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A comprehensive review on formulation characterization and preparation techniques of drug loaded nanosuspension

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Abstract

Nanosuspensions are submicron colloidal dispersions consisting of nanosized drug particles stabilized by surfactants or polymers to enhance the dissolution and bioavailability of poorly water-soluble drugs. Nanotechnology can be used to overcome critical formulation issues such as erratic absorption, low solubility, and permeability related problems. Reduction in particle size increases surface area, which in turn enhances dissolution and absorption rate. The particle size, zeta potential, and crystalline state significantly influence the stability and dissolution rate and *in vivo* performance of nanosuspensions. These characteristics are generally evaluated for properties with methods such as DSC, X-ray diffraction and PCS. There are usually two types of preparation methods, namely, top-down (high-pressure homogenization and media milling) and bottom-up approaches, which include precipitation, evaporation of solvent and supercritical fluid technique. These preparation methods represent a simple, efficient and scalable approach for improving the bioavailability of poorly aqueous soluble drugs. This strategy is versatile and holds tremendous promise in the modern drug delivery system since nanosuspensions can be prepared for different routes of administration such as oral, parenteral, ophthalmic and pulmonary.

Keywords: Nanosuspension; Solubility Enhancement; Bioavailability; Particle Size Reduction; Zeta Potential; Drug Delivery; High-Pressure Homogenization

1. Introduction

Nanosuspensions are submicron colloidal dispersions of nanosized drug particles that are stabilized by surfactants[1]. The water-insoluble drug is suspended in dispersion nanosuspensions without the use of any matrix material[2]. These can be used to improve the solubility of drugs that are poorly soluble in water and lipid media. The rate of flooding of the active compound increases as a result of increased solubility, and the maximum plasma level is attained more quickly. This method is helpful for molecules that are poorly soluble, have low permeability, or both, which presents a significant problem for formulators. Due to the reduced particle size, it is now possible to administer poorly soluble drugs intravenously without blocking the blood capillaries. The suspensions can also be lyophilized and transformed into a solid matrix. In addition to these advantages, it also shares the benefits of liquid formulations over others[3].

Drug nanosuspensions are nanosized, heterogeneous aqueous dispersions of insoluble drug particles stabilized by surfactants. On the other hand, nanoparticles are either lipid colloidal drug carriers or polymeric. When a drug molecule has several drawbacks, such as a high log P and melting point, a huge molecular weight and dosage, and an inability to generate salt, which make it difficult to create acceptable formulations, the nanosuspension technique is the only alternative. The fact that the complexing agent has a high molecular weight is a significant drawback of employing

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cyclodextrin in molecular complexation in pharmaceutical compositions, as it tends to raise the bulk of the formulation[4].

By boosting the saturation solubility and dissolution of the active ingredient, and by improving adherence to the cell surface membranes, NSs improve the oral bioavailability of medications[5]. Because the particle size is on the nanometer scale, NSs may also permit passive targeting[6]. They are simple, easy and inexpensive to manufacture and they create formulations that are both quick and reproducible[7]. The minimal excipient needs during their production result in extremely cheap production costs. Furthermore, their output may be increased[8].

They lessen the bioavailability variations brought about by the effects of meals in fasted and fed conditions[9]. They lessen bioavailability differences across subjects[5]. The quantity of medicine they contain is high (accepted as 100%), hence the dosage utilized in treatment is decreased[10].

Patients can be given solidified formulations in solid dosage forms like pills or capsules because solidified nanosuspensions have greater physical stability[5]. Besides the oral route, NSs can be created for parenteral, pulmonary, topical, and ophthalmic delivery[11]. Several methods, including radiation, steam, dry heat, and filtration, may be used to sterilize them [12].

2. Methods of characterization

The safety, effectiveness and stability of nanodrug delivery systems are all impacted by the particle size, distribution and zeta potential, while the solid form of nanoparticles also affects the dissolution process. As a result, nanoparticle characterization is essential for predicting the *in vivo* and *in vitro* behavior of nanodrug delivery systems. The biological function and *in vivo* pharmacokinetic behavior of nanosuspension are significantly influenced by particle size, charge (zeta potential), crystalline state and particle shape.

2.1. Mean particle diameter and uniformity of particle spread

The saturation solubility, dissolution rate, physical stability and in vivo behavior of nanosuspensions are all influenced by the mean particle size and size distribution of the particles[13]. Using laser diffraction (LD), photon correlation spectroscopy, a microscope and a Coulter counter, the particle size distribution and its range, known as the polydispersity index (PI), may be determined[14]. API value of 0.1 to 0.25 indicates a relatively narrow size distribution, while a PI value of more than 0.5 indicates a very wide distribution[15]. The physical stability of nanosuspensions is given by PI, which should be kept as low as possible for evaluation of nanosuspension stability over time. The drug micro-particles may be identified and quantified during the production process using LD. It also provides a volume size distribution and may be used to measure particles ranging from 0.05 to 2,000 μm[16]. The actual number of particles in each size class per volume is provided by the Coulter counter. In comparison to LD, it is more effective and appropriate for quantifying the contamination of nanosuspensions[17].

2.2. Molecular arrangement and physical state of the particles

To ascertain whether nanoscale particles have any polymorphic or morphological changes, one may analyze their crystalline state and particle shape[17]. High-pressure homogenization is used in the manufacturing of nanosuspension, which can alter the crystalline structure of the formulation, possibly causing it to become amorphous or change its polymorphic form[14]. X-ray diffraction analysis is used to ascertain the extent of the amorphous component and the solid form of the medication particles[18]. This finding is confirmed by differential scanning calorimetry analysis[17].

2.3. Electrical potential present on the particle surface

The zeta potential is used to assess the surface charge characteristics of the nanosuspensions. The macroscopic stability of the nanosuspension is reflected by the particle surface charge value. A minimum zeta potential of ±30 mV is required for electrostatically stabilized nanosuspensions[18,19]. whereas a minimum zeta potential of ±20 mV is needed for sterically stabilized nanosuspensions[20]. The zeta potential values are frequently calculated by first determining the electrophoretic mobility of the particle and then converting it to the zeta potential[21]. In the field of materials science, electroacoustic techniques are also used to measure the zeta potential[22].

3. Advantages of Nanosuspension[23]

- Its simplicity and wide applicability across most medications.
- It works with the water that isn't treated properly and with soluble drugs.

- May be administered via various routes.
- In the event of intramuscular/subcutaneous management, there is less tissue irritation.
- Intravenous administration can achieve the capacity to dissolve quickly and target tissues. The bio-availability and ratio of orally administered nanoparticles are improved in the fed/fasted state and they also have a rapid onset.
- Absorption occurs through the absorption window. because the dose of the medicines may be increased. reduction in particle size.
- Improved bio-availability and consistency in dosing when given via inhalation or ocular delivery.
- The ability to formulate nanosuspensions of medicines with a high log P value to increase their availability.
- Enhanced biological function due to excessive solubility and saturation of the drug's solubility.
- Easy to manufacture and little batch-to-batch variation.
- Long-term physical stability (because there was no Ostwald ripening).
- Hydrogels, pills, suppositories, and tablets can all include nanosuspensions, which are suitable for a variety of management routes.
- Possibility of modifying the surface of Nanosuspension for targeted delivery.
- Raising the amorphous component of the particles, which may result in increased solubility and a change in the crystalline structure. The prerequisite to the introduction of the market's delivery mechanism is the potential for mass production.

4. Preparation Nanosuspension

In theory, nanosuspensions are simpler to create than liposomes and other common colloidal medication carriers, despite what people may believe. Particularly helpful for drugs that are not particularly soluble and for producing a product that is more physically stable. The two methods used to make nanosuspensions are "top-down process technology" and "bottom-up process technology". The top-down approach begins by utilizing the disintegration process to break down bigger particles into micro-particles and then into nanoparticles[24].

For example;

- Homogenization brought about by pressure
- Nano Edge
- Pure Nano
- The equipment used to mill (Nanocrystals).

The bottom-up approach is the name of the construction method a molecule is converted into a nanoparticle[25].

Some instances include;

- The use of a solvent and an anti-solvent in a process
- Use supercritical fluids throughout the process.
- This process causes the emulsification solvent to evaporate.
- A photo of a lipid emulsion or micro-emulsion.

The techniques most often used in recent years for producing nanosuspensions are listed below:

4.1. High pressure homogenization

Using this method, most low water solubility drugs are currently manufactured as nanosuspensions [26].

There are three consecutive steps in the process

First, the drug powders are dispersed in a stabilizer solution to create a presuspension. Next, the presuspension is homogenized in a high-pressure homogenizer at low pressure for pre-milling. Finally, the mixture is homogenized in a high-pressure homogenizer for 10–25 cycles, or until the desired size of nanosuspensions is reached. This concept can be used in a variety of methods to produce nanosuspensions, such as Nano-pure, Disso cubes, Nanoedge and Nanojet [27].

In their aquatic surroundings, disso cubes go through homogenization using a high-pressure homogenizer with a piston-gap, R.H. Muller created this method in 1999 [28]. Using this approach, the mixture of the drug and surfactant is forced through the high-pressure homogenizer's Nono-sized orifice valve.

This approach is based on the idea of cavitation. According to Bernoulli's theory, the fluid flow rate is constant throughout the cross section of a closed system. The dispersion from a cylinder with a diameter of 3 cm is compelled through a tiny 25 m aperture for unknown reasons. As the diameter decreases from 3cm to 25m, the static pressure drops below the boiling point of water at room temperature, while the dynamic pressure rises. Then, at room temperature, the water begins to boil, producing gas bubbles that burst when the suspension leaves the gap, an occurrence known as cavitation, which restores the surrounding air pressure. The potent cavitation forces of the particles convert the drug's micro particles into nanoparticles.

Homogenization carried out in the non-aqueous media

- ***Nano-pure***

The "deep freezing" method involves homogenizing suspensions in aqueous or water-free media, such as PEG 400, PEG 1000 and others. Temperatures for the mixing process can range from ambient to 0°C or even lower at -20°C[29].

- ***Nanoedge***

Nanotechnology is the term for the process of mixing precipitation with homogenization. The underlying concept is the same as that of homogenization and precipitation[30]. The Nano-edge approach tackles some of the main disadvantages of precipitation processes, like crystal creation and the preservation of long-term stability. Smaller, more stable particles can be produced in a matter of minutes.

- ***Nanojet***

The process causes a decrease in particle size due to the intense shear forces it produces. The method, sometimes known as the reverse stream approach, involves dividing a suspension stream into two or more segments within a chamber that combine under high pressure[31].

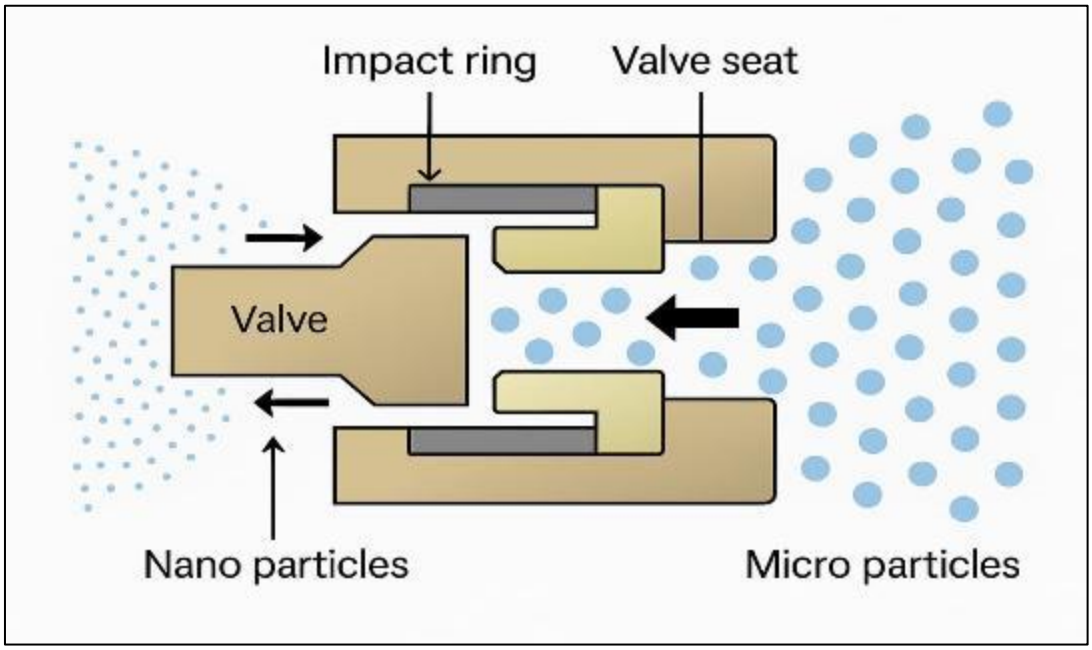

Figure 1 High Pressure Homogenization[32]

4.2. Milling operation

- ***Media Milling***

In 1992, Liversidge initially developed and published this idea[33]. Using this procedure, the nanosuspensions are created in a high shear media mill. The temperature in the milling chamber was maintained by the addition of water, medication, a stabilizer, and the grinding media for the two to seven days that the high shear rate was maintained.

The grinding medium is made of zirconium oxide, glass, or a highly cross-linked polystyrene resin. The medicine is impacted by the milling media, which breaks down drug microparticles into nanoparticles, resulting in powerful high energy shear forces.

- ***Dry Co-grinding:***

The production of nanosuspensions now frequently uses dry milling as its method. Dry co-grinding is a simple and affordable procedure that doesn't involve the use of organic solvents. Co-grinding improves the physicochemical characteristics and solubility of drugs that are hardly water soluble by increasing the surface polarity and transforming a crystalline drug into an amorphous form.

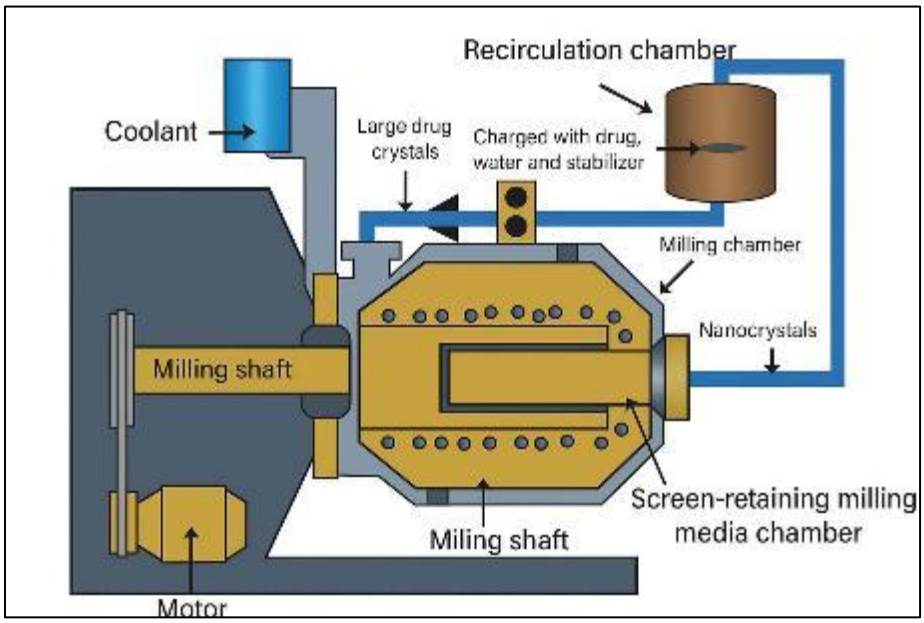

Figure 2 Milling Operation[3]

4.3. Method of emulsifying solvent evaporation

The method involves first making a drug solution, then emulsifying it in a different liquid, which is the drug is not dissolved by it. The solvent evaporates then the medication precipitates out of the solution. The accumulation of particles and the production of crystals may be caused by be governed by producing large shear stresses with the use of a fast blender.

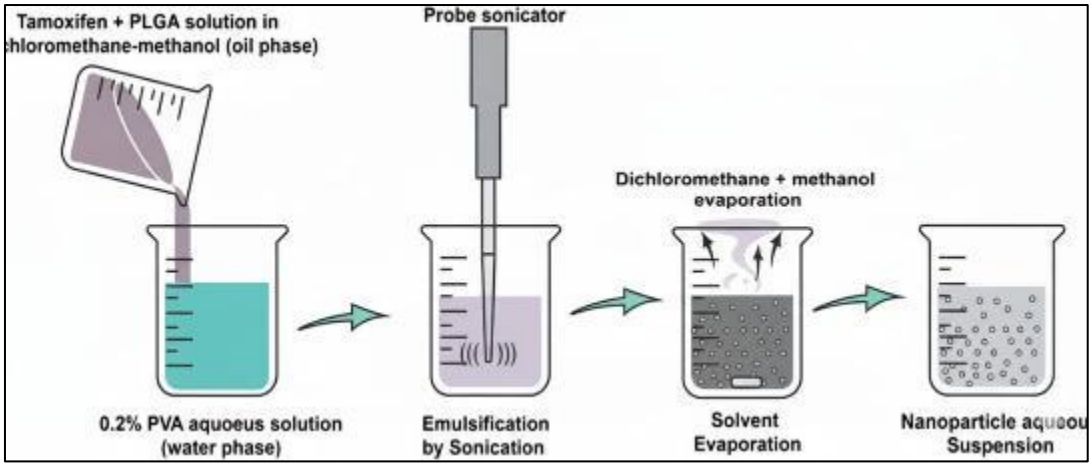

Figure 3 Method of emulsifying solvent evaporation[34]

4.4. Precipitation

In the past decade, there has been more rain. used to create sub-microns particles, particularly those with low solubility medications[35]. The treatment is initially diluted in the solvent is then combined with this solution. if the anti-solvent is miscible surface-active chemicals. Quickly introducing new drugs.

When the drug is added to the anti-solvent solution, it quickly becomes supersaturated, resulting in the production of very tiny crystalline or amorphous drug solid materials[36].

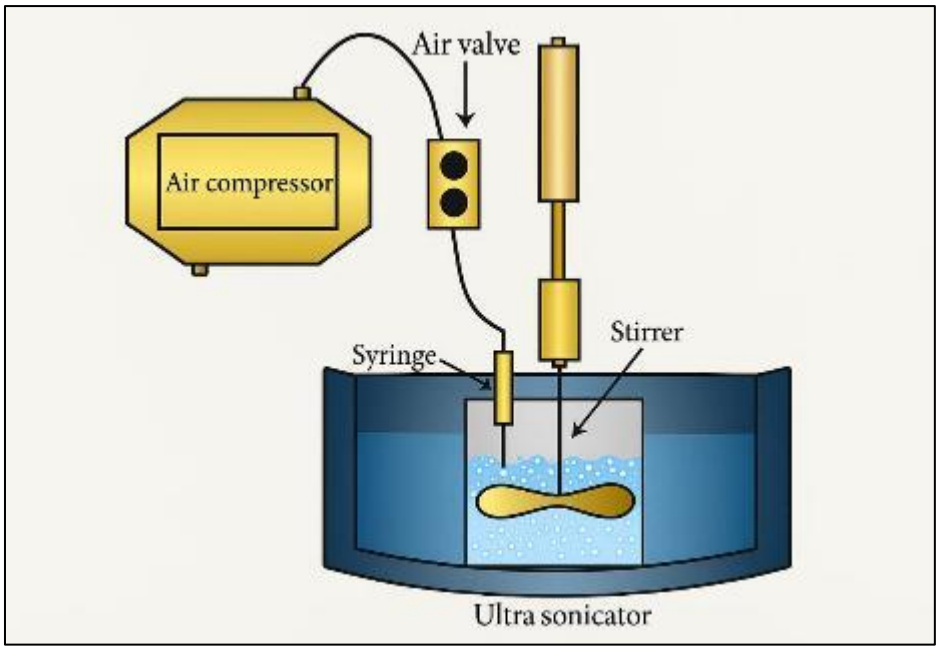

Figure 4 Precipitation[37]

4.5. The Supercritical Fluid method

The particle size was reduced mostly due to the solubilization and nanoscale reduction supercritical fluid processing techniques. A supercritical fluid (SCF) is a high-density, non-condensable liquid with a molecular structure that cannot be condensed.

Due to the fact that this procedure occurs at a temperature and pressure that are higher than its critical temperature (Tc) and critical pressure (Tp), it facilitates the micronization of drug particles at the sub-micrometer level. Recent improvements in SCF, the goal of the process is to produce nanoparticles.

The particle size in suspension varies from 5 to 2000 nm in diameter[17]. The low solubility due to the high pressure necessary for these processes in supercritical CO2, this technology is limited to the treatment of drugs and surfactants that have low water solubility in the pharmaceutical industry.

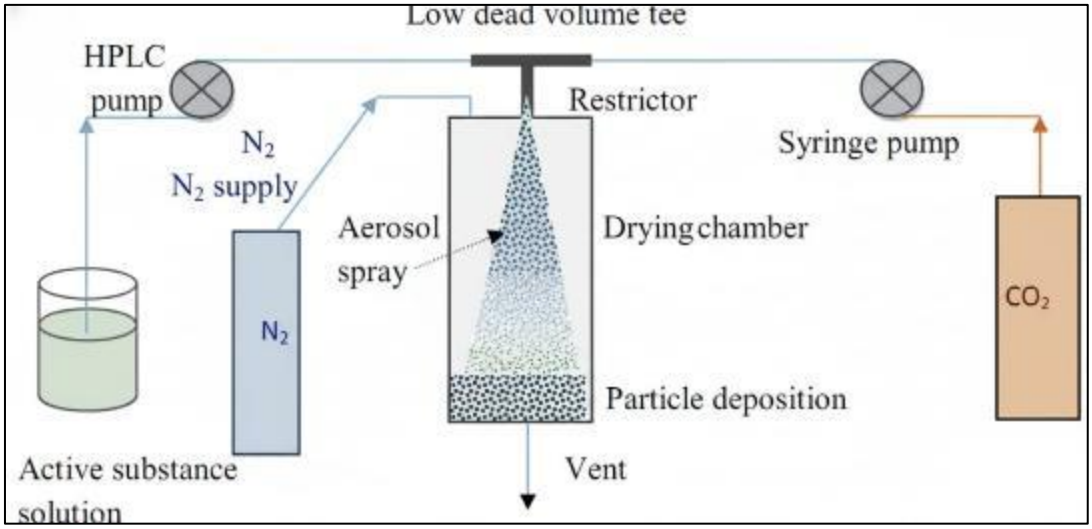

Figure 5 The Supercritical Fluid method[38]

4.6. The Melt Emulsification Approach

This method is used to distribute the medicine throughout the body a warm, aqueous solution of stabilizer above the drug's melting point, as well as in order to create an emulsion, the combination is homogenized.

During the procedure, the following takes place throughout the entire procedure, the sample holder was used covered with a heating tape that has the temperature control and the mixture's temperature remained the same throughout over the thermal melting behavior of the drug.

The emulsion was then cooled or on a slowly increasing basis to room temperature, or on an ice bath.

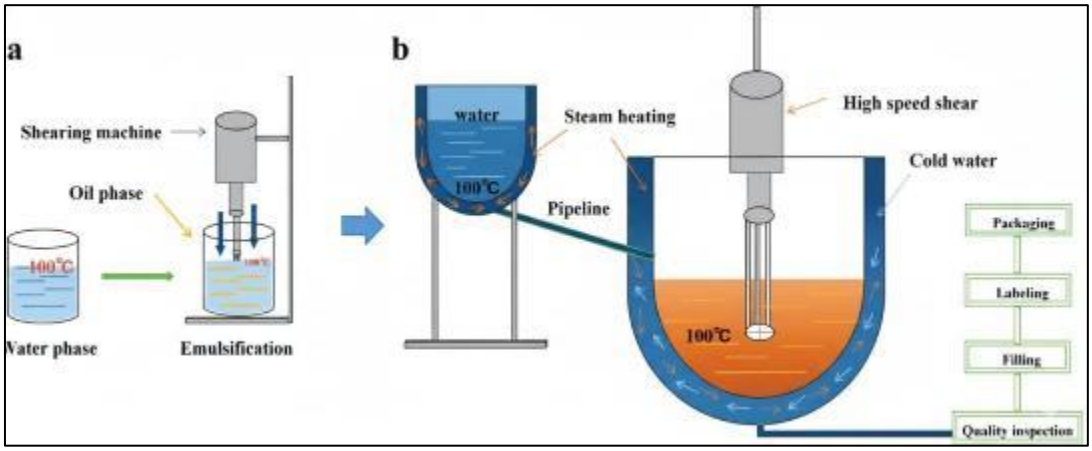

Figure 6 The Melt Emulsification Approach[39]

4.7. Microemulsion/Lipid Emulsion Templates:

For medicines, this approach is typically effective that are soluble in volatile organic solvents only slightly soluble in water or other solvents materials. The medication was dissolved using this procedure soluble in a decent organic solvent and the drug particles then precipitate in the aqueous phase as a result of the organic solvent progressively evaporating under low pressure, yielding the aqueous suspension of the drug with the specified particle size. The resulting suspension can then be diluted as needed to produce nanosuspensions. In addition, microemulsions can be used as templates for creating nanosuspensions. A micro-emulsion is a thermodynamically stable, isotropically clear

combination of two immiscible liquids, such as oil and water, that is maintained by an interfacial film of surfactants. Then, using appropriate surfactants, the mixture is emulsified in the aqueous phase.

The medication can be introduced into the interior phase, or it can be thoroughly combined with the surfactant and co-surfactant to saturate the produced micro-emulsion with the drug. The combination can then be diluted as necessary.

Microemulsion is used to manufacture the drug nanosuspension. The benefits of lipid emulsions acting as templates for nanosuspensions are performed due to the following consideration. Simple to manufacture because the emulsion droplets can be controlled and easy to increase. The environment, however is impacted by the usage of organic solvents and significant quantities of surfactants or stabilizers are required.

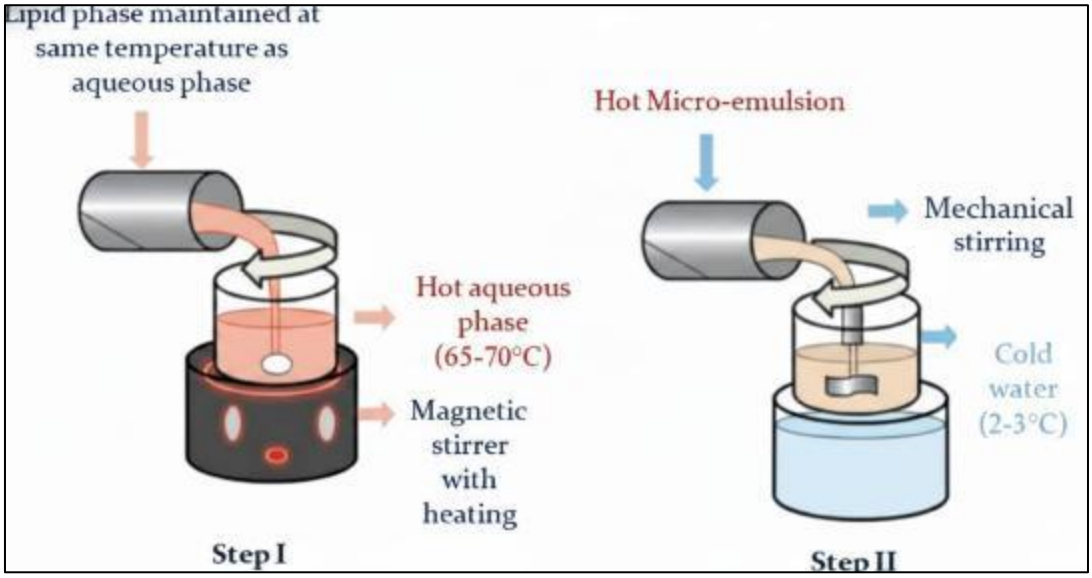

Figure 7 Microemulsion/Lipid Emulsion Templates[40]

4.8. The Evaporation of Solvents:

The solvent evaporation method makes use of the preparation of polymer solutions occurs in volatile solvents and emulsions. However, from dichloromethane and the previous years chloroform, which is no longer in use, was used in the treatment.

Ethyl acetate, which has a better toxicology profile, has taken its place. The polymer's solvent evaporates, enabling it to diffuse through the emulsion's continuous phase, which is subsequently converted into a nanoparticle suspension. The two main approaches for creating emulsions are the preparation of single-emulsions, such as oil-in-water (o/w), or double-emulsions, such as (water-in-oil-in-water) (w/o/w). These methods require that the solvent evaporates, either by continuous magnetic maintained at or below ambient temperature via ultracentrifugation at a lower pressure.

The nanoparticles that have hardened are collected and cleansed with distilled water. Following the removal of the additives, such as surfactants, the sample was lyophilized. The polymer concentration, stabilizer, and drying rate all influenced the particle size homogenizer[41].

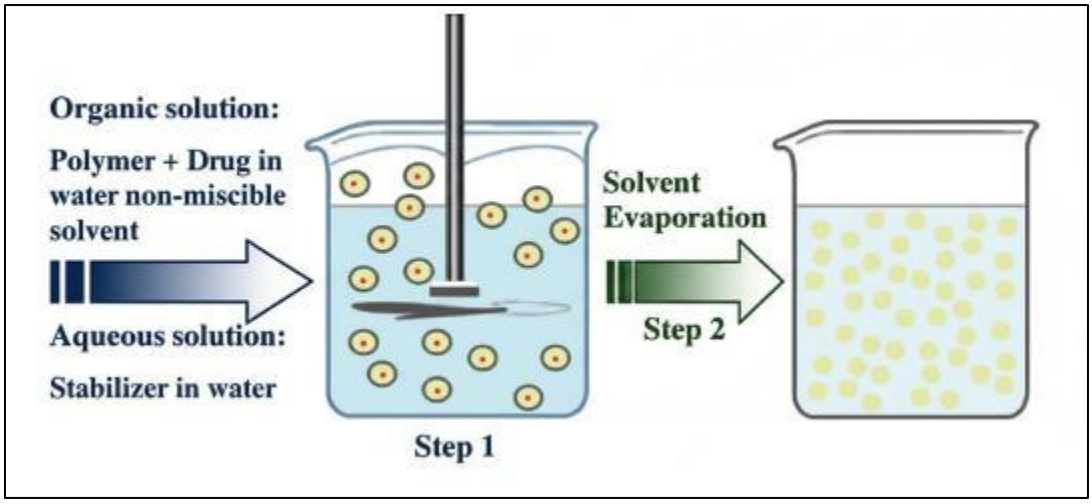

Figure 8 The Evaporation of Solvents[42]

5. Conclusion

Nanosuspensions represent a promising and versatile strategy for enhancing the solubility, dissolution rate, and bioavailability of poorly water-soluble drugs. By reducing particle size to the nanometer range, they significantly increase surface area and saturation solubility, leading to improved therapeutic effectiveness and reduced variability in drug absorption. Various characterization techniques including particle size analysis, zeta potential measurement and solid-state evaluation play a crucial role in understanding the stability and performance of nanosuspensions. Both top-down and bottom-up preparation techniques offer efficient, scalable, and flexible options for formulating nanosuspensions suitable for oral, parenteral, ophthalmic and pulmonary delivery. Their ability to improve drug targeting, stability and patient compliance highlights their growing importance in modern drug delivery systems. Overall, nanosuspensions continue to be a valuable tool in overcoming formulation challenges and advancing the development of effective pharmaceutical products.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

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