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IMPORTANCE & APPLICATIONS OF NANOTECHNOLOGY

New trends of antimicrobial packaging applying nanotechnology

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Published Online: May 27, 2019

eBook: Importance & Applications of Nanotechnology

Publisher: MedDocs Publishers LLC

Online edition: http://meddocsonline.org/

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Introduction

Modernity has brought great comfort for society but to maintain that there is a continually increasing demand especially with population growth. One major concern is associated with the food demand that is rising fast, especially for emerging countries, particularly in Asia, Eastern Europe, and Latin America [1]. The Food and Agriculture Organization of the United Nations (FAO) and the International Food Policy Research Institute (IFPRI) have published projections of an increase in global food demand out to 2050 with projections that indicate that world food demand may increase by 70 percent by 2050 [2] . According to Gustavsson et al. [3], one-third of the food produced worldwide for human consumption is lost, totaling approximately 1.3 billion tons per year, with spoilage as one of the leading causes of this issue [3].

Food packaging englobes functions of containment, protection, convenience, and communication [4]. The challenge for the food industry is to produce safe, high-quality and shelf-stable food because food deterioration can occur by the action of microorganisms, moisture, gases, dust, odors as well as mechanical forces [5,6].

Most spoilage processes are due to biological reasons such as auto-degradation of tissues by enzymes, viral contamination, protozoa and parasite contamination, microbial contamination, and loss by rodents and insects. The growth of microorganisms is the major problem of food spoilage leading to degraded quality, shortened shelf life, and changes in natural microflora that could induce pathogenic problems [3,7].

Foodborne diseases are a significant concern for consumers, the food industry and food safety authorities. The consumers are gradually demanding food to be microbiologically safe, closer to natural, with no chemical preservatives and with longer shelf life. Thus, the use of antimicrobial agents is interesting because they can eliminate or delay the action of pathogenic microorganisms, and so control of the processes of deterioration in the food [8]. Nevertheless, the use of natural preservatives obtained from plants, like the essential oils, shows excellent antimicrobial activity, can ensure the organoleptic characteristics of food and are considered as "Generally Recognised As Safe" (GRAS), and so can be consumed without health risk [9-11].

The production of safe, high-quality and shelf-stable food has become a challenge to the food industry and based on those new technologies of packaging for safer and healthier food have been researched ant the active packaging, and intelligent packaging concepts are promising ways to address those problems. These packages can incorporate active substances, like the essential oils that can diminish the microbial activity [12-14].

However, in order, to take full advantage of these active substances in marketable products, the development of new materials with higher properties are needed, and in this scenario, the use of nanotechnology is an appealing way to solve this problem [15-17].

Nanotechnology is an interdisciplinary research field that aims at the study and manipulation of matter in atomic and molecular scale. It can also be explained as the control of elements on an atomic and molecular level with at least one dimension measured in nanometer [18].

The National Nanotechnology Initiative (NNI) in 2016 gives a new definition: "Nanotechnology is the understanding and control of matter at dimensions of roughly 1–100 nm, where unique phenomena enable novel applications. Encompassing nanoscale science, engineering, and technology, nanotechnology involves imaging, measuring, modeling, and manipulating matter at this length scale" [19]. Already the European Science Foundation on Nanomedicine (ESFN) also made a definition as "In case of these devices, nanoscale objects were defined as molecules or devices within the size range of one to hundreds of nanometers that are the active component or object, even within the framework of a larger micro-size device or at a macro interface" [20].

It is worth mentioning that sometimes a material surpasses the size range but presents different effectiveness depending on their size, they may also be included in the definition. That is an essential aspect of these nanomaterials, adopt unique properties that were not present when the materials were in their original form. Understanding these unique properties to develop new and improved products are the goal of many types of research nowadays [15,19].

Nanostructures applications

Nanomaterials or nanostructure materials exhibit different morphologies like clusters, nanofibers or crystallites. The combining of nanostructure materials with a polymer, biomolecule, and other nanostructure material leading to the formation of a nanocomposite. These nanomaterials have high surface-volume ratio exhibit unique physio-chemical characteristics, such as solubility, toxicity, strength, magnetism, diffusivity, optics, color, and thermodynamics [15].

Recent development has opened the door for innovation in many industrial sectors, including agriculture, public health, electronics, medicine, diagnostics, military, clothing, cosmetics, animal feed and treatment, food processing, and food contact materials [21]. Briefly, the various sectors where nanotechnology can play a role and a few examples where it can be applied are shown below [22]:

- Agriculture – enhancing the efficiency of fertilizers and pesticides;
- Handling and Storage – pest-resistant nanomaterial coatings;
- Processing – nanoencapsulation, nanoemulsions;
- Packaging – biodegradable, edible packaging material, and antimicrobial packaging;
- Distribution and Marketing – enhanced shelf lives using nanocoatings of oxidative barriers;
- Consumption – nutraceuticals, food additives;
- Site-Specific Delivery – especially of functional foods;
- Production and Processing – improving security using nanosensors that can detect microbial and chemical attack;
- Tracking Production and Logistics – gadgets to document records of articles and tracking specific shipments.

Food packaging industry

The application of nanotechnology in the food industry, while not being a recently explored concept, has been gaining considerable research effort in the last few years. One area that gained spotlight of researches is associated with the packaging since food requires protection, tampering resistance, and unique physical, chemical, or biological needs [23,24].

Conventional packaging of the modern era provides the four basics aspects of the food packaging; they are Protection, Communication, Convenience and Containment. However, to meet the demands of modern society, new types of packaging have been targeted for research such as smart packaging, and active packaging [23]. Smart packaging informs the consumer about the kinetic changes related to the quality of the food or the environment it is contained. In order to do so, they are integrated with a sensor, associated with time-temperature, gas indicator, and biosensor. The problem with this system lies in the production of sensitive sensors that are safe, easy to interpret and keep the cost of packaging competitive [25-27].

Active packaging, on the other hand, is designed with a component that enables the release or absorption of substances into packaged food or the environment surrounding the food to improve the safety, quality, and convenience of the food. These systems are already a focus of research and application, and the majority of active packaging systems include O_2 scavengers, moisture absorbers, and CO_2 emitters [28-30].

However, microorganism contamination and lipid oxidation are common causes of food spoilage. Because of the expansion of the worldwide market in fresh foods and centralized logistics, there is a need to implement their distribution, which is increasing the transit time. So, there is a need to find new ways to inhibit microbial growth, and so, there is a considerable scientific and commercial interest in the production of active antimicrobial packaging (AAP)z. In that way, the smart packing has a great significance in preserving the food to make it marketable, and among the innovations on the sector, the application of active packaging seems like a good way to approach this problem [18,31].

Metal nanoparticles as antimicrobial agents

In food technology, many different synthetic compounds have been used as antimicrobial agents to inhibit the growth of pathogenic microorganisms and deterioration of packaging. Generally, these agents have been used in the preparation of packaging materials. Among them can be exemplified inorganic,

organic or biologically active substances [30-33].

The metal NPs have also been found to display promising antimicrobial activity including in their nanoscale form. Among metal Nanoparticles (NPs), silver NP is the one most commercially made and applied due to its antimicrobial activity. Silver nanoparticles have a high surface area and a fraction of surface atoms; as a result, have high antimicrobial effect as compared to the bulk silver [34]. Antimicrobial property of silver nanoparticles has been used against a broad range of human pathogens [34-36].

Another NP that has been applied is zinc oxide that exhibits antibacterial nature that increases activity with decreasing particle size, it can be stimulated by visible light, and they are incorporated in many polymers including polypropylene [18,37]. Copper nanoparticles also showed antibacterial properties [38,39]. Titanium dioxide NPs are also well studied as a disinfecting agent, as well as, food additive (white color pigment) and flavor enhancer [40-42].

However, the nanomaterials drive their commercial applications and open new scenarios, and the new preoccupation arises from the food safety point of view. The question is whether nanomaterials are still present in the final products as a consequence of direct use during the production system and if they can migrate to food from contact materials. In particular, the use of Nanoparticles (NPs) that might cross biological barriers and has raised concern, due to the increase surface-to-mass ratio and surface reactivity, in a way that they might have new potential toxicological properties. Many NPs have distinctly different physicochemical properties, behavior, and interactions, compared to their conventional form, which makes measuring their potential toxic effects more problematic. As a consequence, to predict the effects and impacts of NPs by extrapolating the existing knowledge on risks for larger sized particles having the same chemical composition is almost impossible [13,21]. In that way, the long-term exposure to such nanomaterials may cause adverse damages and has also attracted public attention regarding the potential risks [34,44].

With the growing consumer interest in functional food products with nutritional quality, safety, improved shelf-life, and which can offer health benefits, researchers and companies have seek to substitute artificial substances to natural bioactive compounds from fruits, vegetables, pulses, roots, and other plant sources additives with antimicrobial and antioxidant properties that do not have any adverse effects on the human health [9,18,43].

Polymeric nanoparticles with natural compound as an antimicrobial alternative

Pure active substances or their mixtures could be extracted from plant leaves, flowers, stems, fruits, vegetables, or several agricultural residues. Examples of such materials are a natural antioxidant and bioactive compounds (carotenoids, phenolic compounds), vitamins, flavors, enzymes, polysaccharides, peptides, and mainly essential oil [44,45].

Among these types of additives, the Essential Oils (EO) are gaining attention because they offer action against a significant number of microorganisms. The Essential Oils (EO) or essences of aromatic plants are bioactive, volatile and fragrant compounds formed by a mixture of substances. They are typically produced by the secondary metabolism of plants [46]. Essential oils have the potential to be applied as food preservatives with antimicrobial and antioxidant action, and so much attention has been addressed to its use. Also, most of them are classified as Generally Recognized As Safe (GRAS) which opens the application in the food sector [9,47,48].

The actual mechanism of EO based antimicrobial activity are yet not understood, but they tend to accumulate in cell membranes, disturbing the structures and causing an increase of permeability. Leakage of intracellular constituents and impairment of microbial enzyme systems can then occur, and extensive loss of the cell contents will cause the cell death [49,50]. Different EO and their mixes which may act in a few different ways against various microorganisms. One example is the use of carvacrol, a noteworthy phenolic compound in oregano and thyme oil, in a way that together they can disturb the external layer of different sorts of gram-negative microscopic organisms [51].

The activity of EO can be affected by composition, functional groups present, and their synergistic interactions. The effect of EO is more pronounced for Gram-positive bacteria than for Gram-negative. This difference arises from the fact that Gram-negative bacteria have an outer membrane which is rigid, rich in lipopolysaccharide (LPS) and more complex, thereby limiting the diffusion of hydrophobic compounds through it [52,53]. While this outer membrane is absent in Gram-positive bacteria which instead are surrounded by a thick peptidoglycan wall not dense enough to resist small antimicrobial molecules, facilitating the access to the cell membrane. Moreover, Gram-positive bacteria may ease the infiltration of hydrophobic compounds of EOs due to the lipophilic ends of lipoteichoic acid present in the cell membrane [44,45].

Odor, aroma, and taste are critical sensory attributes, the perception of which may significantly affect the overall decision of the consumer (Mariod, 2016). When a natural volatile antimicrobial is applied, it is expected to evaporate within the packaging headspace and diffuse in the food. Consequently, before the development and commercialization of an AAP through carriers, monitoring the volatilization and migration profile of the applied antimicrobial is crucial [15,31,54].

Despite the exceptional properties of natural bioactive components, they are unstable, being prone to oxidation, which is increased by exposure to light, and is also affected by heat, pH, and moisture content. As such, the food industry is interested in stabilization technologies for the preservation of the functional properties of bioactive materials during processing and storage, in modifying the physical properties of bioactive compounds to allow easier handling, in designing the release at the desired time and to specific targets, and in the increase of their bioavailability [18,51].

One way of working with these compounds is by the use of encapsulation. Encapsulation is a process in which small particles are enclosed in solid carriers to increase their protection, reduce evaporation, promote easier handling, and control their release during storage and application. EO exist in liquid form at room temperature. Therefore, the first step of encapsulation techniques consists of emulsifying or dispersing EOs in an aqueous solution. EOs are entrapped in nanocapsules or nanospheres. The difference between them arises from their internal structure and morphology: nanocapsules are hollow internally possessing a reservoir system, while nanospheres are dense matrix systems [15,55,56].

The size and structure of forming nanoparticles depend on the wall materials and the physicochemical properties of the core used. Natural and synthetic polymers are utilized as wall materials. The nanocapsules may guarantee excellent protection of EOs, but in general, they do not affect antimicrobial activity. Nanoencapsulation is the coating of various substances within another material at sizes in the nanoscale. This system can increase the passive cellular absorption mechanisms, to reduce mass transfer resistances and to increase antimicrobial activity due to its subcellular size [22,46].

The encapsulated material needs a wall material that has different chemical structures and physicochemical properties that influence the efficiency of the encapsulation process. As such, their correct selection is an essential step due to their direct effect on the stability, the efficiency of core material retention, and shelf life. The wall material must have suitable rheological properties at high concentrations and the ability to emulsify the active material, stabilize the produced emulsions, and keep the core material within its structure during processing or storage [18,48,57].

The polymeric materials are shown as candidates for use as wall materials. Usually, these materials are produced from petroleum sources and do not have a biodegradable character. However, the concern with the pollution associated with the disposal of these materials due to the high time of permanence in the environment brought concern about the impacts of its use. As a result, research involving the production of biodegradable polymers has been the focus of research and has shown itself as a candidate for application in the food industry[56,58].

Biodegradable polymers are the materials that undergo degradation that result in inorganic substances through the process of mineralization in aerobic as well as anaerobic conditions by the enzymatic action of microorganisms. One significant differentiation that has to be made is about the biopolymers which are synthesized based on a renewable substrate, while there are synthetic biodegradable polymers [22,52,58].

The interest in those materials is that they can mimic the properties of conventional polymers like Polyethylene (PE), Polypropylene (PP), Polyethylene Terephthalate (PET), among others. Thus, their application in the form of packaging materials is an exciting innovation that can help in reducing the environmental impact of plastic production and can have a high-value generation [54].

Techniques of encapsulation

The choice of nanocapsules preparation technique depends on the characteristics of the bioactive compound, such as hydrophilicity or lipophilicity, solubility, and stability, and the desired properties of the product, such as the particle size and bioavailability, among others [56].

Different methods can be used for the production of nanoparticles. Different classification can be used, but a general approach involves the use of a polymerization reaction or use of a preformed polymer [33].

Emulsion polymerization

This type of emulsion consists of oil or oil/polymer globules, dispersed in an aqueous phase. These structures formed are innovative because to encapsulate some additives that are an incompatible molecule. The control of sphere size and size distribution has several important implications in the release kinetics [16,59]. In this technique, the monomer is added in an aqueous solution containing a surfactant (polymerization medium) under vigorous mechanical stirring to polymerize at room temperature. During the polymerization process, stabilizers and surfactants are added in the formulation, and the type and concentration of these constituents are responsible for particle size and molecular mass of nanocapsules obtained; the solvents are used to disperse the oil in the aqueous phase and serve as a vehicle for monomers [60]. The compound of interest is incorporated either by solubilization in the polymerization medium or by adsorption after completed polymerization. After the concentration under reduced pressure at room temperature, the suspension has to be purified to remove stabilizers and surfactants by ultracentrifugation and, then, the particles are suspended in a surfactant-free medium [22,61]. In Figure 1 is illustrated the methodology of the emulsion polymerization process.

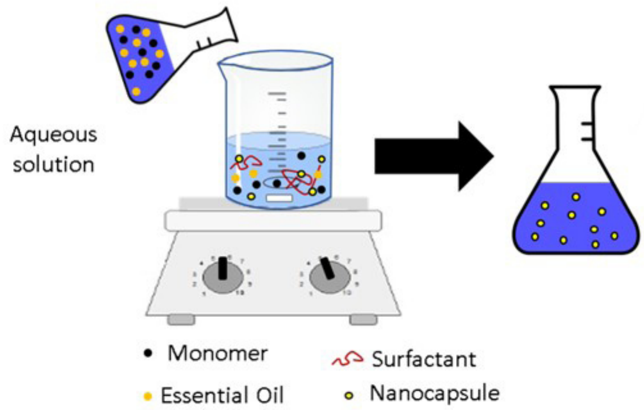

Figure 1: Schematic representation of nanocapsules synthesis by emulsion polymerization technique.

The monomer should present a fast polymerization rate between the organic phase and the aqueous phase in order to produce nanocapsules. As an example, poly(alkyl cyanoacrylate) presents a fast polymerization rate, and it is biodegradable and biocompatible. Furthermore, polymerization must be carried out in acidic medium and further pH increase to produce high molecular mass, as well as stable nanocapsules [62,63].

The main advantage of this nanoencapsulation technique is the formation of the wall in contours of emulsion since the polymer is formed in situ; however, undesirable reactions between monomers and the compounds of interest may occur during the polymerization process. The possible presence of residual monomers or undesirable products formed after polymerization can be toxic and limit the potential use of these kinds of nanocapsules. The main applications of polymerization of monomers technique in bioactive compounds are associated only with proteins and peptides [22].

Preformed polymers

In general, in the preformed polymer technique, the aqueous insoluble polymer is dispersed in an aqueous phase in the presence of stabilizers, surfactants, and oil. Emulsification/solvent evaporation, interfacial deposition, emulsification/ solvent diffusion, and salting-out are typical examples of preformed polymer techniques [33,61,74].

Emulsification with solvent evaporation

This is the first technique employed to prepare nanocapsules by preformed polymer was using solvent evaporation aiming to synthesize more stable and resistant nanocapsules to settling or sedimentation, and it has been widely used to synthesize nanocapsules in the current literature on techniques using dispersed preformed polymers [64,65].

Emulsification with solvent evaporation involves two steps. First, the polymer solution is emulsified in an aqueous phase. Then the solvent is evaporated which leads do precipitation of the polymer in nanospheres. For the preparation of the emulsion system, dispersion agent and high-energy homogenizer are required and play an essential role in the size of the nanospheres produced. In these systems, oil/water emulsion is interesting because it simplifies the processes and has an advantage for industrial application. However, it can only be applied to fat-soluble compounds, limiting the application for other compounds [33,66]. In Figure 2, it is possible to illustrate an example of methodology to do emulsification with solvent evaporation.

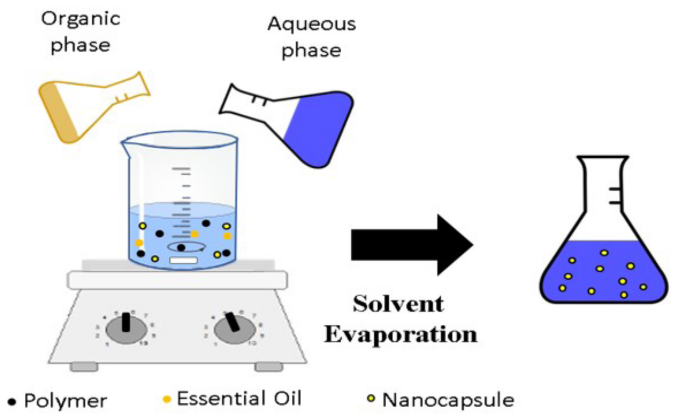

Figure 2: Schematic representation of nanocapsules preparation by solvent evaporation technique.

Emulsification with solvent diffusion

The process is based on organic solvents and where the polymer used to prepare the emulsion needs to be partially soluble in water. First, the polymer is dissolved in a partially water-soluble solvent and saturated with water to ensure the initial thermodynamic equilibrium of both liquids. By adding an excess of water to the system, the diffusion of the solvent occurs and by emulsification the solution, leading to the formation of nanospheres or nanocapsules, depending on the oil-to-polymer ratio. With evaporation or filtration, the solvent is removed from the system [67,68].

The advantages include high encapsulation efficiencies, no need for homogenization, high batch-to-batch reproducibility, ease of scale-up, simplicity, and narrow size distribution. The drawbacks are the volumes of water and the possible leakage of drug that can reduce the efficiency of the processes [22]. In Figure 3, it is possible to illustrate an example of methodology to do emulsification with solvent diffusion.

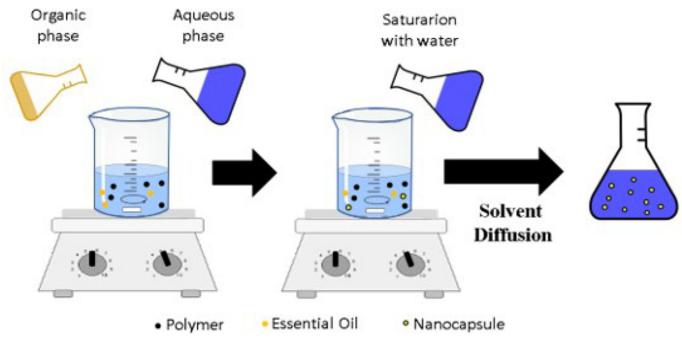

Figure 3: Schematic representation of nanocapsules preparation by solvent diffusion technique.

Salting out

This method derives from the solvent diffusion method and is based on the separation of water-miscible solvent from aqueous solution by the salting-out effect that consists of the use of electrolytes for polymer desolvation. The polymer and additive (for example a drug) initially are dissolved in a solvent, been subsequently emulsified into an aqueous gel containing a salt. By diluting the emulsion with a sufficient volume of water or aqueous solution, the salting-out take place, and the diffusion of the organic solvent happens, inducing the formation of nanospheres. The selection of the salting-out agent is crucial because it participates in an essential role for the encapsulation efficiency. Cross-flow filtration can be used to eliminate the solvent and the salting-out agent [17]. In Figure 4, it is possible to illustrate an example of methodology to do Salting out method.

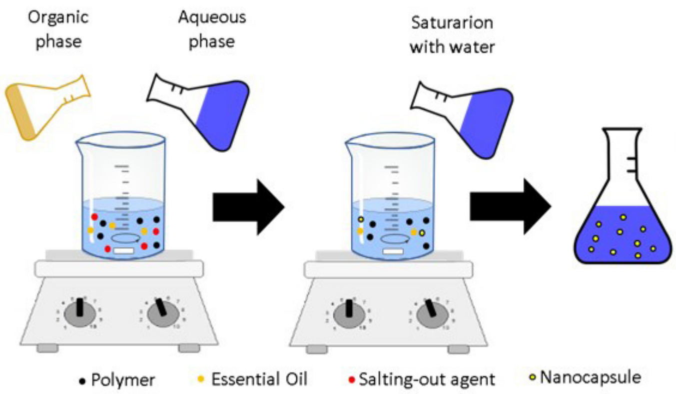

Figure 4: Schematic representation of nanocapsules preparation by salting-out technique.

Interfacial deposition

The most used technique to prepare nanocapsules with bioactive compounds is the interfacial deposition, also named nanoprecipitation, and it is based on the deposition of a polymer after displacement of a semi-polar solvent (miscible in water) from a lipophilic solution [22].

In deposition interfacial of preformed polymer technique, the organic phase containing the polymer and the compound of interest is injected in an aqueous phase containing water and a tensioactive compound under magnetic stirring. After that, the polymer deposition occurs immediately on the interface between the water and the organic solvent, induced by the rapid diffusion of the solvent, leading the instantaneous formation of nanocapsules [69,70].

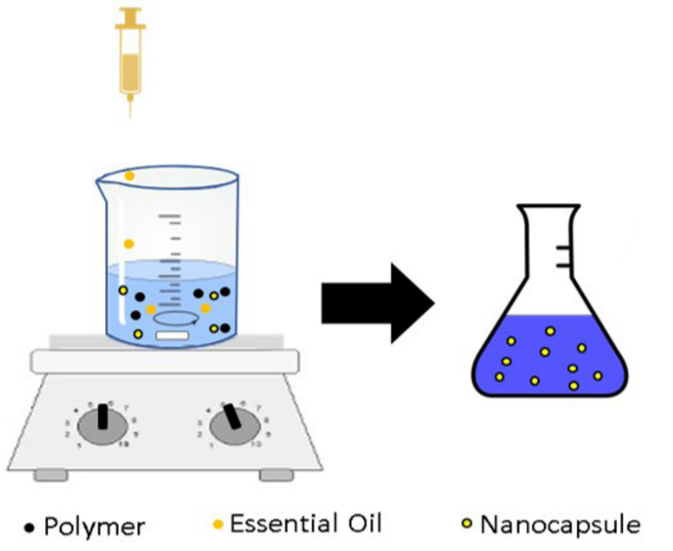

Figure 5: Schematic representation of nanocapsules preparation by interface deposition technique.

This process can also take place by forcing the polymer solution through a nozzle. In that way, the method can be used on an industrial scale to produce biopolymer particles rapidly. On a laboratory scale, the biopolymer solution is loaded into a syringe and extruded through a needle into the water solution [33,71]. Figure 5 illustrates the methodology involved in the interfacial deposition methodology. The size of the particles obtained is dependent on the diameter of the needle, the flow rate and viscosity of the solution, and the tensioative used [72].

Recent observations

In a recent work produced in our laboratory, we propose the use of Poly (Butylene Adipate-co-Terephthalate) (PBAT), which is among the biodegradable polymers with the highest commercial growth, and we were able to produce nanocapsules from it. PBAT has a synthetic origin, and has properties similar to those of low-density polyethylene, such as ductility and flexibility, but stands out in terms of biodegradability and biocompatibility [73]. The PBAT is a linear random copolyester consisting of two types of dimers: the first has a rigid region composed of an ester repeat unit consisting of 1,4-butanediol and terephthalic acid monomers, and the second has a flexible region consisting of 1,4-butanediol and adipic acid monomers [75,76].

In our work, we used the extrusion process considering the interfacial deposition system. We worked with the EO of linalool, and it was possible to produce nanocapsules. In order to stabilize the production of nanocapsules, different conditions were considered, such as polymer concentration, solubilization time, use of surfactant (Tween-80), stirring time, liquid Insertion rate in the solution and droplet size.

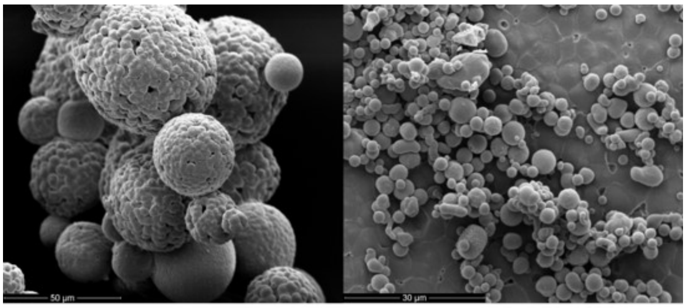

Figure 6: In the left side, we have an illustration of the nanospheres with aggregation behavior in microspheres. In the right, we observed a greater stabilization of the structures due to the control of the experimental parameters of production.

We obtained nanospheres that showed some tendency to agglomerate in larger structures like presented in Figure 6 left, but we also were capable of obtaining isolated structures by controlling the parameters of production, Figure 6 right. We also see that by the control of the parameters, we can control the size of particles produced, which can provide industrial application since this method is straightforward and can be easily scalable. This result is exciting because it expands the application of different biodegradable polymers, into systems that are arising with the nanotechnology production.

Conclusion

Nanotechnology is a promising strategy to improve the application of bioactive compounds in the food industry. Aiming to produce packaging that contains antimicrobial compounds that can limit microbial populations, providing high quality and safety of food, and extending its shelf life, the use of nanoparticles is growing. Nevertheless, the risk for human health has driven the search for new food, and the use of natural products, like the essential oils, can guarantee these characteristics [77-79].

We have shown that different methodologies can be applied aiming at encapsulating these compounds in order to use them to packaging systems. In this scenario, biodegradable polymers present great perspectives of use, and it is expected to have important applications in the near future. Of course, the identification of new polymers that can produce nanoparticles with improved functional attributes is a current topic of research.

In order to take full advantage of these technologies, we still need to expand our knowledge towards the action mechanism of interaction that these antimicrobial compounds possess, and also, we need reasonable control of the release kinetics aiming at the development of products economically feasible for large-scale production.

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