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An Overview of the Preparation Methodologies for the Synthesis of Organic and Bioorganic Nanoparticles

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ABSTRACT

Since the development of nanotechnology in recent decades, there has been a notable increase in research on the synthesis and design of organic and bioorganic nanomaterials. These materials have many uses in sectors that impact our way of life and society, such as photonics, electronics, and biology. The discovery of new functions and the development of features are essential aims that cannot be achieved without a better grasp of the preparation processes that serve as the base for the construction of certain organic substances. In this context, this overview offers a fundamental summary of the methods employed for the production of nanoparticles, encompassing both organic and bioorganic techniques. The most often used techniques for organic nanomaterials can be categorized into two families: one-step and two-step processes. In this article, we will discuss some generic concepts of organic nanomaterials and provide descriptions of organic materials.

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1. INTRODUCTION

In the twenty-first century, nanotechnology emerged as a scientific accomplishment. This field encompasses several disciplines and deals with the synthesis, handling, and use of materials smaller than 100 nm. Many industries, including the environment, agriculture, food, biotechnology, biomedical, and pharmaceuticals, have found great use for nanoparticles. The potential applications of nanoparticles are vast, including their use in the wastewater treatment industry [1], observation of the environment [2], as a functional food additive[3], as well as antibacterial substances [4]. Nanoparticles (NPs) are increasingly used in biotechnology and microbiological applications due to their novel properties, which include their nature, biocompatibility, anti-inflammatory and antibacterial effects, effective delivery of drugs, bioactivity, bioavailability, cancer targeting, and bio-absorption. A nanoparticle is a matter particle with a size ranging from 1 to 100 nanometers (nm). Because of their small size and large surface area, nanoparticles usually display unique size-dependent properties. When a particle approaches the de Broglie wavelength, commonly known as the wavelength of light, the periodic boundary conditions of the crystalline particle are eliminated [5]. As a result, a great deal of the physical properties of nanoparticles are different from those of bulk materials, which opens up a variety of new applications for them [6]. According to Figure 1, there are two primary categories of nanoparticles: nanospheres and nanocapsules. Comparatively speaking, nanocapsules consist of an organic solid shell enclosing a liquid or empty core, while nanospheres are matrix particles with a solid mass throughout. Although they can have nonspherical geometries, nanospheres, and nanocapsules are typically spherical. The preparation techniques chosen will

determine the variety of nanoparticles that are produced [7].

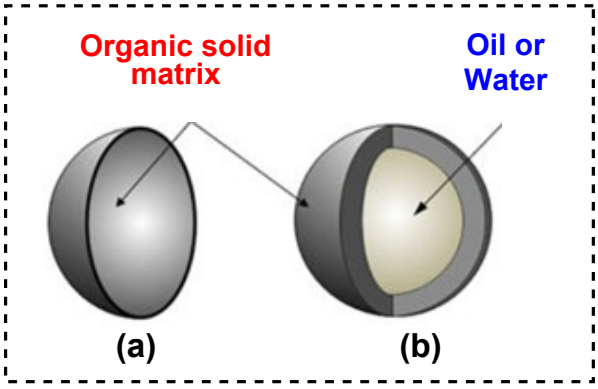

Figure 1: The two kinds of nanoparticles a) nanospheres, b) nanocapsules.

Organic nanoparticles are defined as solid particles with a diameter ranging from 10 nm to 1 µm that are made up of organic substances, mostly lipids or polymeric materials [8]. This review article focuses on the description of the preparation techniques utilized to create organic nanoparticles followed by the description of the fundamental concepts and mechanisms of nanoparticles and the parameters that control the particle formation and their properties.

2. Organic materials make particles

2.1 Polymer nanoparticles

The nanoparticles of polymeric materials are the most extensively researched organic substances in the literature [9-13]. There are two main groups of polymeric nanoparticles, even though they may be created for a vast range of uses. The first one has to do with nanoparticles that have been developed for pharmaceutical delivery or biological applications [14-17]. Here, the macromolecules must have the ability to degrade or be compatible with biological systems. Even though polymer chemistry has a lot of potential, there aren't many compounds that can be utilized to make drug-delivery nanocarriers. This is especially because of the stringent toxicity and biocompatibility standards and limitations that define in vivo application. The second group of polymeric particles includes conjugated nanoparticles of polymeric material having optoelectronic or electrical characteristics [10, 18]. The intrinsic conductivity of these conjugated polymers, such as polyaniline, polypyrrole, and polyacetylene, has been extensively examined [19-25]. In contrast, the electrooptical and photoluminescence behaviors of polythiophenes, polyfluorenes, poly(p-phenylenevinylene), and poly(p phenyleneethynylene) derivatives have received more attention [26-33].

2.2 Solid lipid nanoparticles

The lipid matrices that make up solid lipid nanoparticles (SLNs) are typically generated from glycerol esters of fatty acids [34-36]. To guarantee solidification at physiological temperature, the lipid molecule has a melting point greater than 37 oC. As a good substitute for polymeric nanoparticles, especially in the parenteral route, SLNs are regarded as potential drug delivery methods because of their excellent biocompatibility, low toxicity, and great stability (several years). However because most medications are poorly soluble in lipids, this kind of particle has its limitations [37]. Research on using lipid-drug conjugates or nanostructured lipid matrices to boost encapsulation rates is still ongoing [38, 39].

3 Nanoparticle preparation methods

There are two primary techniques for creating organic and bioorganic nanoparticles [9, 11, 12]. The first method relies on a two-step technique that usually entails emulsifying a mixture to produce nanodroplets of a specific size that already include solubilized organic molecules (polymer, monomer, and lipid). Their high- or low-energy stirring techniques are not the same as the emulsification strategies described in the literature. The tiny particles are created in the second stage of the process using a variety of processes, which include polymerization, gelation, and precipitation. The second approach is carrying out one-step procedures that enable the creation of nanoparticles without the requirement for emulsification. Usually, the techniques rely on the organic molecules in solution precipitating by several different mechanisms, including the formation of polyelectrolyte complexes, solvent displacement-induced nanoprecipitation, and ionic gelation-induced self-assembly processes. Some alternative methods based on spray-drying strategies have also been reported recently [40, 41], supercritical fluid technologies [9, 42, 43], or piezoelectrical ways [44].

Two-step procedures based on emulsifying

Emulsion and emulsifying techniques

The primary definition of an emulsion is a mixture of two or more liquids that are wholly or partially immiscible, formed with or without the use of a surface-active agent (Figure 2). However, more complicated systems such as O/O (oil in oil) or several emulsions of various types (W/O/W, O/W/O, W/O/O) can be formed. In general, depending on the dispersed phase and distribution mediums, O/W (oil in water) or W/O (water in oil) backward fluid emulsion can develop.

The resulting emulsion can be divided into three primary groups based on the sizes of the droplets: a microemulsion type, which has droplet diameters between 10 and 100 nm and is thermodynamically stable; a

miniemulsion or macroemulsion system, which is thermodynamically unstable and has drop sizes between 100 nm and 1 µm and up to 1 µm, respectively [45-47]. Because of technological developments in emulsifying devices and environmental constraints, methodologies for producing suitable emulsions with nano-scaled droplets to produce organic nanoparticles have changed dramatically over the last decade. This development has been credited to the growth of low-energy stirring pathways. Nanodroplets can be generated in two different ways: by high-energy and low-energy emulsification techniques, respectively, yielding nanoparticles.

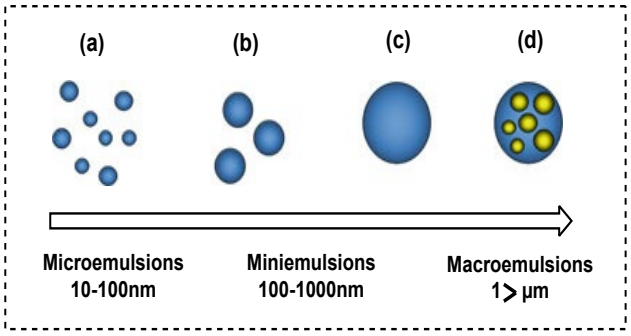

Figure 2: Different forms of emulsions. a) Microemulsion, b) nanoemulsion, c) simple macroemulsion, d) multiple emulsions

Low-energy emulsification methods

Two categories of low-energy emulsification strategies have been identified in the literature for the generation of nanoemulsions. First up is a process known as spontaneous emulsification [45, 46, 48-50] generated by the fast dispersion comprising oily stage dissolution of a water-soluble solvent followed by the mixing of the two phases and the watery stage. This process is presented as a feasible alternative to high-energy procedures and has been characterized as a solvent movement approach in various studies [51-56] (also known as the "Ouzo effect"), wherein an organic solvent, usually ethanol or acetone, swiftly diffuses from the oily phase into the aqueous phase to form a nano-emulsion. This allows for the production of both conventional O/W and inversion W/O emulsions. Interfacial turbulence associated with the surface tension differential created by solute diffusion between two phases is the source of the spontaneous emulsification process [49]. The interfacial corrugations that result from a Marangoni effect that causes extreme interfacial fluctuations are thought to be the source of drops. When surfactants are present, changes in the interfacial amphiphile's concentration led to localized supersaturation of the surfactant close to the interface, which initiates the formation and proliferation of droplets [57-59]. A straightforward ternary water/alcohol/oil system may be used to explore the fundamental process at play. This can be done by determining a phase diagram, which is necessary to target the spontaneous emulsification region and define the diffusion path [49]. Spontaneous emulsification may also be achieved at constant temperature by applying the so-called emulsion inversion point technique (EIP). The process creates kinetically stable nanoemulsions by gradually diluting liquid crystals or microemulsions with water or oil [60-67].

The phase inversion temperature (PIT) method is a low-energy emulsification technology that falls under the third category [68, 69]. The key advantages of creating tiny emulsions are a reasonably low surfactant concentration (typically less than 5 mass %), lesser toxicology due to no organic solution being needed, and relatively simple management. This renders the process appropriate for biotechnological uses (nanotechnology in medicine, drug development, and cosmetics) since the substance to be encapsulated will not decay. This flexible technique takes advantage of the ability of poly(ethylene oxide) (PEO) surfactants to change their attraction for both water and oil in response to temperature to create an emulsion's "changing states the reverse." As the temperature rises, the PEO blocks often dry, causing surfactants to behave as more lipophilic allies and less amphiphilic allies. As a result, an emulsion with an O/W ratio created at Lower temperature transforms into a W/O molecule as the temperature goes up. Similarly, at temperatures where the surfactant is present and has an equivalent attraction for both indistinguishable phases due to ultralow surface tension and curvature, bi-continuous small emulsion nanomaterials are formed in the transitional region. Therefore, the PIT approach's concept is to quickly cool down or dilute these structures, which are maintained at the PIT temperature, in order to suddenly disintegrate them and produce kinetically stable nano-emulsions [70-74].

High-energy emulsification methods

The majority of nanoemulsion preparation techniques rely on mechanical procedures associated with high-energy stirring methods. The most often used equipment in this sector is a rotor-stator apparatus, which breaks pre-emulsion droplets into smaller, uniformly sized ones by applying shear stress to cause deformation (Figure 3). The applied stress is the primary determinant of the ultimate diameter of the daughter droplets, with the viscosity ratio between the dispersed and continuous phases having a minor influence [75-79]. Another method for nanoemulsification that is often utilized in the literature is sonication [80], furthermore for the synthesis of polymer or lipid nanoparticles [81, 82].

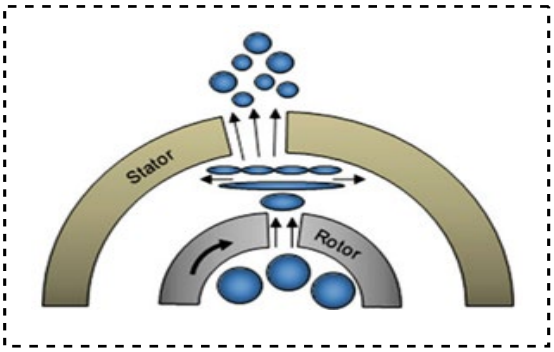

Figure 3: Diagram illustrating the emulsification principle using a rotor-stator apparatus

Preparation of nanoparticles from emulsion

The following techniques are employed to create nano-organic particles from emulsions: i) Precipitation induced by solvent removal, ii) Solvent Evaporation, iii) Solvent Diffusion, iv) Salting-Out, v) Gelation of the Emulsion droplets, vi) Polymerization in Emulsion, vii) Conventional Emulsion Polymerization, viii) Surfactant-Free Emulsion Polymerization, ix) Interfacial Polymerization, and x) Controlled and Living Radical Polymerization

Precipitation caused by elimination of solvent

The scattered phase (usually the oily part) may precipitate macromolecules dissolved in it when the organic, often volatile solvent is withdrawn from the emulsion. This solvent extraction can be done using a variety of processes, including solvent evaporation, Liquid dispersion, and the salting-out process. These are among the more widely used techniques for creating nanoparticles of organic substances from emulsified systems. This approach employs an extensive spectrum of organic substances, such as artificial polymers and naturally found bio-organic aggregates like alginate, chitosan, gelatin, and carbohydrates [83].

Solvent evaporation

The process entails creating a nanoemulsion by dissolving a polymer in a volatile solvent solution [84]. The most commonly used solvents are dichloromethane and chloroform; however, ethyl acetate is frequently employed instead since it is less hazardous and hence much better suited to the production of controlled release systems, which are typically engaged in drug encapsulation. Suspension is created in this vacuum-assisted approach by emulsion droplets that are allowed to spread throughout the continuous phase releasing the polymer solvent [14]. Two stages make up this sluggish process: a fast phase that extracts the majority of the polymer solvent (at least 90%), and a slow phase that extracts the remaining few percent. Droplet sizes sharply decrease in the first stage due to the significant solvent loss, eventually approaching a negligible value. However, because of coalescence, the second stage is distinguished by a notable rise in droplet sizes. When a polymer has interfacial adsorption qualities, the coalescence process can be enhanced; however, when a polymer exhibits low surface-active characteristics, the coalescence process is diminished. Additionally, the evaporation conditions can be altered by using partly miscible solvents during the emulsion preparation process. In this instance, distillation can be used to achieve the removal of the volatile solvent [55].

3.2.3 Solvent diffusion method

As shown in Figure 4, the experimental process consists of three phases: organic, aqueous, and dilution in order to produce nano-organic particles using solvent diffusion technique [85]. The goal of nano-encapsulation is to contain a lipophilic active ingredient. The organic phase contains the polymer, the active ingredient, oil, and a somewhat miscible organic solvent that has to be saturated with water. Researchers claim that the solvent diffuses out of the droplets too quickly—less than 20 milliseconds—and continuously. There are no discernible discontinuities that would refer to the change from homogenous droplets to heterogeneous tiny capsules. Tiny Quintanar et al [56].

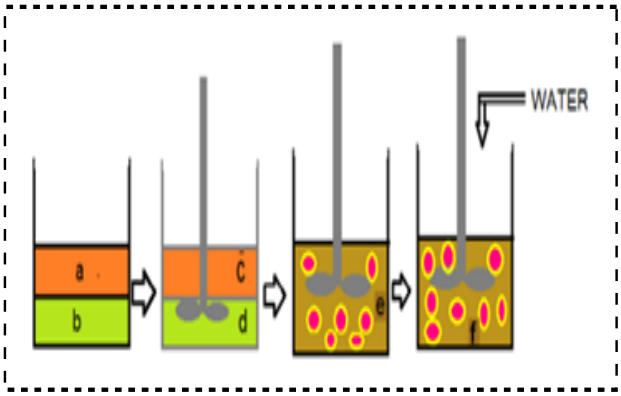

Figure 4: Diagram illustrating the emulsion diffusion process of nanoparticle synthesis. The alphabets in the illustration stand for (a) A moisture-miscible liquid that has been saturated with water. (b) Solvent-saturated water. (c) A soluble or water-saturated solvent. (d) Water treated with a surfactant or solvent. The emulsion by mechanical stirring (e). (f) Diluting the emulsion and producing nanoparticles made from polymers from it.

Salting out

Similar to the solvent-diffusion approach, this process involves emulsification using acetone, a polymer solvent that is completely miscible with water. To emulsify water with acetone, a high concentration of salt or sucrose is dissolved in the aqueous phase, causing a

strong salting-out affect that changes the solubility of water with the solvent [86]. As a result, a polymer dispersed in the solvent droplets can form the emulsion. Similar to the solvent-diffusion process, diluting the emulsion and introducing a significant amount of water to the continuous phase lowers the salt content and causes the solvent to be extracted from the droplets, hence inducing particle precipitation.

Formation of emulsified tiny particles

This process turns the nanoemulsion into gel-like polymer drops, which are then transformed into nanomaterials. In the case of agarose or gelatin, for example, the nanoemulsion can be prepared at a somewhat high temperature above the melting point; cooling the mixture subsequently causes the emulsion droplets to gel and transform into nanoparticles. The process of crystallising the lipid at the melting temperature can also be used to generate solid lipid nanoparticles [34].

Polymerization in emulsion

Polymerization is the most studied technique for generating nanoparticles from emulsions because it produces precise, targeted particles with different properties depending on the intended use [87-92]. In this instance, macromolecules are created by polymerizing monomers as opposed to the previously discussed methods that involve preparing a solution of a prepared polymer. The main emulsion polymerization techniques can be divided into several categories, including surfactant-free emulsion polymerization, conventional emulsion polymerization, and mini- (or nanoemulsions) and microemulsion polymerizations, which vary from the various emulsion behaviors in terms of kinetics and thermodynamics. Moreover, we can mention interfacial polymerization, which is currently much more effective at controlling the polymer's properties than earlier, more traditional polymerization methods. It is also a very helpful technique for creating nanocapsules and living, controlled radical polymerization.

Conventional emulsion polymerization

Traditional emulsion the conventional method of creating nanospheres from emulsions, is called polymerization, which takes place when an initiator molecule and a monomer molecule collide. Another method involves the use of UV, γ, or ultrasonication to generate radicals directly from the monomer. Solid particles may develop either before or after the polymerization ends [93].

Surfactant-free emulsion polymerization

The main advantage of this approach is that it produces nanoparticles without removing surfactant molecules, in contrast to traditional emulsion polymerization, which polymerizes emulsion without the addition of emulsifiers [93].

Controlled/living radical polymerization

Producing hydrophilic polymeric nanoparticles, especially meant for biological applications with environmental considerations has been the focus of a relatively new subject in recent years: controlled/living radical polymerization. As a consequence, the molar weight, distribution of mass, and macromolecular structure may be better regulated. Reversible addition and fragmentation transfer chain polymerization (RAFT), nitroxide-mediated polymerization (NMP), and atom transfer radical polymerization (ATRP) are the major methods for controlled/living radical polymerization that are used in this procedure [93].

One-step procedures

Nanoprecipitation

Fessi et. al [58]. devised the solvent displacement method, often known as the nanoprecipitation technique, near the close of the eighties. It is among the simplest, most affordable, and most reliable methods for creating nanospheres with premade polymers rather than monomers. The mechanism involves the displacement of a semipolar solvent that is miscible with water from a lipophilic solution, followed by the interfacial deposition of a polymer. It resembles the previously developed spontaneous emulsification technique in several ways. The procedure requires a total of three parts: polymer, polymer solvent, and polymer non-solvent. The most often used solvents for polymers include methylene chloride, dioxane, ethanol, acetone, and hexane. Polymer compounds may be artificial, partially artificial, or natural. The polymer's excellent solubility in water and ease of evaporative removal are two advantages in the solvent of the choice selection process. To fulfill these requirements, Natural, semisynthetic, or synthetic polymers are possible. Two characteristics of the polymer—a high solubility in water and ease of evaporation removal—help in the solvent selection process. To meet these requirements, acetone is frequently chosen [58, 94, 95]; nevertheless, a binary mixture of a solvent, such as acetone mixed with a small quantity of water or acetone and ethanol [96, 97], or methanol [98] utilized.

Conclusion

This study is a summary of the primary techniques for creating organic nanoparticles that have been documented in the literature. Based on either one- or two-step methods, two techniques are outlined. When using two-step processes, the transformation of nanodroplets into nanoparticles must come first through a nano-

emulsification phase. The issue of obtaining materials with well-defined morphologies and structures is significant. Although low-energy emulsification is still relatively uncommon, they are rapidly expanding due to its primary benefit in terms of environmental effect. Emulsifications at high energies are by far the most often used technique. In the second stage, nano-gelation, polymerization, salting out, and solvent removal are a few techniques that might be applied to turn nano-emulsions into nanoparticles. Nano-emulsification is not necessary when employing one-step procedures; other mechanisms, such as nanoprecipitation, can be employed to produce nanoparticles.

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Competing interests: The authors state no conflict of interests.

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