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Review Article

NANOSUSPENSIONS: A STRATERGY TO INCREASE THE SOLUBILITY AND BIOAVAILABILITY OF POORLY WATER-SOLUBLE DRUGS

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ABSTRACT

The process that occurs at the molecular level and at the nanoscale is the subject of nanotechnology. Nanotechnology includes nanosuspension. Nanosuspension is a colloidal dispersion of medication particles that are nanometer-sized and stabilized with surfactants. To manufacture and scale up nanosuspensions, conventional size reduction tools such as media mills and high-pressure homogenizers as well as formulation strategies including precipitation, emulsion-solvent evaporation, solvent diffusion, and microemulsion procedures can be successfully used. The main elements to be taken into consideration for the effective manufacture and scale-up of nanosuspensions are maintaining the stability in solution as well as in the solid form, and resuspendability without aggregation. The flexibility for surface modification and mucoadhesion for drug targeting have substantially broadened the scope of this innovative formulation method as a result of the significant improvement in bioavailability. Extensive research is now being done on the use of nanosuspensions in various drug delivery methods, including oral, ophthalmic, brain, topical, buccal, nasal, and transdermal routes. The majority of permeability limiting absorption and hepatic first-pass metabolism associated difficulties that negatively affect bioavailability can be resolved with oral drug delivery of nanosuspension with receptor mediated endocytosis, which is a promising capability. The development of enabling technologies like nanosuspension can address several formulation issues that protein- and peptide-based medicines currently encounter.

Keywords: Nanotechnology, First-pass metabolism, Bioavailability, Mucoadhesion, Microemulsion.

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INTRODUCTION

Low bioavailability and irregular absorption are common issues with poorly soluble medications. Early oral formulation development has a significant hurdle due to the therapeutic substance's poor solubility. A medicine's capacity to be absorbed into a patient's gastrointestinal tract can be significantly impacted by a drug candidate's poor or low solubility. These substances are categorized as either BCS Class IV, which are substances with low permeability and poor solubility, or Biopharmaceutical Classification System (BCS) Class II, which means that they have high permeability and low solubility. Formulation specialists must be ready to overcome this difficulty by utilizing a variety of techniques to enhance an API's pharmacokinetics [1]. Enhancing the rate of dissolution and preserving the supersaturated solubility state at the site of absorption must be the major goals of the development procedure [2]. Various methods have been employed to address issues with low bioavailability and poor solubility. These include solid dispersions, nanoparticles, microspheres, and nanostructured lipid carriers [3]. Nanocrystals are produced when drug particle size is reduced to less than 1 m. To create nanosuspensions, nanocrystals can be distributed in aqueous or non-aqueous environments and stabilized with polymers or surfactants. Nanosuspensions are colloidal medication particles that are less than one micron in size and are stabilized in water. The solid particles in nanosuspensions typically have a particle size distribution that is <1 μm, with an average particle size range of 200–600 nm [4]. The Noyes–Whitney equation states that when particle size is decreased, total effective surface area increases, enhancing the dissolving rate [5]. In addition to addressing the issues of poor solubility and bioavailability, a nanosuspension modifies the medication's pharmacokinetics, enhancing medicinal efficacy and safety. The medication is kept in the necessary crystalline or amorphous condition using nanosuspension technology.

NEED FOR NANOSUSPENSION

At present, more than 40% of medications are not well soluble in water, making it challenging to formulate them as standard dose forms [6]. Additionally, BCS Class-II drugs demonstrated low oral bioavailability, which may be related to the drugs helpless water solubility The issue with media is more complicated to preparation. Such chemicals are chosen for nanosuspensions which are soluble in oil but insoluble in water with elevated log *P* value [7]. Various approaches to resolution issues with limited bioavailability and low solubility solvency, aqueous solution, salt, and micronization additional methods of production include liposomes, ß-Cyclodextrin inclusion complex, solid dispersion, emulsions, and microemulsions [8]. However, a lot of these methods are not always effective for each medication. In such circumstances, nanosuspensions are preferred. In these cases nanosuspensions are preferred. In case of drugs that are insoluble in both water and in inorganic media instead of using lipidic systems, nanosuspensions are used as a formulation approach. The most suitable situation is the high-log *P* value, high-melting-point compounds point, and a large dosage. Useful nanosuspensions can make poorly soluble medicines more soluble in lipid and aqueous media. As a result, the active compound's flooding rate increases until the peak plasma level is reached (e.g., oral or intravenous (IV) administration of the nanosuspension)[9]. This is a typical example of advantages over alternative methods for boosting solubility.

BENEFITS OF NANOSUSPENSIONS

- It can be helpful for poorly water-soluble pharmaceuticals, due to its simplicity and wide applicability to all medications.
- Depending on the needs of the formulator, it can be transformed into appropriate dosage forms such tablets, capsules, pellets, hydro gel, and suppositories [10].
- The IV method of administration facilitates fast dissolution and tissue targeting [11].
- Oral nanosuspensions administration gives quick onset and lower fed/fasted ratio enhanced bioavailability, too [11].
- To increase their bioavailability, medicines having high log *P* values can be produced as nanosuspensions [7].
- Change in biological performance as a result too much saturation and dissolution drug's ability to dissolve.

- Simple manufacturing processes and minimal batch-to-batch variance.
- Reduced tissue irritancy whether administered subcutaneously or intramuscularly [11].
- A greater tendency to be sticky, which improves absorption.
- Surface modification of nanosuspension is a possibility for site-specific delivery [7].
- Increasing the amount of amorphous material in the particles, which is crucial to any potential changes to the crystalline structure increased solubility [7].

NEGATIVE ASPECTS OF NANOSUSPENSIONS

- Problems can be caused by physical instability, sedimentation, and compaction [11,12].
- Due to its weight, handling and transportation must be done with care [10].
- It is impossible to provide uniform and correct dosing without suspension when taken as directed [13].

FORMULATION CONSIDERATION

Following agents are used in the preparation of nanosuspensions.

- Stabilizer
- Organic solvent
- Surfactants
- Cosurfactant
- Other additives.

Stabilizer

Without a suitable stabilizer, the high surface energy of nanoparticles can cause the drug crystals to aggregate or clump together [14]. To provide a physically stable formulation, a stabilizer must thoroughly wet the drug particles and prevent Ostwald's ripening and agglomeration of nanosuspensions by supplying steric or ionic barriers [7,10]. The kind and quantity of the stabilizer significantly affects the *in vivo* behavior and physical stability of nanosuspensions [15]. Up till now, lecithin, poloxamer, polysorbate, and cellulosic have all been utilized as stabilizers [12].

Organic solvent

Formulating nanosuspensions utilizing emulsions or microemulsions as templates requires taking into account the acceptance of organic solvents in the pharmaceutical industry [5,13], their potential for toxicity, and how simple it is to remove them from the formulation. It is preferred in the formulation to use pharmaceutically acceptable and less dangerous water-miscible solvents, such as ethanol and isopropanol, as well as solvents that are only partially water-miscible, such as ethyl acetate, ethyl formate, butyl lactate, triacetin, propylene carbonate, and benzyl alcohol [16].

Surfactants

Surfactants are substances that reduce the surface tension between two liquids [13], a liquid and a solid, or a gas and a liquid. Surfactants can function as wetting agents, detergents, emulsifiers, foaming agents, dispersants, or emulsifiers. Surfactants like Tweens and Spans are frequently utilized in nanosuspension [7].

Cosurfactant

When creating nanosuspensions using microemulsions, the choice of co surfactant is crucial. Since cosurfactants have a significant impact on section behavior, it is important to explore how they affect drug loading and the uptake of the inside section for a given microemulsion composition [16]. As an illustration, cosurfactants can include transcutol, glycerol, ethanol, and isopropanol bile salts as well as dipotassium glycyrrhizinate.

Other additives

Depending on the route of administration or the characteristics of the drug moiety, nanosuspensions may contain additives such buffers [12], salts, polyols, cosmogenic, and cryoprotectants [4,7].

Applications for nanosuspensions

- Oral drug delivery
- Parental drug delivery
- Ocular drug delivery
- Pulmonary drug delivery
- Targeted drug deliver
- Topical
- Mucoadhesion of the nanoparticles.

Oral drug delivery

Drugs that have been nanosized have higher oral absorption and hence higher bioavailability [16]. The higher saturation solubility of the drug nanoparticles and the increased concentration gradient between the blood and gastrointestinal tract lumen are the two factors that contribute to improved bioavailability. Both a dry dosage form, such as a tablet or hard gelatine capsule with pellets, and a liquid dosage form, such as aqueous nanosuspensions, can be utilized directly [13,16,17]. Nanosuspensions can also be sprayed dried to form granulates.

Parental drug delivery

Several parental routes, including intra-articular, intraperitoneal, intravenous, are used to administer nanosuspensions [18]. Parenteral use of a nanocrystals aims to alleviate the toxicity problems associated with non-aqueous formulations while also providing tailored effects. When compared to traditional drug delivery methods, a parenterally delivered nanosuspension formulation exhibits reduced toxicity [13]. For the increased permeability and retention effect (EPR effect) to obtain medication concentration in solid tumors, which are said to have particularly dense vasculature, a size range between 100 and 300 nm is suitable [19]. Poorly soluble medication tarazepide has been made into injectable nanosuspensions in an effort to improve on the limited efficacy of traditional solubilization methods, which include the use of surfactants and cyclodextrins to increase bioavailability.

Ocular drug delivery

The recommended method of administering medications for eye diseases such as infections, inflammation, dry eye syndrome, glaucoma, and retinopathies is through ocular drug delivery [13]. Some medications do not dissolve well in lachrymal fluid. Since many of the biological barriers of the eye can be overcome by nanocarrier-based drug delivery systems (such liposomes and polymeric micelles), research has concentrated on these methods for improving ocular medication bioavailability. Due to the rapid clinical development and commercialization of nanocrystals compared to other types of nanotherapeutics, such as liposomes and dendrimers [20], the use of nanocrystals as an ocular formulation method for poorly water-soluble medicines has recently grown in favor. Improved ocular safety, increased formulation retention in cul-de-sac, improved corneal permeability across the corneal and conjunctival epithelium, improved ocular bioavailability, dual drug release profile in the eye, and improved tolerability are all benefits of using nanocrystals for drug delivery to the eye.

Pulmonary drug delivery

Drugs with poor pulmonary secretion solubility may be delivered most effectively by nanosuspensions. Mechanical or ultrasonic nebulizers can be used to nebulize aqueous nanosuspensions for lung administration [21]. Given their small size, it is likely that each aerosol droplet contains at least one drug particle, resulting in a more even dispersion of the medication throughout the lungs. The drug's nanoparticulate structure enables quick diffusion and disintegration at the site of action.

Targeted drug delivery

Because their surface characteristics and the behavior of the stabilizer may be easily changed *in vivo*, nanosuspensions can also be employed for targeting. The mononuclear phagocytic system will take the medication up and administer it locally [22]. If the infectious pathogen is still present inside the macrophages, this can be utilized to direct antifungal, antifungal, or antileishmanial medications to the cells.

Topical drug delivery
Creams and waterless ointments can contain drug nanoparticles. Medication diffusion into the skin is improved by the nanocrystalline forms' higher saturation solubility of the drug in the topical dose form. As a result, topical lotions serve as the best illustration of suspensions with slow settling rates [23].

Mucoadhesion of nanoparticle
If the nanosuspension is taken orally, it clings to the mucosal surface and diffuses into the liquid medium before being absorbed [21]. For example, buparvaquone against cryptosporidium parvum enhances bioavailability and targeting to the parasite inside the gut [13,21,24-26] (Table 1).

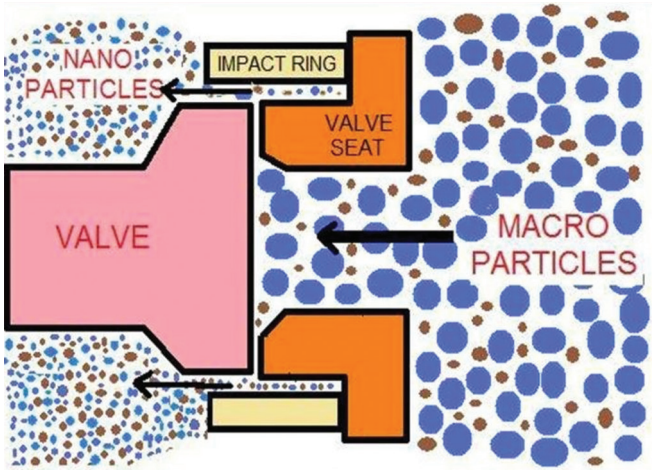
PREPARATION METHODS FOR NANOSUSPENSION

Technically, nanosuspension preparations are a less complex alternative to liposomes and other common colloidal drug carriers, but they are reportedly more economical. It produces a physically more stable product and is especially for medications that are poorly soluble (Fig. 1). There are two opposing techniques, known as "Top-down process technology" and "Bottom-up process technology," for producing nanosuspensions [7,25,27-29]. The top-down method adopts a disintegration strategy starting with large particles and progressing to microparticles and nanoparticles.

TOP-DOWNMETHOD

High-pressure homogenization method
The following three phases are included in this technique: Presuspensions are created by first dispersing drug powders in a stabilizing solution. Presuspensions are then homogenized by high-pressure homogenizers at low-pressure occasionally for premilling. Finally, presuspensions are homogenized at high pressure for 10–25 cycles [30] until the nanosuspensions are formed with the desired size. On the basis of this idea, various methods have been developed for making nanosuspensions, including:

a. Homogenization in aqueous media (Disso cubes)
b. Homogenization in non-aqueous media (Nanopure)
c. Combined precipitation and homogenization (Nanoedge)
d. Nanojet



Schematic representation of high-pressure homogenization [31].

Homogenization in aqueous media (disso cubes)
Using a piston-gap type high-pressure homogenizer, R.H. Muller created this technology in 1999. The basic idea is high pressure with a volume capacity of 40 ml and pressures between 100 and 1500 bar and up to 2000 bar (for laboratory scale). We can easily change micron-sized particles into nanosized particles by applying this pressure. We must obtain the sample from the jet mill so we can utilize it to lower the particle size down to 25 microns [32], which is what it initially requires as a micron range particle. In addition, we may perform batch and continuous operations with this equipment. Here, we must first transform the particles into a presuspension state [33].

Principle
The cavitation principle is the main foundation of this technique [29]. The 3 cm diameter cylinder's dispersion is suddenly forced into a 25 m-wide opening. The drift volume of liquid in a closed system per cross-section is constant, according to Bernoulli's law. Due to a decrease in diameter from 3 cm to 25 m, it causes an increase in dynamic pressure and a decrease in static pressure below the boiling point of water at ambient temperature. Then, as the suspension leaves the gap (a process known as cavitation) and normal air pressure is reached, water begins to evolve boiling at room temperature and generates gas bubbles that implode. The drug nanoparticles are created when the particle cavitation forces are sufficiently high.

Homogenization in non-aqueous media (Nanopure)
Nanopure consists of homogenized suspensions in water-free media or water-based media such as PEG 400, PEG 1000, etc. [30]. The non-aqueous drug suspensions were homogenized at 0°C or even below the freezing point, which is known as "deep-freeze" homogenization. The results were comparable to DissoCubes, so they can be employed effectively for thermolabile compounds under more tolerant circumstances. Drug suspensions made from drug nanocrystals suspended in liquid polyethylene glycol (PEG) or a number of oils can be put straight into HPMC capsules or gelatin.

Combined precipitation and homogenization (nanoedge)
To precipitate the medication, the organic solvent in which it is dissolved is mixed with a miscible anti-solvent. The medication precipitates due to the low solubility in the water-solvent mixture. High-shear processing has also been combined with precipitation [34]. Rapid precipitation and high-pressure homogenization are used to accomplish this. To fragment materials, the nanoedge patented technique through Baxter relies on the precipitation of friable materials under conditions of high-shear and/or thermal energy. When a medication solution is added quickly to an antisolvent, the blended solution unexpectedly becomes supersaturated and produces fine crystalline or amorphous particles. When the solubility of the amorphous state is exceeded, precipitation of an amorphous material may also be observed at high supersaturation.

Precipitation and homogenization have the same fundamental principles as nanoedge. Combining these techniques yield faster improvement in stability and lower particle sizes. The nanoedge technology can address the primary drawbacks of the precipitation method, such as crystal development and long-term stability [35].

Nanojet
This process, also known as opposite stream or nanotechnology, makes use of a chamber, in which a stream of suspension is split into two or more components that collide under high pressure. Particle size reduction is a result of the process's strong shear force [36]. The M110L and M110S microfluidizers (Microfluidics), which are used in the preparation of atovaquone nanosuspensions, operate on this concept [37]. The main drawback of this method is the high volume of passes through the microfluidizer and the correspondingly higher percentage of microparticles found in the final product [38].

Media milling (nanocrystal)
This process was first patented by the "Nanosystems" group after being developed by Liversidge *et al*. in 1992 [39]. It has now been licensed to "Elan medication delivery." Here, the high-shear rate reduces the particle size. In addition, the entire procedure is carried out at a controlled temperature [40]. Otherwise, a temperature will develop up at high-shear rates, degrading some of the dosage form's contents.

High-shear media milling or pearl mills are the names given to this machinery.

Three main columns make up this mill (Fig. 2):

- The milling chamber,
- The milling shaft,
- Recirculation chamber

PRINCIPLE

The energy input required to break down the drug's microparticulate form into nanoparticles comes from the high energy and shear pressures produced by the drug's impaction with the milling media. Glass, zirconium oxide, or strongly cross-linked polystyrene resins make up the milling media. The procedure can be run either in batch mode or in recirculation mode. It takes 30–60 min to create dispersions in batch mode with unimodal distribution profiles and mean diameters of 200 nm. Both micronized and non-micronized drug crystals can be successfully processed by the media milling method. Once the technique and formulation are adjusted, there is relatively little batch-to-batch fluctuation in the dispersion's quality.

BOTTOM-UP PROCESS

It is a technique for achieving nanosize by increasing particle size from the molecular to the nanoscale region. Bottom-up technique refers to the conventional precipitation ("Hydrosol") methods. The medication is dissolved in an organic solvent using the precipitation process, and the resulting solution is combined with a miscible anti-solvent [28]. The medication precipitates due to the low solubility in the water-solvent mixture. The main issue is that, to prevent the creation of microparticles during the precipitation process, the crystal development must be regulated by adding surfactant [41].

Advantages

1. Use of simple and inexpensive equipment and
2. Greater saturation solubility is advantages of precipitation over other nanosuspension guiding techniques [28].

Disadvantages

1. Precipitation system no longer contains drugs that are insufficiently soluble in fluid and non-watery conditions. The drug should dissolve in at least one dissolvable that is miscible with non-solvent in this

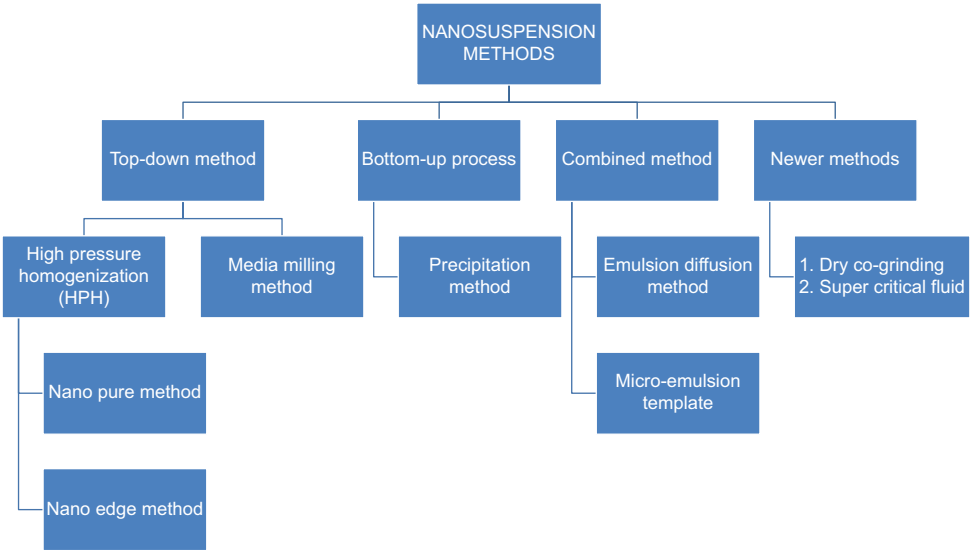


Fig. 1: Methods for nanosuspensions

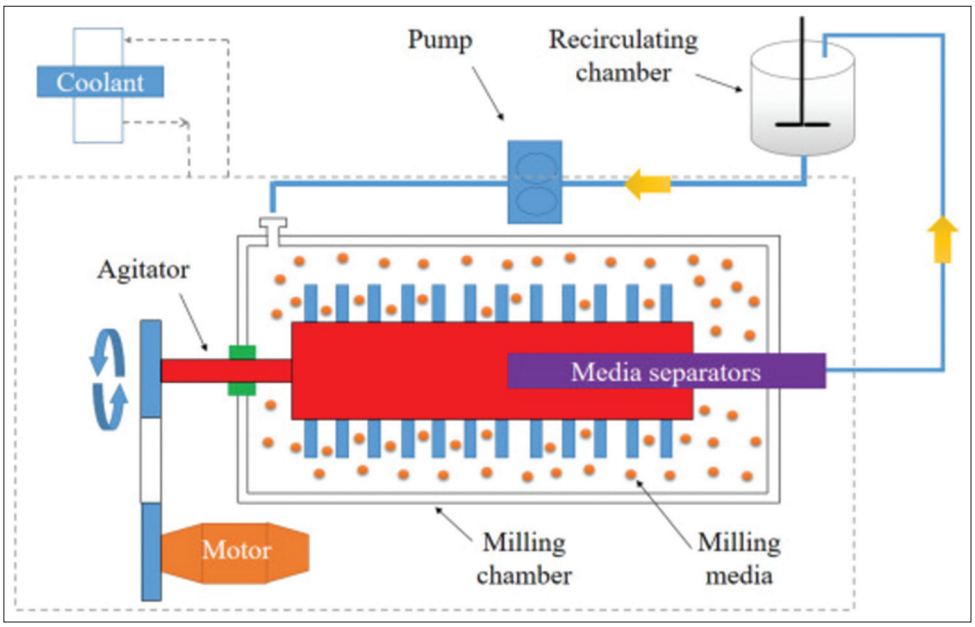


Fig. 2: Schematic representation of Media milling [22]

Table 1: Current marketed formulations of nanosuspensions [13,24-26]

Trade name/company	Drug	Dosage form and route of administration	Nanosuspension method	Indication
Triglide/First Horizon pharma	Fenofibrate	Tablet/oral	Nanocrystal elan nanosystems	Hypercholesterolemia
Emend/Merck	Aprepiant	Capsule/oral	Nanocrystal elan nanosystems	Antiemetic
Rapamune/Wyeth	Sirolimus	Tablet/oral	Nanocrystal elan nanosystems	Immunosuppressant
Giris-PEG/Novartis	Griseofulvin	Tablet/oral	Coprecipitation	Antifungal
InvegaSustenna/Johnson and Johnson	Paliperidone palmitate	Liquid Nanosuspension/ parental	High-pressure homogenization	Schizophrenia
Megace ES/Par pharmaceutical Companies	Megestrol-acetate	Liquid nanosuspension/ oral	Nanocrystal Elan Nanosystems media milling	Anti-emetic

PEG: Polyethylene glycol

system [28].

2. Stop crystal growth from Ostwald ripening, which is caused by special saturation solubilities near particles of different sizes.

PRECIPITATION METHOD

A common technique for creating submicron drug particles that are poorly soluble is precipitation [42]. This procedure involves dissolving the drug in a solvent before adding the solution to the solvent, which the drug cannot dissolve in the presence of. Rapid addition of the solution to such a solvent (often water) causes the drug to quickly become supersaturated in the solution and forms an ultrafine amorphous or crystalline drug [43]. This process involves crystal growth and nucleus production [44], both of which are largely temperature-dependent. To create a stable suspension with a small particle size, high-nucleation rate, and low crystal growth rate are essential [45] (Fig. 3).

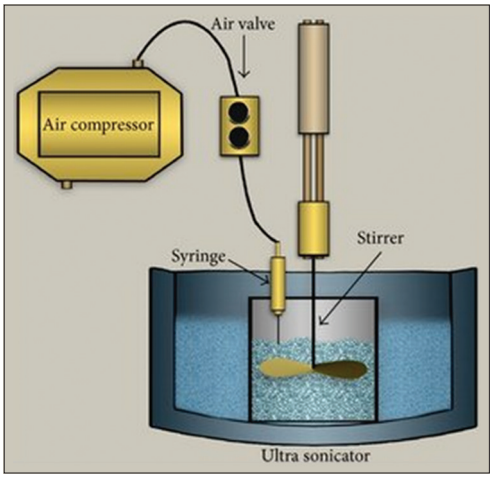


Fig. 3: Schematic representation of precipitation method [4]

COMBINED METHODS

Emulsification-solvent evaporation technique

This process requires making a pharmaceutical solution, then emulsifying it in a different liquid that isn't the drug's solvent. The solvent evaporates, causing the medication to precipitate. High-shear forces produced by a high-speed stirrer can be used to control crystal formation and particle aggregation.

Hydrosol method

The emulsification-solvent evaporation technique is comparable to this. The fact that the drug solvent and drug anti-solvent are miscible is the only difference between these two techniques [46]. Higher shear forces assure that the precipitates stay smaller by preventing crystal development and Ostwald ripening [47].

Emulsion as templates

Emulsions can also be utilized as templates to create nanosuspensions in addition to being a drug delivery system. For pharmaceuticals that are soluble in both volatile organic solvent and a somewhat water-miscible solvent, emulsions can be used as templates. To create an emulsion, a drug-loaded organic solvent or combination of solvents is dispersed in an aqueous phase with the right surfactants. The drug particles instantly precipitate to create a nanosuspension that is stabilized by surfactants as the organic phase is subsequently evaporated under lower pressure [48]. Since one particle develops in each emulsion droplet, it is possible to regulate the nanosuspensions particle size by adjusting the emulsion's size.

Microemulsion as template

The majority of medications that can be dissolved using this method are those that can be dissolved in partly water miscible solvents or volatile organic solvents [12]. This process involves dissolving the drug in an appropriate organic solvent, followed by emulsifying it with an appropriate surfactant in an aqueous phase. The organic solvent was then gradually evaporated under reduced pressure to create drug particles that precipitated in the aqueous phase and created the necessary particle size for the aqueous suspension of the drug. The created suspension can then be appropriately diluted to create nanosuspensions. In addition, nanosuspensions can be created using microemulsions as templates. Microemulsions are isotopically transparent dispersions of two immiscible liquids, such as oil and water that are thermodynamically stable and held together by an interfacial coating of surfactant and cosurfactant. Either the drug can be intimately mixed into the pre-formed microemulsion or it can be loaded into the internal phase. The medication nanosuspension is produced by appropriately diluting the microemulsion. Lipid emulsions have the benefit of being simple to scale up and easy to generate when used as templates for the production of nanosuspension. However, the use of organic solvents has an impact on the environment, necessitating the employment of substantial volumes of surfactant or stabilizer.

NEWER METHODS

Supercritical fluid method

To create nanoparticles, a variety of techniques are employed, including the rapid expansion of supercritical solution (RESS) process, the supercritical antisolvent process, and the precipitation with compressed antisolvent (PCA) process. In the RESS technique, drug solution is expanded through a nozzle into supercritical fluid, causing the supercritical fluid to lose some of its solvent power, precipitating the drug as small particles [49]. Young *et al*. created cyclosporine nanoparticles with a diameter of 400–700 nm using the RESS technique. The medication solution is atomized into the CO_2 compressed chamber while using the PCA method. The solution becomes oversaturated when the solvent is removed, which leads to precipitation. When a drug solution is injected into a supercritical fluid during a supercritical antisolvent procedure, the solvent is removed and the drug solution is transformed into supersaturated.

Dry-co-grinding

Many nanosuspensions are being made using the dry milling process. Dry-co-grinding can be done quickly, affordably, and without the need of organic solvents. Due to an improvement in surface polarity and a change from a crystalline to an amorphous drug, co-grinding improves the physicochemical characteristics and dissolving of poorly water-soluble medicines.

Techniques for characterizing nanosuspensions

The safety, effectiveness, and stability of nanodrug delivery systems are affected by the particle size, particle size distribution, and zeta potential. The solid state of nanoparticles also affects how efficiently they dissolve. As a result, nanoparticle characterization is crucial for predicting the effectiveness of nanodrug delivery systems both *in vitro* and *in vivo*. Nanosuspension's *in vivo* pharmacokinetic performance and biological function are highly influenced by the particle size and distribution, charge (zeta potential), crystallinity, and shape of the particles [50].

Particle size distribution

The mean particle size and width of the particle size distribution, which control the physicochemical features such as saturation solubility, dissolving velocity, physical stability, and even biological performance, are the most relevant characterization parameters for the nanosuspension. The saturation solubility and dissolving speed varies with particle size. The saturation solubility and dissolution will be greater the smaller the particle size.

Photon correlation spectroscopy (PCS), laser diffraction (LD), and coulter counter multisize are three different techniques for detecting particle size distribution.

Even the width of the particle size distribution can be assessed using PCS (polydispersity index, PI). For long-term stability of nanosuspensions, the PI, an important parameter that controls the physical stability of nanosuspensions, should be as low as possible. A highly broad distribution is indicated by a PI value greater than 0.5. Since PCS only measures particles with a size between 3 nm and 3 μm [51], it is challenging to predict whether microparticulate medicines (those with a particle size higher than 3 m) could contaminate the nanosuspension. Laser diffractometry (LD) analysis of nanosuspensions should therefore be performed in addition to PCS analysis to detect and quantify any drug microparticles that may have been created during the manufacturing process. Particle sizes in the range of 0.0580–2000 m are determined by LD [52]. Along with PCS and LD measurements, particle size analysis using the Coulter counter technique is important. Due to the fact that the Coulter counter provides the absolute number of particles per volume unit for the various size classes.

Surface charge (zeta potential)

Zeta potential is used to examine the nanosuspensions' surface charge characteristics. The particle surface charge value reveals the stability of macroscopic nanosuspensions. For steric stabilization, a zeta potential of at least 20 mV is needed, whereas at least 30 mV is needed for electrostatic stabilization. The electrophoretic mobility of the particle is typically determined, and the electrophoretic mobility is then converted to the zeta potential to determine the zeta potential values. In the field of material sciences, the zeta potential is also determined using the electroacoustic approach**.**

Crystalline state and particle morphology

Determining the polymorphism or morphological changes that a medicine may go through when subjected to nanosizing is made easier by combining an evaluation of the crystalline state and particle morphology. In addition, it is conceivable that drug particles in an amorphous state will be produced during the preparation of nanosuspensions [50]. Therefore, it is crucial to look into how much amorphous drug nanoparticle is produced during the creation of nanosuspensions. Differential scanning calorimetry can be used in addition to X-ray diffraction analysis to evaluate the extent of the amorphous fraction and changes in the physical state of the drug particles. Scanning electron microscopy is preferred to provide a more accurate picture of particle morphology.

Saturation solubility and dissolution velocity

The dissolving velocity and saturation solubility are both accelerated by nanosuspension. Reduction in size causes the dissolving pressure to rise. A change in surface tension that results in a rise in saturation solubility may be the primary cause of an increase in solubility that happens with relatively little particle size decrease.

Evaluation parameters

The nanosuspension was evaluated for various parameters:

- Content uniformity
- pH
- Particles size and shape
- *In vitro* drug release studies

Content uniformity

Each formulation was diluted in 10 ml of isotonic solution, and then left overnight. The substance was diluted to 10 g/ml after being administered in doses of 10 mg (identical to the formulation). The dilutions' uniformity in content was checked by UV analysis after filtering. In a UV-Vis spectrophotometer, the absorbance of the formulations was measured using a 1 cm cell. The device was calibrated at 245 nm. The absorbance readings of well-known reference solutions were used to calculate the drug content in each formulation.

pH

A pH digital meter set at 20°C was used to measure the pH readings at 25°C. The mixture was placed in close proximity to the electrode of a pH meter and allowed to equilibrate for 1 min. The mean and standard deviation were computed using this method in triplicate.

Particles size and shape

Scanning electron microscopy was used to analyze the nanosuspension formulation's particle size and shape.

***In vitro* drug release studies**

The paddle approach was used in *in vitro* drug release experiments in a dissolving system with a rotation speed of 50 rpm. The dissolving media had a volume of 900 ml and a temperature of 37.0 0.2°C, respectively. Samples were taken out at predetermined intervals, filtered, and tested using a UV-Visible spectrophotometer to measure their ultraviolet absorbance at 245 nm.

CONCLUSION

Hydrophobic pharmaceuticals and medications that are poorly soluble in aqueous and organic solutions have poor bioavailability issues that have been resolved by nanosuspension. The development of therapeutic nanosuspensions made using a variety of methods, including high-pressure homogenization, media milling, and emulsification, is presented in this review. The uses of nanosuspensions for different routes have expanded due to their desirable properties, such as higher dissolution velocity, increased saturation solubility, improved bioadhesive, variety in surface modification, and ease of postproduction processing. Although uses for pulmonary and ocular distribution still need to be assessed, the applications of nanosuspensions in oral and parental routes are extremely well-established. However, their topical, nasal, and buccal administration methods have not yet been completed. Consequently, nanotechnology can be quite useful in drug discovery programs to both enhance.

AUTHORS CONTRIBUTIONS

All authors contributed equally to this work.

CONFLICTS OF INTEREST

The authors have no conflicts of interest regarding this investigation.

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