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NANOSUSPENSIONS: A REVIEW OF FORMULATION STRATEGIES, CHARACTERIZATION TECHNIQUES AND APPLICATIONS

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ABSTRACT

Nanosuspension is the colloidal dispersion of nanosized drug particles stabilized by surfactants for oral, topical, or parenteral routes of administration. Nanosuspensions have become a viable method for effectively delivering hydrophobic drugs with adaptable qualities and distinctive advantages. The composition of nanosuspension includes stabilizers, surfactants, co-surfactants, polymers, organic solvents and other additives like salts, polyols, buffering agents, etc. The challenge becomes even more intricate when dealing with drugs classified under BCS Class II. Facilitating greater interaction with biological media was significantly achieved through a nanosuspension formulation. Nanosuspensions that have attracted particular attention are those sterically stabilized by steric polymers with a typical size range of 10-100nm. The review aims to strengthen the therapeutic efficacy and bioavailability of various properties of nanosuspensions made using commercially accessible techniques including melt emulsification, high-pressure homogenization, media milling, emulsification and other techniques will be progressed.

KEYWORDS

Nanosuspension, Bioavailability, Homogenization, Polymer and Solubility.

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INTRODUCTION

As any medication formulation is being performed, solubility is one of the key and crucial parameters examined in preparing medications that dissolve in water. Drugs with low water solubility will provide several challenges for formulation and research. Newly screened medicinal compounds with low water solubility comprise 40% of them. BCS classes II and IV are used to categorize drugs with poor solubility. The effective formulation of pharmaceuticals is dependent on various

formulation factors, including water solubility, stability and humidity, photostability, compatibility and compliance with the solvent and the excipient[1]. It is now a significant and difficult scientific, industrial, and medical problem to create novel, weakly water-soluble compounds to achieve sufficient bioavailability. Strong intermolecular bonds and high lattice energy in a solid state are the reasons for their poor solubility in water[2].

Nanosuspensions (NSs) are colloidal dispersions of submicron drug particles, which are colloids with solid drug particles smaller than 1µm that are very finely dispersed and biphasic. While the terms "nanosuspensions" and "nanocrystals" are used interchangeably and there are differences in the literature regarding their definitions, they are defined as "particles with a particle size of approximately 200-600nm below 1 micrometer, formed by 100% pure active substance" and "pure active pharmaceutical ingredients (APIs) between 10-1000nm stabilized with surfactant or polymer". When stabilizers are synthesized in the form of small drug crystals, a nanosuspension is expressed[3].

The bioavailability of an oral medication may vary depending on whether the patient is fasting or eating. Food can delay the stomach emptying period, alter the pH of the gastrointestinal tract, stimulate bile flow, increase organ blood flow, or physically interact with medications to impact how well they are absorbed. The precipitation technique is used to increase the bioavailability and effectiveness of many medications by causing dissolved molecules to precipitate and form solid nanocrystals[4].

In the topical formulation, three categories are liquids, semisolids, and solids. Nanosuspension can be further processed into a semisolid formulation for topical application, where it can be made into gels, creams, ointments and lotions. Although formulations for nanosuspensions have been specifically researched for parenteral and oral administration, there is also significant promise for topical distribution via cutaneous, pulmonary and ophthalmic routes. For topical nanosuspension, it can be converted to solid formation by lyophilization, spray drying, and other methods. Oral medication has poor patient compliance or may undergo the first metabolism, so the topical route is more convenient than the oral route. One of the most practical ways to provide pharmaceuticals is through topical application, which avoids the stomach and gastrointestinal tract's acidic environment. The main aim for delivery of the medication to the target should be safe and efficient throughout the topical modes[5].

Compared to a micronized product, the increases in surface area and concentration gradient cause a considerably more noticeable increase in the dissolving velocity. The Greek term for "dwarf" is nano. Nano refers to a factor of one billionth or 10^{-9}[6]. The Nernst-Brunner/Noyes-Whitney equation can be used to describe the surface area available for dissolution, which in turn describes the solid drug dissolution rate. Because of the increased effective surface area, the dissolving rate will be significantly increased by size reduction to the nanoscale range[7].

NEED OF NANOSUSPENSION[8,9]

The low oral bioavailability of BCS class-II medications was revealed by pharmacokinetic investigations, which could be attributed to the drug's weak water solubility. Several traditional pharmaceutical techniques exist for enhancing drug dissolving rate, including the use of an organic solvent to dissolve aqueous mixtures, the formation of complexes, solid dispersions, and the use of drug salts. In the last 20 years, a novel technique for speeding up medication has been developed by decreasing drug particle size[8].

Poor bioavailability, Inadequate dose-response correlation. Using severe primary or acidic environments to enhance solubilization

Inability to choose lead compounds optimally based just on protection and efficacy -Fed/fast variance in bioavailability. Inadequate dosage -Hard excipient use, such as excessive co-solvent and excipient usage[9].

ADVANTAGES OF NANOSUSPENSION[10-12]

An increased rate of medication dissolution and saturation solubility.

Greater drug loading is feasible. Enhance biological functionality, adaptability, and simplicity in production.

Greater bioavailability for inhalation medication del ivery and ocular administration

Creams, gels, pills, capsules, and pellets can all be made with nanosuspension.

Nanosuspensions are polymeric colloidal carriers of lipids, as opposed to solid lipid nanoparticles (SLN), which are lipid-based nanocarrier drugs.

Lessened tissue irritation whether administered subcutaneously or intramuscularly.

The intravenous method of delivery allows for rapid breakdown and tissue targeting.

Oral administration of nanosuspension provides rapid onset, reduced fed/fasted ratio and improved bioavailability.

A decrease in particle size can lead to an increase in absorption.

TECHNIQUES USED IN THE PREPARATION OF NANOSUSPENSION

Two techniques are in use for the formation of nanosuspensions: Bottom-up technology and Top-down technology (FigureNo.1).

Bottom-up technology

As the name implies, to formulate small solid particles, this method begins at the bottom, that is, at the molecular level, and ends with molecular interaction. This indicates that it is a unique precipitation approach where a smaller amount of solvent is needed.

Precipitation Method (solvent anti-solvent method)

Precipitation method that produces submicron particles of poorly soluble medications. This approach consists of dissolving the medication in a solvent, which is subsequently combined with another solvent that contains a surfactant, making the drug insoluble. Fast supersaturation of the drug in the solution and the formation of an ultrafine amorphous or crystalline drug occur from the rapid addition of the solution to such a solvent (usually water) which is represented in Figure No.2. This process involves the formation of nuclei and the development of crystals, both of which are mostly temperature-bio-dependent. A stable suspension with the smallest possible particle size can be prepared primarily by having a high nucleation rate and a low crystal growth rat[13].

Top-down technology

The method of disintegration is top-down technology. The emulsion diffusion method, media milling, high-pressure homogenization, and supercritical fluid method are examples of top-down technologies that are favored above the precipitation approach[14].

High-Pressure Homogenization

The three phases involved in this technique are as follows: Drug powders are first dispersed in a stabilizing solution to produce a pre-suspension. This is then homogenized using a high-pressure homogenizer at low pressure periodically for pre-milling and lastly homogenized at high pressure for 10 to 25 cycles to form the desired size nanosuspensions[15] represented in Figure No.3.

Media Milling Technique

One of the oldest methods for reducing particle size is the media milling method. This technique, which was patented, divides the active medicinal ingredient into the necessary size range by using acoustic radiation to form nanosuspensions. It makes use of media, which are essentially different sizes, densities, and kinds of pearls or beads. The most widely utilized beads are made of glass, stainless steel, zirconium, or very cross-linked polystyrene resin[16]. A stirrer is used to agitate the pearls and the medication is ground into nanocrystals between them. The method reduces the particle size by using impact and shearing forces in addition to the mill. This is the fundamental technology, although it has the drawback of eroding the mill and increasing the possibility of product contamination[15]. This technique is represented in Figure No.4.

Nano-edges (Combined precipitation and homogenization)

It is referred to as Combination technology and was developed by Baxter on October 9, 2001. The technology behind this trademark is intended to turn pharmaceuticals that are insoluble in water become medications. It successfully addresses both high-pressure homogenization and microprecipitation techniques by combining them. The first stage is microprecipitation using the solvent-antisolvent approach, which means adding an antisolvent to a medication solution that contains stabilizing substances to produce precipitates in the micro range. The slurry is then homogenized at high pressure to bring the precipitates together. This process checks the crystal development of nanoparticles, resulting in particles in the nanometer range with enhanced thermodynamics[17].

Nanopure (High-pressure homogenization in nonaqueous media)

A suspension homogenized in water-free media or water mixtures is called Nanopure. Patents about high-pressure homogenization-induced polymeric material consist of disintegration increases at temperatures over 80ºC, making them unsuitable for thermolabile substances. With this approach, drug suspensions in non-aqueous fluids were homogenized at 0ºC, or lower than the drug's freezing point; this low-temperature processing led to the term "deep-freeze" homogenization[18].

Dissocubes (homogenization in aqueous media)

To homogenize, the suspension must be forced through a valve with a small aperture while under pressure. Muller *et al*. developed Dissocubes in 1999. In this case, the drug suspension is allowed to pass through a tiny opening, which lowers the static pressure below the boiling point of water and causes the water to boil and produce gas bubbles. The bubbles burst and the surrounding area holding the drug particles rushes to the center, in the process colloids and reduces the particlesize until suspension exits the gap and normal air pressure is restored. Depending on the drug's hardness, requires many passes or cycles through the homogenizer. Pre-milling is a useful technique to start homogenization with very tiny drug particles to produce a nanosuspension with a higher concentration of solids. The main benefit of high-pressure homogenization over medium milling is that it enables aseptic production and may be applied to both concentrated and diluted suspensions[19].

Nano jet technique

This technique known by another name, "opposite stream technology," this method involves splitting a suspension stream into two or more sections within a chamber. High pressure is present when the two streams collide with one another. Particle size is reduced as a result of the high shear force generated throughout the operation. This technique's primary drawback is the high number of passes through the microfluidizer and the resulting product's significantly higher fraction of microparticles[15].

Emulsification solvent evaporation method

This method involves preparing a drug solution and then emulsifying it in a different liquid that does not contain the drug's solvent. Precipitation of the medication results from solvent evaporation. The process of controlling crystal formation and particle aggregation involves using strong shear forces through the use of a high-speed stirrer[13] as shown in Figure No.5.

Melt emulsification method

Melt emulsification is the primary process used to generate solid lipid nanoparticles. Using the melt emulsification approach, Kipp and colleagues first developed ibuprofen nanosuspensions. It follows a four-step process. The medication is initially added to a stabilizer-containing aqueous solution. To create an emulsion, the solution is homogenized using a high-speed homogenizer after being heated to a temperature greater than the drug's melting point. The medication is kept at a temperature higher than its melting point throughout the entire operation. To precipitate the particles, the emulsion is finally refrigerated. The key factors influencing particle size are the drug concentration and type of stabilizers employed, the cooling temperature, and the homogenization process[20].

Supercritical fluid process

Nanoparticles are produced using a variety of techniques, including the precipitation with compressed antisolvent (PCA) process, the supercritical antisolvent process, and the rapid expansion of the supercritical solution (RESS) process. The RESS technique involves expanding a drug solution through a nozzle into a supercritical fluid, which causes the drug to precipitate as small particles due to the supercritical fluid's insufficient solvent power. The solution becomes supersaturated as the solvent is removed, leading to precipitation in the end. The drug solution is injected into the supercritical fluid during the supercritical antisolvent procedure, which extracts the solvent and causes the drug solution to become supersaturated[15,21].

Dry co-grinding

Using a media mill or pearl mill for high-pressure homogenization includes wet grinding. To prepare nanosuspension, dry grinding is a technique that is similar to wet grinding. Dry co-grinding is a simple, low-cost procedure that doesn't require the use of an organic solvent. This method can be used to decrease the particle size to the submicron region and create stable amorphous nanocrystals. This approach has the benefit of increasing physicochemical properties since it changes the drug's surface characteristics and causes it to change from a crystalline to an amorphous state[22].

EXCIPIENTS USED FOR FORMULATION OF NANOSUSPENSION[23-25]

Organic Solvent

If emulsions or microemulsions are employed as a template, then organic solvents are used in the formulation of Nanosuspension. In the formulation, less hazardous water-miscible solvents that are pharmaceutically acceptable-such as methanol, ethanol, chloroform, isopropanol-as well as partially water-miscible solvents-such as ethyl acetate, ethyl formate, butyl lactate, triacetin, propylene carbonate and benzyl alcohol-are preferred over traditional hazardous solvents like dichloromethane.

Polymer

Drug-containing colloidal polymer dispersions also known as nanosuspensions, polymers made using a microfluidizer and a high-pressure emulsification-solvent evaporation technique are to be evaluated. Through polymerization, biodegradable nanoparticles for parenteral applications have been developed. During the process of producing acrylic nanoparticles, the medication can be introduced straight into the water-impermeable monomer, the external aqueous phase before polymerization, or the aqueous phase following polymerization. Before emulsification in an aqueous phase, the medication is added to the polymer solution using the solvent evaporation method. Drug targeting using these nanoparticles seems promising. Additional uses of nanoparticles are topical and ocular administration.

Stabilizer

A stabilizer's major purpose is to provide an ionic or steric barrier to prevent Ostwald's ripening and agglomeration of Nanosuspensions, which results in a physically stable formulation. It also does this by fully wetting the drug particles. The type and amount concentration of stabilizer significantly impact the *in vivo* behavior and physical stability of nanosuspension. The lecithin, poloxamer, polysorbate, cellulose, and povidones are examples of stabilizers that have been employed. The stabilizer preferred to produce a nanosuspension that is autoclavable and acceptable to parents is lecithin.

Surfactants

By lowering the interfacial tension, surfactants are added to enhance dispersion. They also serve as wetting or deflocculating agents; two common examples of these surfactants are tweens and spans.

Co-surfactants

Co-surfactants have a significant impact on phase behavior; hence it is important to look at how they affect drug loading and internal phase uptake for certain microemulsion compositions. The development of nanosuspensions can safely use a variety of solubilizers, including, ethanol and isopropanol, despite literature describing the usage

of bile salts and dipotassium glycyrrhizinate as cosurfactants.

Other additives

Additives such as buffers, salts, polyols, osmogene, and cryoprotectants may be added to nanosuspensions based on the requirements of the drug moiety or the mode of administration**.**

CHARACTERIZATION OF NANOSUSPENSION[26-28]

Physical

Color, Odor, Taste

Particle-size distribution

Particle-size distribution in reaction to mechanical agitation, centrifugation, freeze/thaw, accelerated aging, and shipping

Dissolution in bio-relevant medium or water

Injectability and syringe-ability

Resuspendability

Drainability (from container sides)

Zeta potential (electrostatic self-repulsion of particles)

Compatibility studies [Fourier Transform Infrared Spectroscopy (FTIR)]

Crystal morphology [Differential Thermal Analysis (DTA), X-ray diffraction analysis (XRD), Differential Scanning Calorimetry (DSC) and Scanning Electron Microscopy (SEM)]

Chemical

Preservatives

Moisture (for lyophilized and solid dosage forms)

Degradation products

pH

Active ingredient

Biochemical

In vivo Pharmacokinetics

Sterility

Pyrogenicity

APPLICATIONS[29-35]

Topical formulation

Supersaturated structures (extended saturation solubility) created by incorporating nanosuspensions into topical formulations increase drug diffusion pressure. Applying liquid formulations such as nanosuspensions and semisolid formulations such as gels, creams, ointments, and lotions. Topical formulations based on nanocrystals have been investigated for a broad range of uses, including fungal infections, skin diseases, psoriasis, frostbite, anti-aging therapies, and anti-acne effects.

Oral-cavity formulations (paste, gel, patches)

In conventional oral formulations, tiny particles enhance adherence and prolonged residence for medicines with insufficiently high bioavailability. The decrease in the inter-issue version led to progress in dosage proportionality and a rise in availability due to a growth in bio-adhesion.

Oral administration

Nanosized drugs have higher oral absorption and, thus, higher bioavailability. Because drug nanoparticles stick to mucosa more readily and have higher saturation solubility, which increases the concentration gradient and improves bioavailability results, both liquid and dry dosage forms, such as tablets or hard gelatin capsules containing pellets, can be utilized directly with aqueous nanosuspensions. Moreover, nanosuspensions can be sprayed and dried to create granulates.

Ocular medication administration

It has been demonstrated that nanosuspensions are essential for medications with low solubility in lachrymal fluids. Suspensions provide benefits such as longer residence times, which are ideal for treating most ocular disorders effectively, and the ability to avoid increased tonicity caused by water-soluble medications. Their actual efficacy is contingent upon the drug's inherent solubility in lachrymal fluids. The releasing and ocular bioavailability of the medication are therefore controlled by its intrinsic dissolving rate in lachrymal fluids.

Parenteral Administration

Parenteral administration is the primary line of treatment in emergencies including cardiac arrest and anaphylactic shock. It involves subcutaneous, intravenous, intramuscular, and intra-arterial delivery of dose forms. This mode of administration has the advantages of consistent dosages, reduced

first-pass metabolism, and increased bioavailability. Compared to oral administration, intravenous administration yields more predictable pharmacodynamic and pharmacokinetic characteristics due to control over the dose and rate. To avoid capillary obstruction, administered medication particles must be less than 5μm. The study on the rate at which tumor growth is inhibited in mice revealed that oridonin in nanosuspension significantly reduced the tumor's weight and volume.

Pulmonary administration

The purpose of pulmonary medication delivery is to treat a variety of respiratory ailments, including chronic obstructive lung disorders and asthma. One of the benefits of pulmonary medication delivery over parenteral and oral drug administration is that it goes directly to the site of action, reducing dosage and adverse effects. Improved selectivity results from nanosuspensions' ability to stick to mucosal surfaces because of reduced drug loss and extended residence times at the target region. By enhancing drug diffusion and dissolving rate, pulmonary nanosuspensions enhance bioavailability and avoid unfavorable drug deposition in the mouth and throat.

Muco-adhesion of the nanoparticles

The mucosal surface is quickly encountered by oral nanoparticles that are supplied as a suspension and diffuse into the liquid medium. "Bio adhesion" is the name of the adhesion mechanism that immobilizes the particles at the gut surface. At this point, an immediate adsorption process occurs as the concentrated suspension serves as a particle reservoir. Before particle absorption, there is a bio-adhesive phase in which the particles come into direct touch with the intestinal cells. Enhancing bioavailability and improving selectivity of the parasites that continue to reside in the gastrointestinal tract are the benefits of the nanosuspensions' adhesiveness.

Targeted Drug Delivery

Since nanosuspensions have a surface that acts as a stabilizer or milieu, they can be utilized for targeted drug delivery. The enhancement of commercially useful nanosuspensions for targeted distribution can be achieved by modifying their characteristics and *in-vivo* behavior, which can be easily scaled up and modified.

Table No.1: Nernst-brunner/noyes-whitney equation

$$\frac{dX}{dt} = \frac{AD}{h}\frac{(Cs - Xd)}{V}$$

Where,

dx/dt = The rate of dissolution velocity,

D = diffusion coefficient,

A = The surface area of the particle exposed to the dissolution media,

H = the thickness of the diffusion layer,

Cs = The saturation solubility of the solute at a defined temperature,

X_d = The concentration of the solute in the media at time t,

V =The volume of the dissolution media.

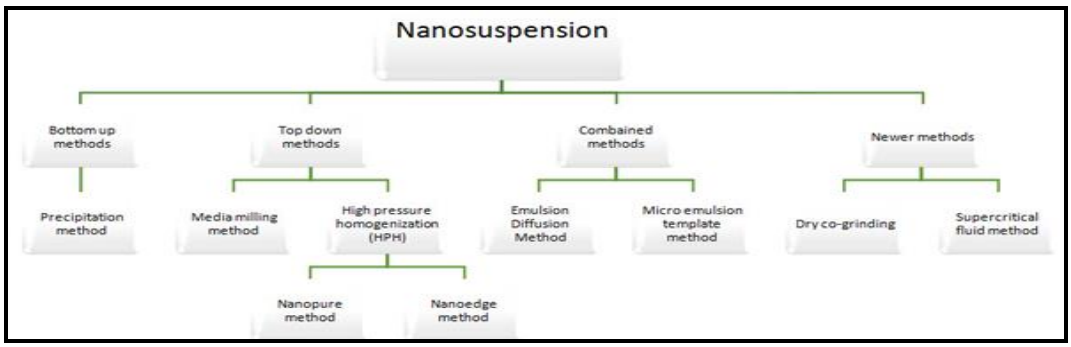

Figure No.1: Schematic representation of the method of preparation

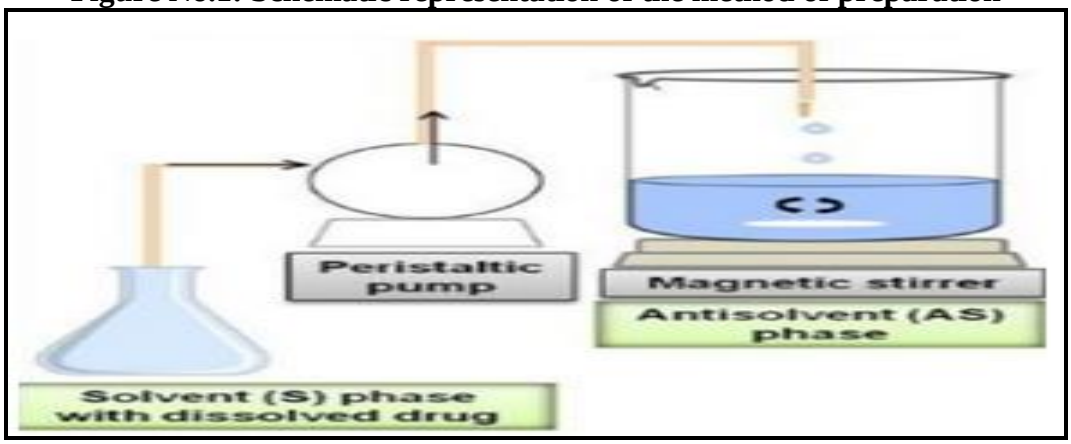

Figure No.2: Schematic representation of antisolvent precipitation technique

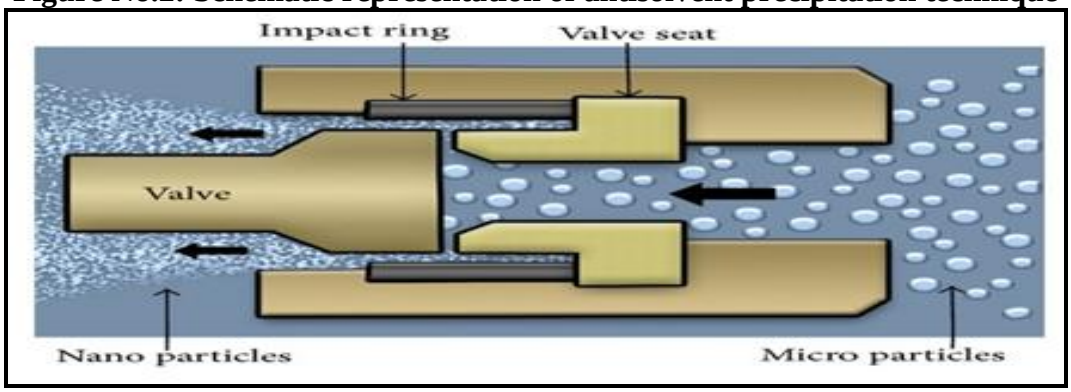

Figure No.3: Schematic representation of high-pressure homogenization

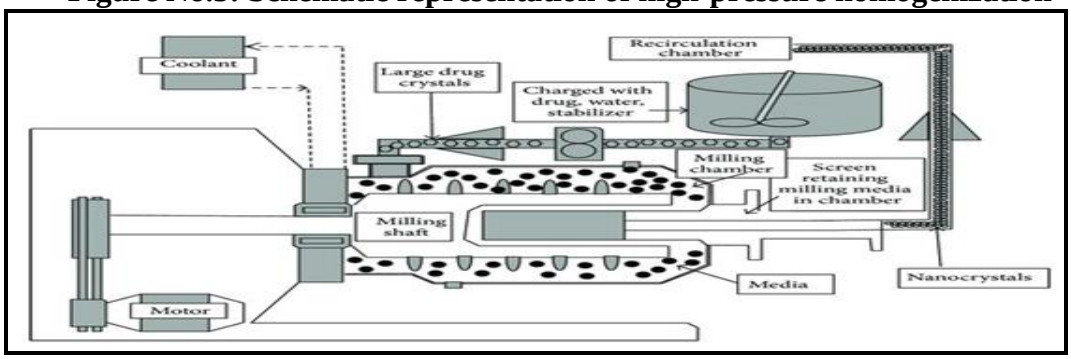

Figure No.4: Schematic representation of media milling technique

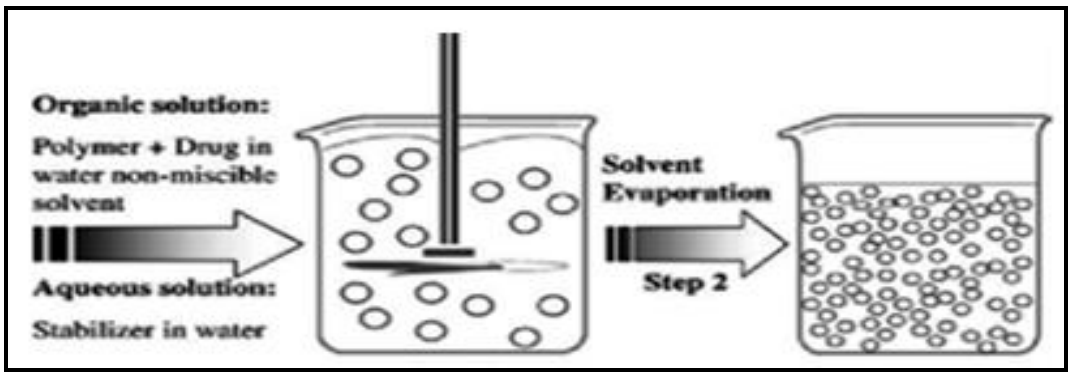

Figure No.5: Schematic representation of solvent evaporation technique

CONCLUSION

Nanosuspension differs depending on the compositions used. This Nanosuspension can be administered by different routes of administration which are oral, transdermal, ocular, parenteral, pulmonary, etc. In this nanosuspension, some of the techniques have been included and employ a composition that either resembles or differs from one of the techniques evaluated to increase the solubility of drugs, hence boosting therapeutic efficacy. The review concentrated on the topical route and various characterization involved like the physical, chemical, or biochemical characterization of nanosuspensions utilizing the different medication compositions in the formulation to improve its bioavailability. Additionally, nanosuspensions can be evaluated solely based on future-oriented characteristics relevant to traditional formulation products across all administration routes.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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