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Nano- and Micro-Particles by Nanoprecipitation: Possible Application in the Food and Agricultural Industries

Carlos Gregorio Bareras-Urbina[1], Benjamín Ramírez-Wong[1], Guadalupe Amanda López-Ahumada[1], Silvia Elena Burruel-Ibarra[2], Oliviert Martínez-Cruz[1], José Agustín Tapia-Hernández[1], and Francisco Rodríguez Félix[1]

[1]*Departamento de Investigación y Posgrado en Alimentos, Universidad de Sonora, Hermosillo, Sonora, México*

[2]*Departmento de Investigación en Polímeros y Materiales, Universidad de Sonora, Hermosillo, Sonora, México*

The nanoprecipitation method has been investigated to obtain particles in a nanometric and micrometric scale. The particles obtained by this method have been applied in recent years in the food and agricultural industries. Variations of the method as flash nanoprecipitation and two-step nanoprecipitation are explained in this article, besides its relation with the ouzo effect. This work presents an overview of the nanoprecipitation method, its advantages, and the potential applications in the food and agricultural industries for improving the quality of food products.

Keywords: Nanoparticles, Microparticles, Nanoprecipitation, Agri-food industries.

INTRODUCTION

The application of new technologies in the food industry has been highly researched in the last few decades to obtain benefits in terms of safety, health, and products with high quality.[1] Nanotechnology is a science that offers favorable conditions and qualities for applications in this specific industry and other industries, providing a good alternative for control and food production.[2] The nanoprecipitation method is a good option for the development of nanoparticles as nanospheres, having several advantages—the procedure takes only a short time, only a small amount of raw material is required, and it consumes a low amount of energy.[3–5] Nanoprecipitation was first described by Fessi et al.[6] in 1989. Over the years, several important method variations have resulted as flash nanoprecipitation (FNP) and two-step nanoprecipitation.[7,8] In recent years, the increasing world population requires an increasing quantity and quality of foodstuffs. Accordingly, the exploitation of agricultural fields and the application of fertilizers and pesticides

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Address correspondence to Dr. Francisco Rodríguez Félix, Departamento de Investigación y Posgrado en Alimentos, Universidad de Sonora, Blvd. Luis Encinas y Rosales S/N, Col. Centro, Hermosillo, Sonora, CP 83000, México. E-mail: rodriguez_felix_fco@hotmail.com
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have increased, resulting in soil depletion and environmental contamination. For these reasons, the implementation of nanomaterials developed from natural and biodegradable sources has been important as a viable option for improving conditions and quality of food from agricultural fields. Also, the nanoscale systems are an alternative option for encapsulation of fertilizers, nutrients, and bactericidal compounds.[9,10] In this review, we explore the remarkable importance of the nanoprecipitation method for developing novel nanoparticles for application within the food industry and agricultural fields.

NANOPARTICLES AND MICROPARTICLES

Nanoparticles and microparticles have always been present as part of all materials on this planet. Nanoparticles are defined as particles that are smaller than 1000 nm in diameter, and variation in size will depend on the obtention method and raw material.[11–14] Currently, the literature has become more stringent, attesting that nanoparticles should not exceed 200 nm.[15]

The size of nanoparticles could affect physicochemical stability, biological activity, and especially the characteristics of encapsulation and release of active compounds.[16] Moreover, nanoparticles are defined as sub-micro sized solids that act as carriers of drugs, components of electrical appliances, construction materials, and as metal bound compounds, catalysts, etc., and they can be made from biodegradable or nonbiodegradable materials.[17,18] Thereby, "nanoparticle" is a general term and may include nanospheres and nanocapsules, among others.[19]

During nanoparticle formation, the highly polar particles tend to be solubilized in water, while the particles with nonpolar surfaces tend to interact with other nonpolar particles and form aggregates in an aqueous medium. Whereby, it can be ascertained that nanoparticles can have a positive, negative, or neutral charge, depending on the materials used to develop them and their environment.[16]

Nanomaterials can be classified as nanotubes, nanofibers, nanowhiskers, nanosheets, and nanospheres, where nanotubes and nanofibers have a diameter ratio of 3:1. Nanofibers are solid structures, while nanotubes are hollowed structures, and nanowhiskers are very fine nanofibers, ranging up to 20 nm in cross-section, and length can reach several micrometers. Nanosheets only have a dimension of the material in nanoscale.[20] Nanospheres contain a structural matrix, and the drugs can be linked to the surface by groups that favor binding of compounds, such as COOH, NH_2, OH, etc.[21] Moreover, they may be encapsulated within the particle, which can be defined as a vesicular drug system bordering a central cavity (core) and coated by a polymeric membrane (shell).[22–32]

Furthermore, microparticles are defined as structures with dimensions less than 1000 μm and greater than 1 μm, which can also be obtained from biodegradable and non-biodegradable materials.[33] A variety of materials can be used to prepare nanoparticles and microparticles using different methods, e.g., nanoprecipitation, emulsion diffusion, double emulsion, etc.[34–40] The polymers most commonly used for preparing microparticles are polylactic acid (PLA), poly (D, L-lactic-co-glycolic acid, PLGA), polystyrene, and polyacrylamide.[41–44] Also, some inorganic materials for producing microspheres can be used as zeolites, silicas, and ceramics.[45]

Nanoparticles have been booming in recent years because of their advantage as drug carriers in treating different diseases. Since this was the first application in the pharmaceutical industry, they are considered very important in biomedical and pharmaceutical research,[46] and interest has been increasing through developing nanoparticles that have been used to target cancer tumors.[47]

Nanoparticles have also been developed by using not only synthetic materials but also natural sources, such as proteins, gelatin, gums, chitosan, hyaluronic acid, some polysaccharides, cellulose, agarose, dextran, and starch.[48–51] Materials based on nanoparticles and microparticles are now used in the food industry because of their various applications and possible uses they may have.

APPLICATIONS OF NANOPARTICLES AND MICROPARTICLES IN THE FOOD INDUSTRY

Agriculture has always been a common practice and is a primary source of food. Better agronomic practices are always required to meet the needs of the world population.[52] Using land to produce agricultural products results in soil degradation and pollution of the product and the environment by fertilizers and pesticides, causing an alteration of the nitrogen and phosphorus cycles.

The issues that have arisen while developing agricultural products demanded by global requirements have resulted in implementing new technologies to generate an advantage and get good land productivity.[52] Using materials at the nanometric and micrometric scale is a technology that has been studied extensively in recent years, which can help implement alternative fertilization in agriculture to improve yields and product quality.[53,54] It is convenient, however, to use nanoparticles because of the greater area of contact (reaction) when compared with the microparticles.[55,56] Nanomaterials are being investigated for their wide applications worldwide and already have several functions in the areas of food safety and sanitation.[57] In this sense, Kayaci et al.[58] generated nanofibers from a complex of cyclodextrin and encapsulated eugenol. The results showed that these nanofibers have thermal stability and release eugenol, which is a natural compound extracted from plants and used as a fragrance, flavoring, and natural preservative in the food industry because of its antibacterial and antifungal properties and antioxidant activity.[58] On the other hand, Antiochia et al.[59] developed single-walled carbon nanotube paste, in which they immobilized two enzymes, invertase, and fructose dehydrogenase, with application as biosensors for the detection of sucrose and fructose in some commercial fruit juices. As a result, they had a low detection limit, high sensitivity, high reproducibility, and fast response compared with a commercial spectrophotometric enzymatic kit. Finally, they concluded that development and improvement of such biosensors are important for application in food quality and sanitary control.[59] Moreover, Zhang et al.[60] developed nanorods as sanity indicators for perishable products. They used the reaction of epitaxial overgrowth of Ag-Au shell nanorods to reveal product quality based on an indicator in the package that measures product temperature, which is directly related to the organisms that might be developed. They concluded that this method can greatly affect the food, pharmaceutical, and cosmetic industries.[60] For these applications, using nanomaterials in the food and agriculture industries is not discarded, and both could have been used to combat bacterial contamination as slow and controlled release systems.[61–63]

NANOPRECIPITATION

Nanoprecipitation, also known as antisolvent precipitation, desolvation, solvent displacement, and solvent shifting,[64] was described by Fessi et al.[6] in 1989 and is a method for developing nanoparticles and microparticles. This technique has several advantages compared with other methods, among which stand out the facility to develop nanoparticlesin in one step, not much expense is involved, low electric power is required, and it is fast.[3,4] On the other hand, emulsion-diffusion methods, emulsion-evaporation, and precipitation by salting-out need a precursor emulsion, while nanoprecipitation does not.[65]

The nanoprecipitation technique can also usually produce nanoparticles in the range of 50 to 300 nm, which is an advantage because the smaller particle size generates greater contact area. This characteristic is important for its application in adsorption and desorption systems.[66–68] The size of the nanoparticles depends, however, on the raw material, the concentration of the polymer used, the miscibility of the solvent, the type of agitation, and in general terms, the applied methodology.-[66] Furthermore, this method according Bilati et al.[3] should not use an excessive amount of or prominent stirring, involve high temperatures, and not to create oil-water interfaces.[69] A few years later, Lucas et al.[70] reported that the use of surfactant in the process is not necessary, providing an advantage for obtaining surfactant-free particles.[70] This method can develop particles of about 170 nm, with this size increasing the opportunities of applications and efficiency.

Development of Nanoparticles through Simple Nanoprecipitation

Developing nanoparticles is explained by nucleation theory (Fig. 1), which involves several steps: particle nucleation, growth, and aggregation.[71] Nucleation occurs when the concentration of polymer reaches the critical limit of saturation, i.e., when the breaking of the interface between the polymer and solvent is carried out through the addition of the aqueous phase. Growth occurs with a release of energy, the particles being added to the core by growth through condensation or coagulation. During the aggregation, a release of energy is also present. In this step, it is important to maintain control by some type of stir, which will help homogenize the nanoparticles and achieve uniformity. The temperature also directly affects the rate aggregation. Furthermore, polymer and stabilizer concentrations must be controlled because high concentrations of both can induce excessive aggregation.[72–76]

The method described by Fessi et al.[6] has been modified several times. It creates an organic phase and an aqueous phase. The organic phase contains a solvent that must be miscible or partially miscible in the aqueous phase; the polymer (synthetic or natural), which will be used to create the polymer matrix of the nanoparticles, must be soluble in the solvent and therefore insoluble in the aqueous phase. The active ingredient used must be soluble in the solvent, and it must have some interaction with the polymeric matrix to be formed, and the aqueous phase will be constituted solely of water and a surfactant (stabilizer, tensoactive). During the process, an organic phase is add by dropwise to the aqueous phase under moderate magnetic stirring.[77,78] Another option is to quickly add the aqueous phase to the organic phase, inducing an instant precipitation, mainly in nanoscale.[79]

The basis of this technique involves an organic phase (solvent mix) being added into the aqueous phase. The solvent phase tends to have an effect of diffusion, while the polymer automatically tends

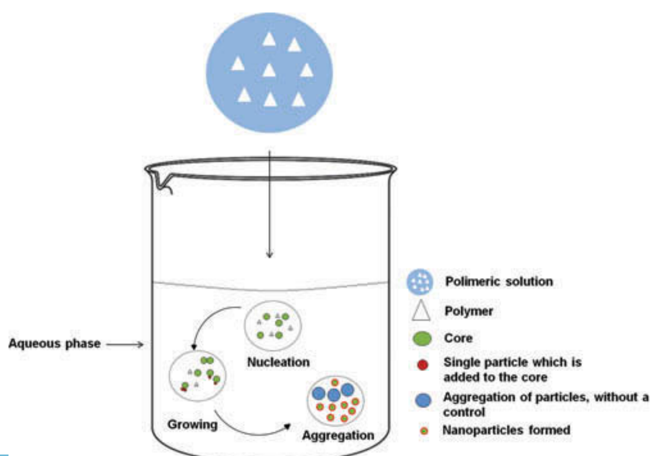

FIGURE 1 Nucleation, growing, and aggregation during the formation of nanoparticles.

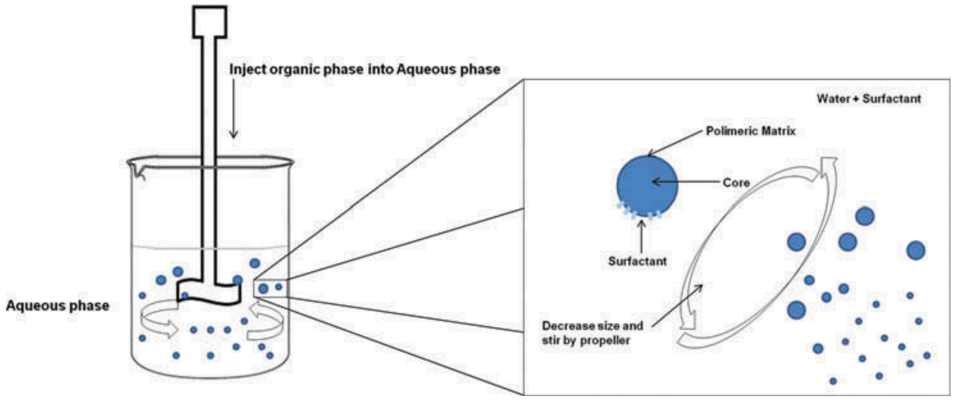

FIGURE 2 Nanoprecipitation technique with stirrer by propeller.

to collapse forming nanoparticles or microparticles that can encapsulate an active ingredient that is contained in the organic phase (Fig. 2). Some important factors to be considered are the characteristics of the raw material, the solvent that has to dissolve the active ingredient and the polymer, and also the effect of diffusion in the aqueous phase must be present. The polymer must be insoluble in the aqueous phase with the objective of showing aggregation.[80–91] The precipitation of the polymer is given by the increase of diffusion of the solvent, adding a larger amount of non-solvent, or by evaporating the solvent.[21] The characteristics of the nanoparticles formed by the nanoprecipitation technique will vary, depending on the modifications to be made to the organic phase and aqueous phase as well as physical variables to be applied to the technique.[92–95] Among the variations involved in this method, we can mention the following: FNP, two-step nanoprecipitation, and the ouzo effect.

FNP

FNP was developed at Princeton University and is a modification of a controlled precipitation that produces small, highly reproducible particles, with a higher load of hydrophobic compounds.[96] Basically, the precipitation of an active compound (organic phase) in a non-solvent phase specifically is mixed in separately or beside the active compound and the polymer in a suitable solvent for both. At the same time, the organic phase and non-solvent phase are added into a mixing chamber. A reaction can be performed in a micro reactor, which carries out the formation of nanoparticles.[73] Moreover, the mix of the polymer with the active compound and the solvent can be added to a central cavity or base. At the same time, the non-solvent phase is introduced, which creates an instantaneous diffusion of the solvent into the non-solvent so that the polymer tends to precipitate and form nanoparticles instantaneously (Fig. 3). This method has the same technical principle as normal nanoprecipitation, but the advantage is that the nanoparticles develop instantly, i.e., within milliseconds or seconds, and the distribution of particle size is better than the original nanoprecipitation. Nanoparticles in the range of 100 to 300 nm are produced compared with FNP, with particles ranging in size from 50 to 150 nm.[97]

Two-Step Nanoprecipitation

The two-step nanoprecipitation method was designed as a solution to the problem of solvent selection that could dissolve the polymer and the active ingredient. Likewise, this solvent will not

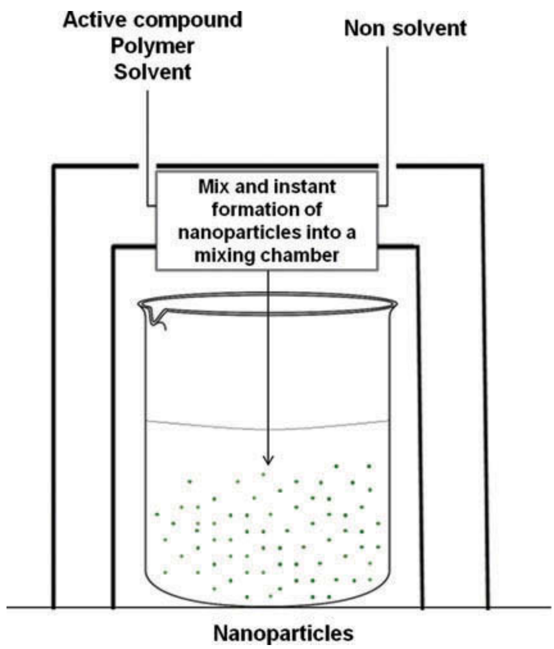

FIGURE 3 Flash nanoprecipitation technique.

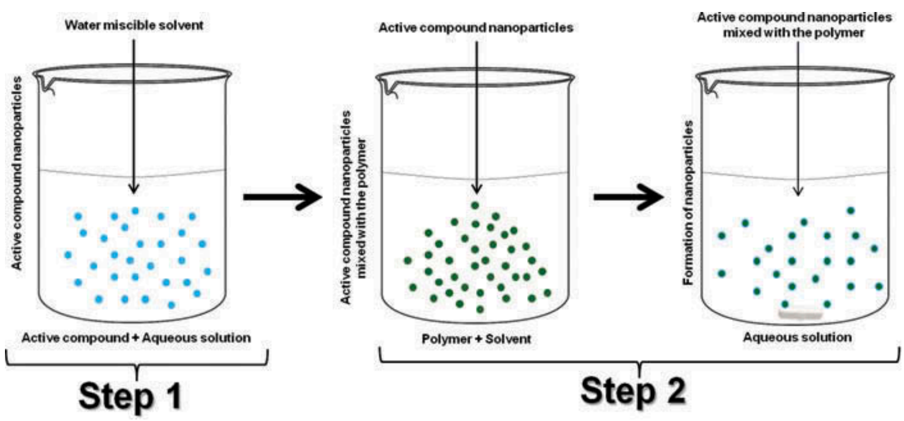

FIGURE 4 Formation of nanoparticles by the two-step nanoprecipitation method with stir bar.

affect polymer structure and thus the functionality.[8] This technique consists of two steps: first to induce nanoprecipitation of the active ingredient by action of the solvent, generating a suspension. Then a solvent is used to dissolve the polymer and have a second nanoprecipitation that encapsulates the active ingredient (Fig. 4).[98]

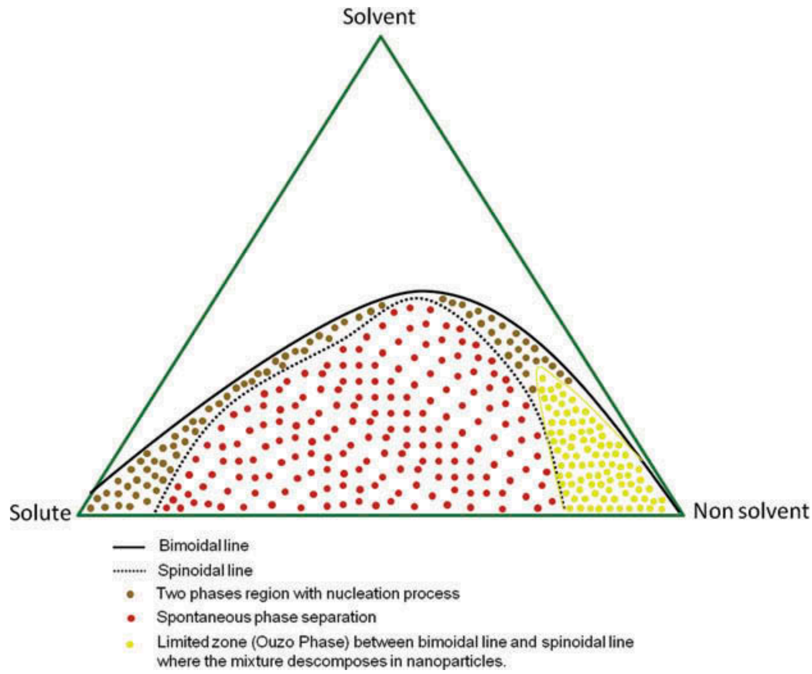

FIGURE 5 Example of the development of nanoparticles by the ouzo effect in a ternary diagram.

Ouzo Effect

The ouzo effect is a method that can create emulsions of various solutes, such as polymers, lipids, or pharmaceutical compounds, which are added to an aqueous phase to form a simple and spontaneous emulsification. This method allows preparation of microparticles in the form of drops in either a solid or liquid state. Formation of nanoparticles is also possible by a simple modification of the process, either by changing the solute used in the aqueous phase or by combining various solutes.[99]

The ouzo effect is also known as spontaneous emulsification, solvent shifting, coacervation with addition of a non-solvent, solvent displacement process, or nanoprecipitation (surfactant free). It is an emulsification process that requires low energy and no surfactant.[70,91,99] The effect can be explained as the quick coupling of the hydrophobic compound in the "ouzo" or metastable region between the spinoidal and binoidal limits shown in a ternary phase diagram. When both the miscibility and stability curves reach their limits, the curves are taken to an oversaturation of the hydrophobic compound which leads to the nucleation process and the end product particle formation (Fig. 5).[66]

POSSIBLE APPLICATIONS OF THE NANOPRECIPITATION METHOD IN AGRICULTURE AND THE FOOD INDUSTRY

The nanoprecipitation technique has been useful in several fields. Nanoparticles have been made from starch and protein because of their physicochemical properties.[100,101] Developing nanoparticles using organic raw material as food, in this case proteins, is a great advantage because these same nanoparticles can be harnessed and applied to the same foods.[53] Protein nanoparticles can be combined with chemical or organic compounds for food application.

Gliadins are wheat gluten proteins that have been used for the production of nanoparticles by various methods, one of which is nanoprecipitation, but implementation has only occurred in the field of pharmacology, although they could also be applied in the food and agriculture industry.[102–107] Development of nanoparticles from natural raw materials is favorable for improving food from agricultural fields and also to avoid environmental damage. The nanoprecipitation method has also been used to develop nanoparticles with possible applications in the food industry.

Noronha et al.[63] developed poly ε-caprolactone (PCL) nanocapsules loaded with α-tocopherol. PCL is a polyester that is nontoxic, biodegradable, and biocompatible and has been used to release drugs. The nanoprecipitation method was used to prepare and load nanoparticles, and these authors concluded that the method is suitable for developing loaded PCL nanocapsules of α-tocopherol. They have a potential application as food antioxidants and preservatives in food packaging.[63] Later, Noronha et al.[108] developed biodegradable methylcellulose films with α-tocopherol nanocapsules incorporated. Methylcellulose is a polymer used in food packaging. The nanocapsules were developed through the nanoprecipitation technique, obtaining successful encapsulation and films with antioxidant potential because of α-tocopherol nanocapsules. Furthermore, they found an effect of protection versus ultraviolet (UV) and visible light to avoid photooxidation and concluded that the films with α-tocopherol could be beneficial for food preservation.[108]

CONCLUSIONS

Nanoprecipitation is a method that compared with emulsion-diffusion techniques, double emulsification, and others has several advantages. The process is easy, presenting a good result in terms of particle size and encapsulation. Furthermore, using natural polymers as proteins to develop nanomaterials or micromaterials has potential applications for the agri-food industries to improve the quality and yield of products. Implementing new technologies could be very beneficial for improving agricultural products during fertilization using materials in the nano and micro range.

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