial and antioxidant activity in the essential oils are highly volatile, thermally unstable, and photodegradable, and in the presence of oxygen, they undergo oxidation. Thus, when they are not protected by a barrier are not very stable and at high temperatures they lose their biological activity and their applications can be compromised [45–48].

Chemical component groups of essential oils are readily converted by oxidation, isomerization, cyclization, or dehydrogenation, which are reactions that can be enzymatically or chemically triggered, and these processes are usually associated with a loss of quality. For example, terpenoids tend to be volatile and thermolabile and can be readily oxidized or hydrolyzed, depending on their structure. Further, the maintenance of essential oil composition depends strongly on the conditions under which it is processed and how it is handled and stored upon production. Certain factors are crucial for maintaining the stability of essential oils, such as temperature, light, and oxygen availability. Therefore, these factors need to be carefully considered [49].

In this way, it is possible to infer that the conditions in which these essential oils are kept are fundamental to their characteristics. Rowshan et al. [50] studied the thermal stability of the *Thymus daenensis* essential oil by storing it at room temperature, under refrigeration (4°C) and frozen (−20°C). The authors verified that the oil composition was a function of temperature and that when frozen, the oil composition underwent only minor changes, and the primary quality was maintained, demonstrating the oil degradation effect under high temperature. The ambient temperature crucially influences the essential oil stability in several respects, and as a rule, chemical reactions are accelerated with increasing temperature because the reaction rates are increased by heat [49].

Turek and Stintzing [51] evaluated the impact of different storage conditions on four essential oils (lavender, pine, rosemary, and thyme) to verify the influence of light and temperature on their composition. The authors obtained interesting results, stating that parameters such as pH, conductivity, and the chemical profile of the essential oils are severely altered when exposed to light and temperature, which modifies their quality. Their work also reinforced that each essential oil responds differently to these external parameters.

One option for minimizing the exposure problems of essential oils is to make use of these compounds in encapsulated form, by means of a protective shell, to limit the degradation/loss of biological activity during processing and storage and to control compound release at the time and site desired [52–54].

Microencapsulation presents a great potential for improvement and development of structures for the conservation of natural products. In the last decade, there has been great progress in the development of microencapsulated compounds in the food and pharmaceutical industries, as they offer greater degradation resistance and compound stability [53, 55–59].

3. Encapsulation

3.1. Approaches

Encapsulation is the process of constructing a functional barrier between the core and the coating material to avoid chemical and physical reactions and to maintain the biological, functional, and physico-chemical properties of the core materials. The proper choice of encapsulation technique and the coating material depends on the end use of the product and the

processing conditions involved. The coating material determines the stability of the particles, the process efficiency, and the degree of core protection [8].

Since bioactive compounds has some limitations in their use, for example, induce negative organoleptic change, are highly volatile, thermally unstable, photodegradable, and therefore, they can be easily deteriorated, the use of a barrier that limits these exchanges is interesting. When encapsulated, these compounds are protected against a number of factors, such as temperature, moisture, light, oxidation, undesirable reactions with other compounds and mechanical stress during handling, processing, and storage of the final product. This leads to a prolonged shelf life and maintenance of metabolic activity for long periods of time during storage, which maintains the biological and functional characteristics of essential oils [60–62].

3.2. Procedure

The encapsulation technique can be used for solid, liquid, or gaseous material packaging using fine polymer coatings to form macrocapsules (>5000 μm), microcapsules (0.2–5000 μm), or nanocapsules (<0.2 μm) [63, 64]. Nanoencapsulation is the coating of one or more substances within another material at the nanoscale. Microencapsulation is similar to nanoencapsulation, but it involves larger particles and is an already consolidated technique, with a longer study time compared to the nanoencapsulation process. On the other hand, macroencapsulation involves a larger scale than microencapsulation [65].

In general, the compound to be encapsulated is suspended in a solution containing the encapsulating agent, and then, this agent is dissolved and precipitated by coating the suspended material, or the compound to be encapsulated and the encapsulating agent are dissolved in a single solvent and simultaneously precipitated (coprecipitation). In this situation, various particles of the compound are within the layer of the encapsulating agent, with the capsule formation, which may be microcapsules and/or microspheres, for example [66]. The encapsulating agent protects the core by isolating it and allows release through a specific stimulus at the time and place desired [64]. **Figure 1** shows a schematic picture of microcapsules and microspheres.

Microcapsules are particles consisting of a substantial central inner core containing the active substance covered by a layer of the encapsulating agent, constituting the capsule membrane, while microspheres are matrix systems in which the nucleus is uniformly dispersed and/or dissolved in a polymer network. The microspheres may be homogeneous or heterogeneous

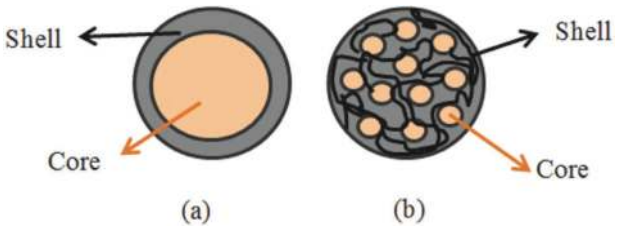

Figure 1. Types of microparticles: (a) microcapsules and (b) microspheres. Source: Adapted [67].

depending on whether the core is in the molecular state (dissolved) or in particle form (suspended), respectively [64, 68].

The encapsulating agent should not react with the core, and it should have the ability to seal and hold the core within the capsule, protecting it from adverse conditions. Interactions between the wall material and the core can affect the release rate as well as the core volatility and particle size [63, 69].

The mechanisms involved in the core release are diffusion, where the active compound is released slowly by permeating the wall of the coating without compromising its physical integrity, or through a release trigger, which involves a change in pH, mechanical stress, temperature, enzymatic activity, time, or osmotic force, among other triggers, that promotes capsule breakdown and instantly releases the active compound [70].

3.3. Techniques

The selection of the encapsulation technique and the coating material depends on the final application of the product, considering the physical and chemical stability, the concentration of the compounds in the encapsulation process, the required particle size, the release mechanism and the manufacturing costs [62, 64].

The encapsulation technique efficiency depends on several parameters. Retention of the active agent within the membrane shell is regulated by factors related to the chemical nature of the core, including its molecular weight, chemical functionality, polarity, and volatility, and by the properties of the coating material and the chosen encapsulation technique [62].

The key steps in an encapsulation method are incorporation of the bioactive compounds; droplet formation; removal of the solvent; collection of the capsules, and drying [71]. Different encapsulation methods have been developed to meet different types of core and shell materials, as well as to generate particles with various sizes, thickness, and shell permeability, thus adjusting the active principle release rate [62]. Some of the main encapsulation methods are spray drying, coacervation, solvent evaporation, extrusion, lyophilization, and encapsulation using supercritical fluids [72]. These methods are described in the following sections.

3.3.1. Spray drying

Very simply, this process consists of (i) preparing, (ii) homogenizing, and (iii) atomizing the suspension and (iv) drying the atomized particles [8]. The encapsulation efficiency using the spray drying technique is dependent on the preparation of a stable emulsion/suspension of oil in water and spraying it into small droplets on the drying bed [63]. Therefore, the bulk ratio of hydrophilic and lipophilic phases, the oil droplet size distribution, the dry matter content, and the emulsion viscosity need to be optimized prior to use in this technique. The emulsions must have sufficient viscosity to be pumped and sprayed, and they should not be sticky and hygroscopic after drying, which will ensure particle stability during storage [7].

This technique requires well-adjusted operating conditions as well as a suitable composition of the solution containing the bioactive compounds. The first includes factors such as inlet

air temperature, atomizing air flow, liquid flow rate, vacuum aspirator velocity, and solid concentration, among others [73]. The success in obtaining particles using the spray drying method depends on factors such as the choice of polymer and the size distribution of the oil droplets in the emulsion [74, 75].

The main advantages of the spray drying technique are the combination of particle formation and drying in a single step, the possibility of using a wide variety of encapsulating agents, potentially large-scale production, simple equipment, low operating costs, high quality capsules with good yield, quick solubility of the capsules, small size, high capsule stability, and continuous operation [61, 64, 73, 76, 77]. The disadvantages are variations in the particle size and shape distribution, high temperatures, and rapid drying rates that normally do not allow encapsulation of thermosensitive compounds [61, 64, 73, 77].

Gallo et al. [76] studied the influence of the operation conditions of the spray drying method on the physical properties of *Rhamnus purshiana* extract powder. Roccia et al. [73] evaluated the influence of spray-drying operation conditions on the qualities of powdered sunflower oil. Fernandes et al. [78], Goñi et al. [79], and Oliveira et al. [80] microencapsulated essential oil of rosemary, eugenol, and passion fruit seed oil, respectively, using the dying spray technique. Gallardo et al. [81] microencapsulated linseed oil by spray-drying for application in functional foods.

3.3.2. Coacervation

Coacervation is one of the oldest and most widely used encapsulation techniques, and it involves electrostatic attraction between two oppositely charged polymers and the formation of coacervates over a narrow pH range. This technique involves the addition of a coacervating agent to a homogeneous polymer solution. The coacervation agent desolvates the polymer solution in a coacervate (polymer rich phase) and coacervation medium (poor polymer phase). During the encapsulation process, the bioactive compound is encapsulated within the polymer rich phase [7, 8].

The coacervation technique may be simple or complex. What differentiates them is the method of phase separation. In simple coacervation, the polymer is salted by the action of electrolytes, such as sodium sulfate, or desolvated by the addition of a water-miscible nonsolvent, such as ethanol, or by increasing/decreasing the temperature. These conditions promote macromolecule-macromolecule interactions, allowing the production of microcapsules containing hydrophobic substances, such as essential oils. Simple coacervation offers important advantages over complex coacervation in terms of cost savings and flexible operations. To induce phase separation, simple coacervation uses cheap inorganic salts, while complex coacervation is more sensitive even at small pH changes. In addition, complex coacervation uses expensive hydrocolloids [8, 82].

On the other hand, complex coacervation involves complexation between two oppositely charged polymers (commonly a polysaccharide and a protein). Complex coacervation involves three basic steps. The first step consists of the formation of an oil/water (o/w) emulsion, and the second step consists of separation of the liquid phase rich in the insoluble polymer; this phase

results from the electrostatic attraction between opposing charges of the polymers caused by a reduction in the pH of the solution. The last step is coating stabilization (coating hardening, using thermal, cross-linking or desolvation techniques, to form self-sustained microcapsules). The formation of the coacervation coating is conducted by the difference in surface tension between the coacervation phase, the water and the hydrophobic material [7, 8, 62].

The main advantage of complex coacervation is that it has a high level payload (up to 99%). In addition, this method is simple, low cost, and solvent free. Therefore, complex coacervation can be used to manufacture microcapsules at an industrial scale [83].

Several investigations have utilized the coacervation method to microencapsulate bioactive compounds, such as propolis extract, sweet orange oil, essential oil of mustard seeds (*Sinapis alba*) and pepper essential oil [52, 84–86].

3.3.3. Solvent evaporation

This technique is based on the evaporation of the internal phase of an emulsion by shaking. Generally, the coating material is dissolved in a volatile organic solvent. The core material is then dissolved or dispersed in the encapsulating agent solution to form a suspension, an emulsion, or a solution. Thereafter, the organic phase is emulsified under agitation in a dispersion phase consisting of a nonsolvent of the encapsulant, which is immiscible with the organic solvent and contains an appropriate emulsifying agent. Once the emulsion is stabilized, the shaking is maintained, and the solvent evaporates after diffusing through the continuous phase, resulting in solid microspheres. The microspheres are recovered by filtration or centrifugation, and washed and dried [87, 7]. Patil et al. [88] encapsulated clove oil in methylcellulose microcapsules using the solvent evaporation method.

3.3.4. Extrusion technique

Oil encapsulation by extrusion consists basically of (i) injection and (ii) melt extrusion, followed by (iii) centrifugal extrusion (coextrusion). The main advantages of the encapsulation of essential oils by extrusion are stability against oxidation, prolonged shelf life, and lower rates of essential oil evaporation. However, this is an expensive process, and the particles do not have a uniform distribution [8]. Soliman et al. [89] microencapsulated essential oils of clove (*Eugenia caryophyllata*), thyme (*Thymus vulgaris*), and cinnamon (*Cinnamomum zeylanicum*) using this technique.

3.3.5. Freeze drying

Freeze drying is a method that involves dehydration of the frozen material under a vacuum sublimation process; the removal of water occurs without subjecting the sample to high temperatures. This method provides products of excellent quality because it minimizes the changes associated with high temperature. However, its high cost and long process time reduce its applicability [64]. Examples of studies that used this technique include Calvo et al. [90] who microencapsulated extra virgin olive oil in the presence of maltodextrin, carboxymethylcellulose, and lecithin; Ezhilarasi et al. [91], who studied microencapsulation of garcinia fruit extract by spray

drying and its effect on bread quality; Piletti et al. [19], who encapsulated eugenol essential oil into β-cyclodextrin molecules through lyophilization; and Hill et al. [21], who encapsulated cinnamon bark extract, trans-cinnamaldehyde, clove extract, eugenol, and a 2:1 mixture (trans-cinnamaldehyde: eugenol) with β-cyclodextrin using the lyophilization method.

3.3.6. Technology employing supercritical fluids

The encapsulation technology employing supercritical fluids has been developed to minimize the disadvantages associated with traditional encapsulation methods, and it has a great relevance for the pharmaceutical, cosmetic, and food industries. It has several inherent advantages: non-toxicity and easy removal of the solvent without degradation of the product, and the process uses a wide variety of materials that produce controlled particle sizes and morphologies. Generally, it is preferred for essential oils that are sensitive to high temperatures, oxygen, and chemicals. Technology using supercritical fluids is considered a green technology because of the use of supercritical carbon dioxide in most cases. Supercritical carbon dioxide (CO_2) has properties that are ideal for bioactive compound encapsulation. The characteristic properties of supercritical CO_2 are lower viscosity, higher diffusivity, lower surface tension, faster process, and high solubility of the active compound [7, 8].

The supercritical apparatus consists of a high pressure stainless steel impregnation cell, a magnetic stirrer plate, a temperature controlled water bath, a high pressure CO_2 pump, and a pressure transducer. The impregnation cell contains two chambers separated by a mesh. The lower chamber is filled with essential oil, and the upper chamber is filled with microparticles or matrices in which the oil needs to be impregnated [7]. The essential oils of lavandin, oregano, canola, and passion fruit seed oil have been encapsulated using this method [80, 92–94].

For the encapsulation process, selection of the encapsulating material is a very important step. This material should be chosen according to its bioactivity, non-toxicity, intended application, and method of particle formation [71]. Biodegradable polymers, such as PLA, PLGA, and PCL, have primarily been used as a coating in the medical field, especially in tissue engineering and drug release. To a lesser extent, inorganic materials such as silicates, clays, and polyphosphates can also be used. Further, proteins (gelatin, casein, and soy proteins), lipids (waxes, paraffin, and oils), and synthetic polymers (acrylic polymers, polyvinylpyrrolidone) may be used. However, the most widespread materials used as encapsulating agents are polysaccharides and sugars (gums, starches, and celluloses), especially cyclodextrins, which are widely used mainly in the food industry due to their interesting properties; specifically, they are inert and non-toxic [7, 62].

4. Cyclodextrins

Cyclodextrin had its origin around 1981, when Villier discovered a new starch derivative obtained from bacterial degradation, which presented properties similar to those of cellulose, and distinguished two types of crystals of cellulosin: the cyclodextrins α and β [95]. Twelve

years later, when studying the bacterial digestion of starch, Szejtli [95] identified two crystalline products with the same characteristics as Villier's cellulosins. Deepening his studies, he perfected the process of obtaining these crystals and isolated the bacterium that produced them, deeming it *Bacillus macerans*. The crystalline products were called crystallized α-dextrin and β-dextrin. Later, λ-dextrin was also isolated, and several fractionation schemes for the production of cyclodextrins were developed [96].

Cyclodextrins (CD's) are cyclic oligosaccharides consisting of glucose units linked by α-(1,4) glycosidic bonds derived from the enzymatic degradation of starch by certain bacteria, and they are chemically and physically stable molecules [95, 97]. The most common natural CDs have six, seven, and eight D-glucopyranose units and are named α, β, and γ cyclodextrin, respectively, and they differ from each other by virtue of ring size and solubility [98]. While the central cavity of CDs has a hydrophobic character, the surrounding walls are hydrophilic, and this feature allows CDs to form capsules, acting as a host for lipophilic compounds in their cavities and forming inclusion complexes [97, 99–101].

The binding of bioactive compounds within the host cyclodextrin is not fixed or permanent, but rather a dynamic equilibrium. This way, the formation of inclusion complexes is result of an equilibrium between the free and CD molecules and the bioactive compounds—CD complex [99]. Therefore, some factors may affect inclusion complex formation, such as type of cyclodextrin, cavity size, pH and ionization state, temperature, and method of preparation [102].

CD molecules are cone-like in shape with a cavity 7.9 Å deep. The upper and lower diameters of the CD wells are 4.7 and 5.3 Å, 6.0 and 6.5 Å, and 7.5 and 8.3 Å for α-CD, β-CD, and γ-CD, respectively [45].

Among the CDs, β-CD is the most used, because its apolar cavity can host molecules of molecular masses between 100 and 400 g mol^{-1}, which is the molecular mass range of most molecules of interest. β-CD is also easy to recover industrially through the crystallization process [103], and it has the lowest solubility and an intermediate size (**Table 1**). In addition, β-CD production is the most economically viable, with an industrial cost per kilogram approximately 20 times lower than that of the other CD types [104].

These inclusion complexes are important because they improve the chemical and physical stability and solubility of the compounds encapsulated in water. Due to the solubility of CDs in water and because they have the ability to form reversible inclusion complexes with non-polar molecules in aqueous solution, the water molecules inside the ring are easily replaced by non-polar molecules or molecules with less polarity than water, forming structures that are energetically more stable [105].

The encapsulation can reduce volatilization rates, and promote the gradual release of the encapsulated molecules, which improves their efficacy and bioavailability. Furthermore, they act as protectors against oxidative damage, light degradation, and heat, and other adverse effects linked to the medium in which they are inserted and maintain the initial characteristics of the compound for a long period. These inclusion complexes are relatively more hydrophilic and larger in size than the non-associated active compound, which helps to increase the retention of the encapsulated substance. They are also very interesting because they can mask undesirable flavors and odors that the encapsulated compounds may present [21, 56, 72, 101, 102, 106–110].

	α-CD	β-CD	γ-CD
Glucose number	6	7	8
Molecular mass	972	1135	1297
Aqueous solution (g 100 mL^{-1} at 25°C)	14.2	1.85	23.2
Cavity diameter (Â)	4.7–5.3	6.0–6.5	1.5–8.3
Cavity volume ($Â^3$)	174	262	427
Crystal form	Hexagonal blades	Monoclinic parallelograms	Quadratic prisms
Pk	12.332	12.202	12.081
Melting point (°C)	275	280	275
Surface tension (nM/m)	73	73	73
Rate of acid hydrolysis (h^{-1})	0.11	0.13	0.23

Source: [95].

Table 1. Physical and chemical properties of α-CD, β-CD, and γ-CD.

Marques [102] notes that the goal of encapsulation using cyclodextrin is to reduce the volatility and toxicity of the encapsulated compounds, provide protection of compounds that are sensitive to factors that promote their degradation, and alter the kinetics of migration and release of the encapsulated active components into the external environment.

The use of cyclodextrins is verified in diverse industrial products, such as pharmaceuticals [107, 111, 112], agrochemicals [113–115], and foods [116–119]. In the food area, cyclodextrins are nontoxic and considered GRAS, and thus are used for several purposes [120, 121]. These structures offer increased resistance to degradation of the active compounds and make the host-microcapsule complex more stable [53, 56, 57, 122, 123].

Szente and Szejtli [104] studied the toxicity of CDs and demonstrated that oral administration of high doses of CDs does not cause any harm. Several studies have shown that CDs are nontoxic and do not present intoxication risks, because they are not absorbed in the gastrointestinal tract or through lipophilic biological membranes, and the same results have been obtained with regard to teratogenicity and mutagenicity [124–128]. Antisperger [129] also evaluated the toxicity of CDs when introduced in an amount equivalent to 20% in the diet of rats and dogs and found no toxicity.

5. Cyclodextrins in thermal protection

The thermal degradation is one of the main natural compounds' degradation forms. In most cases, the increase in temperature is undesirable, as it favors the volatilization of less stable compounds, which are responsible for the biological activity. Therefore, the thermal degradation makes it impossible to apply many of the natural compounds studied, due to the

alteration of their characteristics when exposed to high temperatures. Due to this situation, several authors have studied the encapsulation of these bioactive compounds with cyclodextrin, in order to provide a barrier, aiming the thermal protection of these natural compounds and preventing bioactive compounds from being lost and thus ensuring the application of these products in different situations.

Abarca et al. [130] prepared an inclusion complex of 2-nonanone (2-NN) with β-cyclodextrin by a co-precipitation method. 2-Nonanone are aliphatic hydrocarbons, aromatic volatiles commonly found in plant tissues, presenting antifungal behavior with low mammalian toxicity, a pleasant fruity/floral odor, resistance to rapid decomposition, adequate volatility, environmental acceptability, and a high potential for commercial development. The TGA and DSC analyses showed that thermal stability increased when 2-NN was encapsulated with β-CD. The antifungal activity of the inclusion complex was tested against *Botrytis cinerea*. All inclusion complexes tested showed potential antifungal activity, but the complex 1:0.5 (β-CD: 2-NN) showed the highest antifungal activity with a radius of 0.6 cm and 80% of growth inhibition.

Babaoglu et al. [101] encapsulated clove essential oil in hydroxypropyl-beta-cyclodextrin using the kneading method (a low-cost and easy-to-operate encapsulation technique) with hydroxypropyl beta-cyclodextrin and oil at a molar ratio of 1:1. The study demonstrated that the stability of the inclusion complex formed was greater and that the encapsulation process also increased the total phenolic content and antioxidant properties compared with the essential oil in free form. The authors indicate that this increase is due to an increase in the solubility of the essential oil molecules in water as a result of inclusion complex formation. Furthermore, the release rate of the essential oil was controlled with encapsulation. However, the authors concluded that this rate could be improved with the use of different proportions of essential oils. With this study, the potential for the use of microencapsulated clove oil in the pharmaceutical and food industries is evident, because this formulation keeps the oil constituents active and avoids losses and degradation.

Inclusion complexes formed with cyclodextrin are already being used as additives in final products, as reported by Wang et al. [131], that performed a work demonstrating this possibility when preparing cyclodextrin microencapsulated ammonium polyphosphate (MCAPP), with the goal of improving the water durability of APP and making a novel functional flame retardants. One of the interesting results found by the authors was that cyclodextrin resulted in the transformation of hydrophilic to hydrophobic of the flame retardant surface. Then, MCAPP was incorporated into the ethylene vinyl acetate copolymer (EVA), extensively used for the several applications like electrical insulation, cable jacketing and repair, water proofing, and corrosion protection, in order to improve flame retardancy of the EVA. The results showed that after the incorporation, the EVA composites presented improvements in mechanical, thermal stability, combustion properties, and flame-retardant properties, mainly because cyclodextrin shell improves the compatibility of the composites and the dispersion of APP in the EVA matrix evidencing that the microencapsulation technology with cyclodextrin contributes to obtain products with better characteristics and greater applicability. This study showed that cyclodextrin encapsulation is not only limited to natural products, but can also act as an encapsulating agent for other products as well, increasing its stability.

Another study that inserted the inclusion complex obtained in a final product was done by Kayaci et al. [132]. Geraniol is a natural component of plant essential oils, generally used as a fragrance/flavor in food industry to treat infectious diseases and/or preserve the food. The authors studied solid inclusion complexes of geraniol/cyclodextrins (α-CD, β-CD, and γ-CD). The results showed that the complexation efficiency between geraniol and γ-CD was higher. After this verification, the authors incorporated this inclusion complex into polyvinyl alcohol (PVA) nanofibers (NF) via electrospinning. The SEM analysis showed a homogeneous distribution of the inclusion complex (geraniol/γ-CD) to the PVA nanofibers. PVA/inclusion complex (geraniol/γ-CD) nanofibers presented higher thermal stability when compared to PVA/geraniol nanofibers only. Geraniol is easily volatilized, a fact that can be observed during electrospinning or during storage. When the PVA/geraniol nanofibers are evaluated, it was verified that after one day of its production, the geraniol had already evaporated completely. In contrast, PVA/inclusion complex (geraniol/γ-CD) nanofibers lost only about 10% of geraniol after two years of manufacturing. This result led the authors to conclude that PVA/inclusion complex (geraniol/γ-CD) nanofibers have potential application in the food packaging sector due to the high surface area and nanoporous structure of nanofibers and also due to the high thermal stability and longer durability of the agent active because it is encapsulated.

Hădărugă et al. [133] studied *Ocimum basilicum* L. essential oil and its β-cyclodextrin (β-CD) complex with respect to stability against the degradative action of air/oxygen and temperature using GC-MS analysis. Compounds associated with the degradation of the essential oil, which appear at high concentrations in degraded feedstocks, were limited and nearly constant in the complex formed by oil and β-CD, even at very high degradation temperatures, indicating improvement of the quality and stability of the complex.

Kalogeropoulos et al. [134] performed a thermal study of *Hypericum perforatum* methanolic extract, which is very rich in flavonoids, encapsulated in β-cyclodextrin (β-CD). Through DSC analysis after thermal oxidation, the authors found that the inclusion complex remained intact at temperatures at which the free extract was oxidized. Therefore, they showed that β-CD protected *Hypericum perforatum* extracts against thermal degradation, suggesting that this inclusion complex can be used as a food supplement or a novel additive to enhance the antioxidant capacity of fresh or thermally processed food.

Hill et al. [21] investigated the complexes formed by oils encapsulated in β-cyclodextrin (BCD) and their antimicrobial activity. The natural products studied were cinnamon bark extract, trans-cinnamaldehyde, clove bud extract, eugenol, and a 2:1 (trans-cinnamaldehyde:eugenol) mixture microencapsulated with the freeze-drying method. The oils and their BCD complexes were analyzed for their antimicrobial activity against *Salmonella enterica* serovar Typhimurium LT2 and *Listeria innocua*. In addition to the antimicrobial analysis, the authors investigated, among other things, the protection of the biological compounds against thermal oxidation, which should be the role played by β-cyclodextrin. The authors investigated the thermal stability of the oils through DSC analysis and compared EOs in their free form and their encapsulated form. As noted, there are two exothermic peaks at approximately 265°C and 260°C that, according to the authors, may be related to hydrolysis or oxidation of trans-cinnamaldehyde and eugenol. These peaks were not detected in the thermogram of the inclusion

complex formed by the oils and β-cyclodextrin, suggesting that the EOs were protected at the β-cyclodextrin cavity. The temperature peaks of 100°C were attributed to water evaporation in all the samples, and the exothermic peaks at approximately 300°C for the β-cyclodextrin samples are a result of thermal degradation of the compound itself. Similar results were observed for the extracts and their inclusion complexes formed with β-cyclodextrin, indicating that the encapsulating agent provided thermal protection.

The antimicrobial analysis showed that all the antimicrobials effectively inhibited bacterial growth within the tested concentration range except for free eugenol. The EO-BCD complexes inhibited both bacterial strains at lower active compound concentrations than free oils, likely due to increased solubility in water that led to greater contact between the pathogens and essential oils. Moreover, the results showed that in addition to masking the sensory effect of the attributes of antimicrobial agents, complexation may potentiate their activity.

Wang et al. [103] studied the encapsulation of garlic oil (GO) and obtained an inclusion complex with GO encpasulated by the β-cyclodextrin using the co-precipitation method. The authors also used DSC to evaluate the thermal stability of the complex. The garlic oil is rich in organosulphur compounds that have a variety of antimicrobial and antioxidant activities but are very volatile and have low physicochemical stability.

The BCD thermogram showed a large endothermic peak at approximately 127°C that, according to the authors, is related to elimination of water molecules that are bound to the cyclodextrin molecules. For GO in its free form, the authors verified the existence of two peaks at approximately 186° and 223°C and associated the peaks with GO oxidation. These two exothermic peaks were not found in the GO-BCD complex thermogram, indicating that the biological compound is protected from oxidation within the BCD cavity.

Hădărugă et al. [135] studied the thermal and oxidative stability of Atlantic salmon oil (*Salmo salar* L.) and complexation with β-cyclodextrin. Due to being very unstable, even with low temperature degradation, it is interesting to encapsulate Atlantic salmon oil to ensure the permanence of its characteristics even after some time. The results showed good yields in the preparation of β-CD/Atlantic salmon oil complexes by co-crystallization, thereby increasing the thermal and oxidative stability of this oil.

Li et al. [136] also prepared an inclusion complex of benzyl isothiocyanate (BITC) extracted from papaya seeds with β-cyclodextrin. The thermal properties of BCD, BITC and its inclusion complex (BITC-BCD) were investigated using DSC and TG techniques. The DSC curve of BITC-BCD shows that volatilization of uncoated BITC occurred. The TG curve of BCD showed a slope close to 300°C, which was generally attributed to the onset of BCD decomposition. The BITC is a volatile material and quickly loses mass at 80–165°C. The inclusion complex showed volatility between 140°C and 300°C, indicating that the BCD cavity provides protection against BITC volatilization.

Zhou et al. [137] studied the Baicalein (Ba) encapsulation, an active ingredient extracted from a medicinal herb *Scutellaria baicalensis*, which has anti-inflammatory, antioxidant and anti-tumor activity among other biological activities; however, it presents limited solubility and high instability. In order to overcome the unfavorable physical-chemical properties presented by Ba, the authors performed a study with the various natural forms of cyclodextrin and its derivatives by

using the freeze-drying method to obtain a complex that allows thermal protection of the natural compound. The solubility of Ba in the presence of natural cyclodextrins and its derivatives was higher than that of free Ba, with emphasis on the inclusion complex formed by 2,6-di-O-methyl-β-cyclodextrin (DM-β-CD), which showed the solubility constant of 13672.67 L mol $^{-1}$. The dissolution rate and thermal stability of the inclusion complex were significantly enhanced compared with the Ba pure; thus, DM-β-CD considerably improves the solubility and thermal stability of Ba, which make the chemical application of this drug promising.

Vilanova and Solans [138] studied the inclusion complexes of Vitamin A Palmitate with β-cyclodextrins, without the use of organic solvents. The low stability and low water solubility of some vitamins limit its use as a food additive, so the authors' interest was to use cyclodextrin as an encapsulating agent to overcome these deficiencies, making possible the production of foods enriched with vitamins, in order to prevent diseases related to their deficiency. All results showed a notably increase of Vitamin A Palmitate water solubility and stability in front of temperature, oxygen, and UV light when encapsulated. This works showed that the formation of inclusion complexes is a potential strategy to not only enrich but also to provide stability in surfactant-free food emulsion formulations, which seem to be a promising vehicle to increase the bioavailability of Vitamin A Palmitate in food.

Fernandes et al. [139] evaluated the thermal stability of cyanidin-3-O-glucoside (cy3glc) (major blackberry anthocyanin) and blackberry purees through molecular inclusion with β-cyclodextrin (β-CD). This work evidenced the thermal protection provided by the encapsulating agent, which showed a thermal stabilization of cy3glc, resulting in a decrease of the degradation rate constant (k) and in several alterations in the cy3glc-β-CD DSC thermogram. According to the authors, anthocyanin-loaded β-CD could potentially carry and stabilize anthocyanins, improving their bioavailability, which could be an advantage for efficient utilization in food systems.

All the showed works evidenced the importance of encapsulation to maintain the properties of the studied compounds, allowing their application in different situations. It is evident that cyclodextrin is the most widely used encapsulating agent, as it provides the formation of inclusion complexes with interesting properties.

6. A case study

Eugenol is an essential oil with excellent antimicrobial properties. However, because it is thermosensitive, it has restricted the applicability in processes that require high temperatures. Piletti et al. [19] proposed a method for protecting this oil by encapsulating it in β-cyclodextrin. The authors evaluated the encapsulation of eugenol molecules by means of lyophilization and later evaluated the antimicrobial activity of the complex (eugenol-β-cyclodextrin) against the bacteria *Escherichia coli* and *Staphylococcus aureus* through the diffusion technique in agar. The authors also investigated the thermal and morphological properties of the complex. When evaluating the antimicrobial activity complexes obtained with different concentrations of eugenol (9.68, 10.90, 17.08 mmol L^{-1}) against *Escherichia coli* and *Staphylococcus aureus* bacteria, the authors verified that the antimicrobial activity was maintained even after encapsulation.

However, when using cyclodextrin as an encapsulating agent, the idea was that there would be thermal protection of the essential oil, ensuring that the compound property of interest (antimicrobial activity) was not altered. This was confirmed by the heat treatment of the eugenol-β-cyclodextrin complex in a furnace maintained at 80°C (temperature approximately twice the temperature of free eugenol volatilization) for 2 h and subsequent re-evaluation of antimicrobial activity. **Figures 2** and **3** illustrate the antimicrobial capacity of the complex after the heat treatment against *E. coli* and *S. aureus* bacteria, respectively.

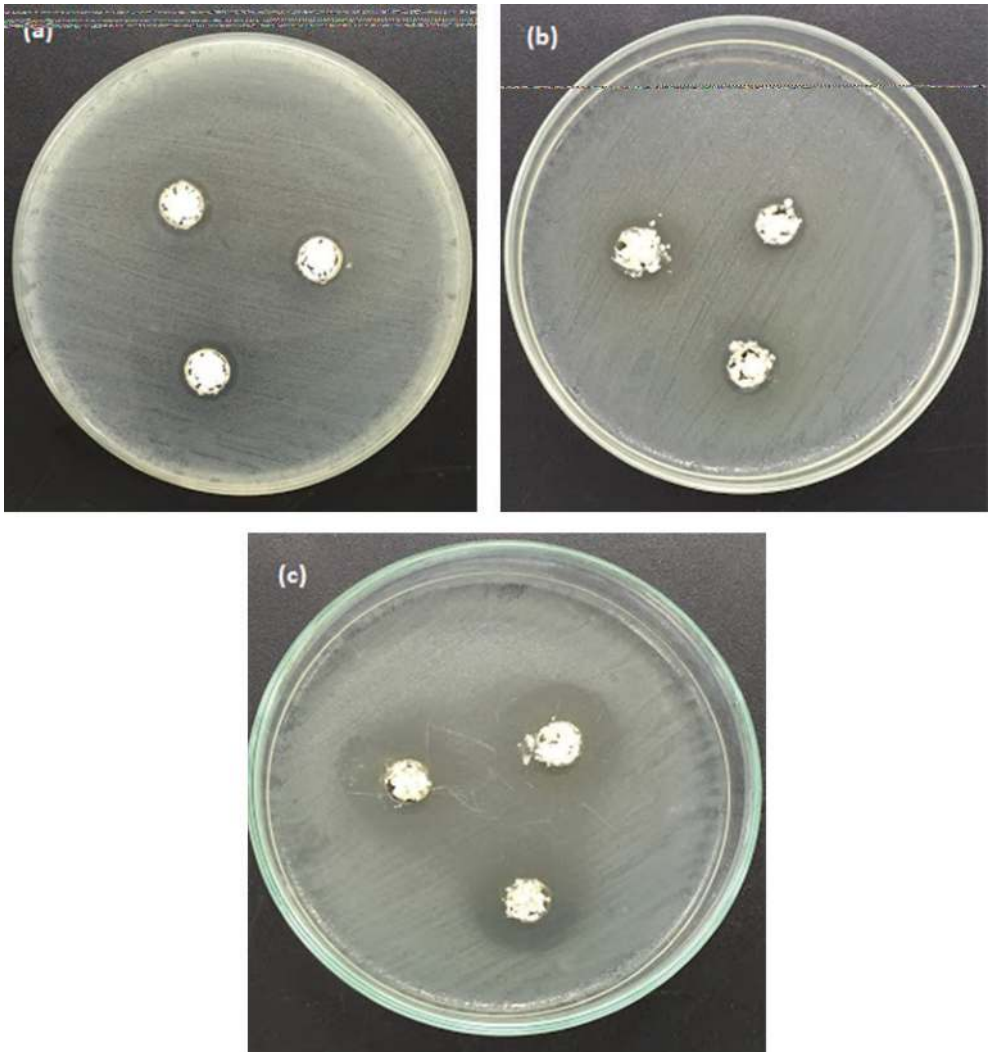

Figure 2. Agar diffusion tests of a eugenol-β-cyclodextrin complex synthesized using different eugenol concentrations in the reaction solution and thermally treated at 80°C for 2 h for *E. coli* bacteria. Eugenol concentration: (a) 9.68; (b) 10.90; and (c) 17.08 mmol L^{-1}.

The encapsulated eugenol molecules were thermally protected, remained in the complexes after heat treatment and manifested the antimicrobial activity of this essential oil. Therefore, encapsulation using β-cyclodextrin is a promising method to protect eugenol, preserving its antibacterial action when it is used under conditions higher than its volatilization temperature.

All these studies show the efficiency of β-cyclodextrin as an encapsulating agent and demonstrate its high thermal protection capacity for bioactive natural compounds, which are highly unstable, without damaging the biological property of interest in these compounds.

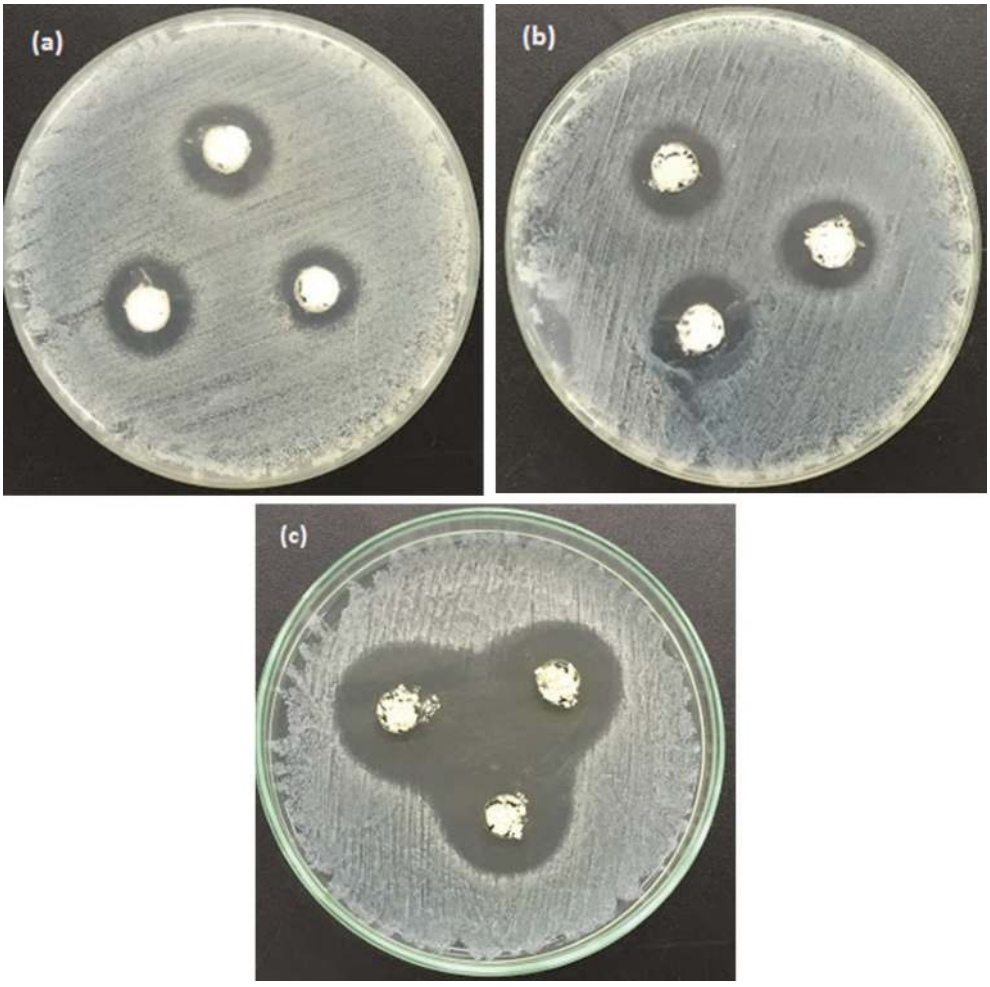

Figure 3. Agar diffusion tests of a eugenol-β-cyclodextrin complex synthesized using different eugenol concentrations in the reaction solution and thermally treated at 80°C for 2 h against *S. aureus* bacteria. Eugenol concentration: (a) 9.68; (b) 10.90; and (c) 17.08 mmol L^{-1}.

Thus, the encapsulation of essential oils using β-cyclodextrin is an alternative to promote the use of these biocomposites as additives, boosting the development of functional materials, providing new applications for them in the diverse areas, such as medical, pharmaceutical, cosmetic, and food, combining the use of technology with the appreciation of natural raw materials.

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