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THE IMPACT OF NANO-SUSPENSIONS ON DRUG DELIVERY: ENHANCING SOLUBILITY AND THERAPEUTIC EFFICACY

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ABSTRACT
At large, poor aqueous solubility remains a significant challenge in drug development and formulation limiting bioavailability and therapeutic efficacy. The formulation is deemed successful when it achieves the desired solubility and better bioavailability of the drug, which is important for pharmacological responses. However, 40 percent of newfound chemical entities (NCEs) industrialized by the pharmaceutical industry are primarily lipophilic and exhibit poor water solubility which result in various challenges in the development and formulation of BCS class II & IV. Nanosuspension, a sub-micron colloidal dispersion of nano-sized drug particles becomes a promising solution to overcome these issues. It involves various techniques top-down (Media milling, High-pressure homogenization) and bottom-up (precipitation, supercritical fluid) technology. In the formulation of nanosuspension excipients, a critical consideration is vital for excipients categories like stabilizers, surfactants, co-surfactants, buffers, preservatives are used for the better output of the product. Characterization of nanosuspension is essential to assess the quality and performance. This review emphasizes various pros and cons, emphasizing the applications of nanosuspensions.

KEYWORDS: Nanosuspension, top-down and bottom-up technology, excipients consideration, poor solubility, and bioavailability.

INTRODUCTION
In the recent past, a significant focus of the pharmaceutical industry is on the development of innovative, cost-effective, and efficient therapeutic agents that exhibit optimal physicochemical and biological properties.[1] The solubility of a drug particles plays critical role in achieving the desired bioavailability, which directly influences pharmacological responses.[2] The drug bioavailability is based on various factors, such as aqueous solubility, dissolution rate, porosity, condition-to-efflux mechanisms, and the effects of first-pass metabolism.[3] The solubility term refers to, the maximum amount of solute that can be dissolved in a specific volume of solvent at selected temperature and pressure conditions, resulting in a homogeneous solution.[4] If a solute and solvent are in an equilibrium state, the solution is considered saturated. Drug solubility can be expressed using various concentration expressions, including parts, percentage, molarity, molality, volume fraction, and mole fraction.[5] The US Food and Drug Administration (FDA) presented the Biopharmaceutics Classification System (BCS), in which the drugs are classified into 4 classes which depend on its solubility and permeability, as shown in Table 1.

Table 1: BCS classification.

Class	Permeability	Solubility
I	High	High
II	High	Low
III	Low	High
IV	Low	Low

Necessity of Solubility
Oral administration is often considered the most convenient method of delivering medication due to its ease of ingestion and pain-free treatment; this approach tends to enhance patient compliance. However, poor solubility can compromise the drug's efficiency. Additionally, it poses significant challenges in the development and formulation of BCS Class II and IV medications, there by complicating efforts to achieve the desired therapeutic outcomes.[6] If a drug has poor

solubility, the amount required for effective action in the target area will be less than what is administered. To address this issue, either the dose or the frequency of dosing has to be increased. However, either of the approaches can lead to adverse effects, as every drug has potential side effects, and patients may experience additional health issues as a result.[7]

FACTORS AFFECTING SOLUBILITY[8-15]

1. Particle size plays a vital role in solubility. As particle size reduces, the surface area increases, resulting in a higher interaction with the solvent and enhanced solubility.

2. Molecular size: The solubleness of substances decreases with an increase in their weight and size because it's more difficult to encircle larger molecules with solvent in order to solvate the substance.

3. Temperature affects solubility: It increases when a solution absorbs energy and decreases when it releases energy.

4. Pressure: In case of gaseous solute, solubility is directly proportional to pressure. The solubility increases with pressure and reductions with a decrease in the pressure. Henry's law clearly defined the relationship between pressure and solubility of a gas, which is termed after its inventor, English physician and chemist, William Henry

$C = k P$

Where the level of dissolved gas at the point of equilibrium.

C = represents the amount of dissolved gas at the point of equilibrium,

P = partial pressure of the gas, and

k = Henry's law constant, should be resolute experimentally for each mixture of gas, solvent, and temperature.

5. Polarity: The solubility can be affected by polarity of the solute and solvent molecules. The basic of principle polarity is "like dissolve like" which means a polar solute molecule dissolves in a solvent and a nonpolar solute molecule dissolves in a non-polar solvent.

6. Crystal Structure: The amorphous form of drugs is more soluble than the crystalline form. In terms of solubility, the order of solubility is solvates > anhydrous > hydrates.

7. Molecular Structure: Minor changes in the molecular structure of solids can significantly affect their solubility. For instance, the introduction of a hydroxy group enhances water solubility, as seen with phenol compared to benzene.

8. Co-solvency: A co-solvent system mixes a water-miscible or partially miscible organic solvent with water to create a modified aqueous solution called co-solvency. Co-solvents, like ethanol, sorbitol, and glycerin, form hydrogen bonds that interact with hydrocarbon regions, resulting in properties between those of pure organic solvents and water. These effects can be diminished by water-water interactions.

TECHNIQUES FOR SOLUBILITY ENHANCEMENT

To improve solubility various techniques are used as follows

I. Physical Methods

1. Reduction of particle size

a) Micronization
b) Sonocrystallization
c) Nano suspension

2. Modification of crystalline structure

a) Polymorphs
b) Pseudo polymorphs

3. Drug dispersion in carriers

a) Solid dispersion
- Fusion method
- Solvent technique
- Fusion solvent technique
- Spray dry technique
- Freeze-drying
- Hot melt extrusion dropping process

b) Solid solution
c) Cryogenic techniques.

4. Complexation

a) Physical mixture
b) Kneading technique
c) Coprecipitation technique
d) Microwave irradiation method.

5. Solubilization through Surfactants

a) Microemulsion
b) Self-micro emulsifying method.

II. Chemical Modifications

a) Salt formation
b) Co-crystallization
c) Change in pH
d) Use of buffer
e) Complexation.

III. Miscellaneous Methods

a) Use of adjuvant
b) Solubilizes
c) Co-solvency
d) Hydro trophy

"This article provides a brief overview of nanosuspension, a technique used to enhance solubility."

In this era, where solubility and bioavailability are becoming challenging, nanotechnology arises as a game changer in pharmaceutical formulation development. There are numerous formulation techniques offered to address the challenges related to drugs that have less solubility and bioavailability.[16] The traditional methods, such as micronization, the use of fatty solutions, the use of co-solvents or penetration enhancers, the wetting agent dispersion technique, Salt formation, Precipitation, etc., are still not very useful for improving the solubility of poorly soluble medications. These methods are effective as drug delivery systems, but their main drawback is that they are not universally applicable to all medications.[17] Over the past few years, nanoparticle manufacturing has remained researched and developed for therapeutic purposes.[18]

WHY NANO SUSPENSION

The nano-suspension means "Nano-sized drug particles are suspended in water-based solutions along with surfactants to keep them stable". The suspended particles are smaller than 1 micrometer, ranging from 0.1 to 1,000 nanometers. The distribution of solid particles in nanosuspension tends to be less than one micron with an average particle size ranging between 200 nanometers and 600 nanometers.[19,20] When the drug particle size is reduced to the nanometer range (small size), It increases the rate of dissolution by increasing the surface area.[21] The nano-size particles can be used in the formulation and development of the drug compounds that belong to BCS class II and IV.[22] This technique is suitable for drug compounds insoluble in water and organic solvents but soluble in oil, characterized by a high log P value, high melting point, and high dose. Hydrophobic drugs like naproxen, clofazimine, and spironolactone are formulated as nano-suspensions.[24-30]

Major advantages of Nano suspensions[31,32]

- Increase in solubility and dissolution rate of the poorly water-soluble drugs.
- Appropriate for hydrophobic drugs.
- Improve the physical and chemical stability of drugs.
- Oral administration of nano-suspensions provides immediate action, lowered fed/fasted ratio, and enhanced bioavailability.
- Nano-suspensions can be used in tablets, pellets, hydrogels, and suppositories, making them suitable for various methods of administration.
- Enduring physical stability (absence of Ostwald ripening).
- Elevating the amorphous fraction within the particles can induce variations in the crystalline structure, thereby enhancing solubility.
- Nano-suspensions offer flexibility in drug delivery and different routes can be used to administer them, including parenteral, oral, dermal, pulmonary, and ocular routes, providing flexible treatment options.

Excipients consideration in formulating Nano suspension[33-36]

Excipients play a vital role in the preparation of nanosuspension as they assistance in stabilizing the nanoparticles and prevent them from aggregation.

Table 2: Consideration of excipients while formulation a nano suspension.

CATEGORY	EXCIPIENTS EXAMPLE	USE
Stabilizer	***Surfactants*:** Tween 80, Poloxamers 188, Sodium lauryl sulfate (SLS), Lecithin ***Co-surfactants*:** Bile salts, transcutol, glycofurol, ethyl alcohol, and isopropyl alcohol. ***Polymers:*** Hydroxypropyl.methylcellulose.(HPMC), Hydroxypropyl cellulose (HPC), Polyvinylpyrrolidone (PVP), Polyvinyl alcohol (PVA) ***Amino-acid-based stabilizers***: Glycine, Histidine, Arginine, Lysine, Proline	• Stabilizers prevent • nanoparticle agglomeration. • Maintain physical stability. • Influence in-vivo behavior. • Can be used in combination. • Lecithin is a popular choice for parenteral formulations.
Organic solvents	Ethyl Alcohol, Acetone, Butanol, Ethyl formate, Ethyl Acetate, Ethyl Ether, Methyl Acetate, Methyl Ethyl Ketone, Triacetin.	• Class three organic solvents exhibiting lower toxicity profiles for human exposure. • **Enhance:** Drug solubility, particle size control, and drug loading
Osmotic agent	Mannitol, Sorbitol	• Used to adjust osmotic pressure in parenteral formulations and control tonicity.
Buffers	Phosphate buffer, sodium acetate	• Maintaining optimal pH for drug stability and activity.
Preservative	Phenoxyethanol and Ethylhexylglycerin (Euxyl PE 9010), Caprylyl glycol	• Protecting the formulation from microbial contamination.

PREPARATION METHODS OF NANO-SUSPENSION

Nanosuspensions are primarily prepared using two main approaches 'Bottom up technology' and 'Top up technology.'

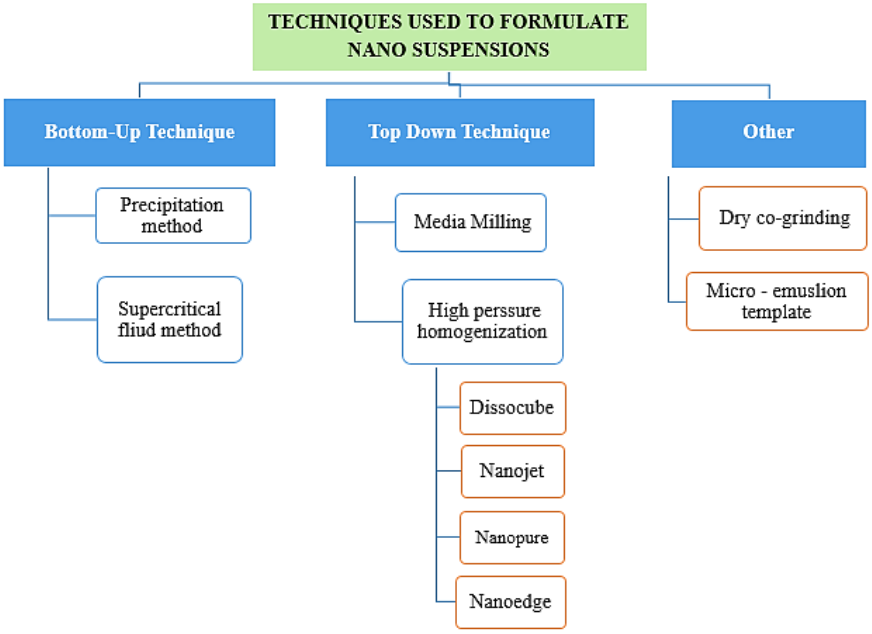

Figure 1: Techniques used in the formulation of nanosuspension.

I) BOTTOM-UP TECHNIQUE

This technique involves obtaining nanoparticles by reducing the size of particles from the molecular range to the nano range. The conventional precipitation methods, known as 'Hydrosol,' are categorized as Bottom-Up technology. In the precipitation method, the drug is dissolved in an organic solvent, which is then mixed with a miscible anti-solvent. The solubility in the water-solvent mixture is low, causing the drug to precipitate. A key challenge during precipitation is controlling crystal growth, which can be managed by adding a surfactant to prevent the formation of microparticles.[37]

ADVANTAGES

- Simple and cost-effective equipment can be used.
- Precipitation offers higher saturation solubility compared to other nano-suspension preparation methods.

DISADVANTAGES

- The drug must be soluble in at least one solvent, limiting the use of this method for new drugs with poor solubility in both aqueous and organic solvents.
- A miscible non-solvent must be available to work with the solvent being used.
- Removal of solvent residues adds to production costs.
- Maintaining particle characteristics, especially size, and amorphous content, can be difficult. To preserve particle integrity, processes like Lyophilization or spray drying are often required.[38-39]

❖ **Solvent-Anti-Solvent Method[40]**

This technique, also known as the precipitation method, involves dissolving a drug substance in a suitable solvent (usually water) to form a solution.

PROCEDURE

Dissolve drug in a suitable solvent (acetone, ethanol, methanol)

↓

Select an anti-solvent in which the solvent is miscible but not the drug solution. To avoid aggregation of particles, add surfactants. (*on Rapid mixing)*

↓

Add drug solution into the anti-solvent rapidly under controlled conditions, resulting in supersaturation of the drug in the mixture.

↓

Temperature should be in optimized condition to promote nanosuspension and to avoid crystal growth.

↓

Formulation of either amorphous or crystalline ultra-fine drug particles.

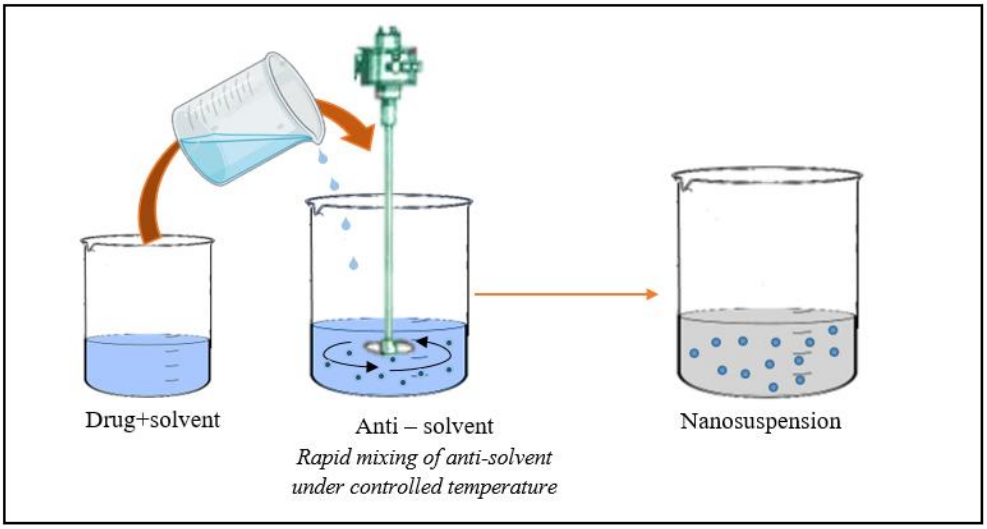

Figure 2: Anti-solvent method.

❖ **Supercritical Fluid Method**

A supercritical fluid refers to a substance that is at a temperature and pressure beyond its critical point, resulting in the absence of liquid and gas phases.[41] A supercritical fluid has a density similar to that of a liquid and a diffusion coefficient (diffusivity) which is like gases. Nanosuspensions can be prepared using techniques like Rapid Expansion of Supercritical Solution (RESS), Supercritical Anti-solvent, and Precipitation with Compressed Anti-solvent (PCA).[42]

II) TOP-DOWN TECHNIQUE

❖ **Media milling (Nanocrystals or Nanosystems)**

In 1992, Liversidge et. al. invented the media milling method, which was subsequently patented by "Nano-Systems" and is currently held by Elan Drug Delivery.[43]

Principle: The milling process uses high energy and shear forces from milling media collisions to break down larger drug particles into nanoparticles. Milling media, such as glass, zirconium oxide, or cross-linked polystyrene resin, are used in batch or recirculation modes. In batch mode, dispersions with unimodal distribution and particle sizes under 200 nm are typically achieved within 30 to 60 minutes. This method works for both micronized and non-micronized drug crystals. Once optimized, batch-to-batch variation in dispersion quality is minimal.[44-45] The equipment used in this technique is called a "high-shear media mill" or "pearl mill." As shown in Figure 3. Advanced equipment like planetary ball mills (e.g., PM200, PM100) can achieve particle sizes below 0.1 µm.[46]

PROCEDURE

Preparation of Drug Suspension

Drug, stabilizer, and liquid medium (e.g., water)

↓

Selection of Milling Media

High-density beads (zirconium, glass, or steel)

↓

Milling Process

High-speed rotation of the milling chamber and beads collide with drug particles, reducing size Continued until desired particle size is achieved

↓

Stabilization and Collection

Stabilizer prevents aggregation of nanoparticles Separation of beads and collection of nanosuspension.

Nanosuspension

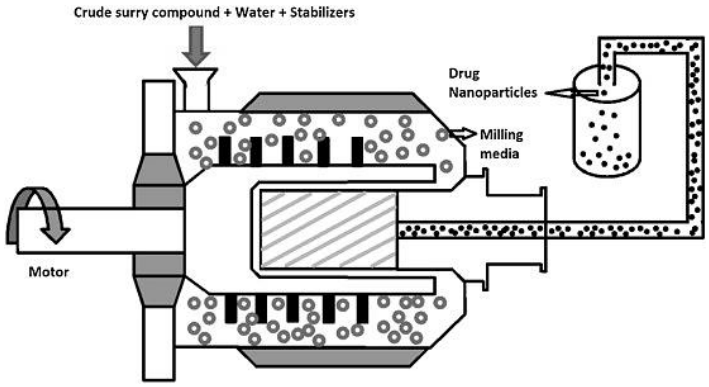

Figure 3: Media milling Schematic demonstration of the media milling method. The milling chamber is charged with milling media. A crude slurry containing of drug, water and stabilizer is fed into the milling chamber and processed into a nano-crystalline dispersion.[47]

Limitations

- Milling nanosuspensions can lead to contamination by media residues, posing health risks for chronic therapies.
- However, advancements in milling technology, specifically with the introduction of polystyrene resin-based milling media, have significantly mitigated this risk.
- Risk of heat-induced degradation of thermolabile drugs.

❖ **High-pressure Homogenization (HPH)**

Skype pharmaceutical currently owns the patent for this process. R. H. Muller discovered the process and the patent was owned by DDS Gmbh.[48] High-pressure homogenization reduces drug particle size by forcing a suspension through a narrow valve under high pressure, causing gas bubbles to implode and break down particles. As shown in **Fig 4.** Pre-milling is recommended for high solid content. This method works for both diluted and concentrated suspensions and allows sterile manufacturing, making it versatile and safe for drug formulation.[49]

***Procedure*[50]**

Preparation pre-suspension

Disperse the drug powders in a stabilizing solution.

↓

Premilling

Low-pressure homogenization.

↓

High-pressure homogenization

(Apply high pressure for 10 to 25 cycles until the desired size of the nanosuspension is achieved)

Nanosuspension

Advantages

- It is a straight forward technology.
- Milling is a cost-effective process.
- Suitable for large-scale production using batch processing.

Disadvantage

- Risk of final product contamination due to erosion of the milling material.
- It's a time consuming process and reduces product efficiency.
- Prolong milling may result in microbial growth in the water phase.

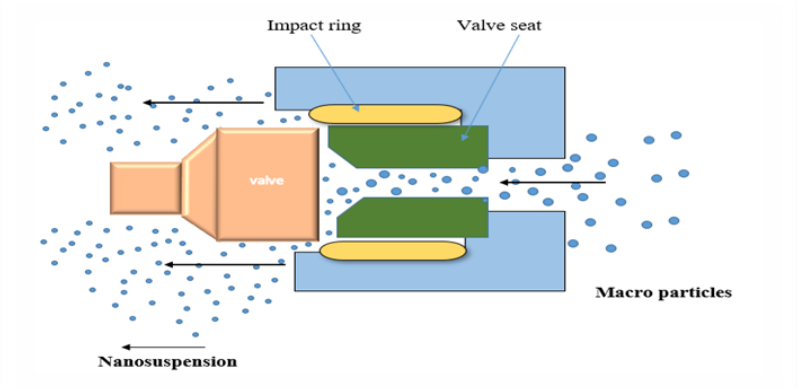

Figure 4: High-pressure Homogenization.

a) Disso cubes[51,52]

Dissocube technology was established by Muller in 1999. The device operates at pressures from 100 to 1500 bars (2800 – 21300 psi), with a maximum of 2000 bars and a volume capacity of 40 ml for laboratory use.

Procedure for Preparing Nanosuspensions using Dissocubes Technology

Prepare presuspension

Disperse the drug in a surface-active agent solution by means of a continues stirring in high speed to form a presuspension.

↓

Homogenization

Use the Dissocubes high-pressure homogenizer, operating at pressures between 100 to 1,500 bars (up to 2,000 bars for laboratory scale). The homogenizer reduces the diameter from 3 cm to 25 μm, increasing dynamic pressure and lowering static pressure below the boiling point of water.

↓

Cavitation Process

Under these conditions, water in the suspension begins to boil at room temperature, creating gas bubbles. These bubbles implode as the suspension exits the gap, causing cavitation, which helps break down particles to nanoscale.

↓

Control parameters for achieving the desired drug particle size in nano-crystals

Adjust temperature, number of homogenization cycles, power density, and homogenization pressure to achieve the desired nanocrystal size.

↓

Some medications, including Amphotericin B, Thiomerasol, Fenofibrate, Melarsoprol, Prednisolone, and Carbamazepine, were created using a specific method.

b) Nanopure

Nanopure is a homogenization method that uses non-water-based media or mixtures. It is a traditional dry dosage form of tablets, pellets, and capsules. In Dissocubes technology, cavitation (bubble formation due to pressure drop) is important, but with non-aqueous media, the pressure drop isn't enough to create cavitation. However, nanopure can homogenize at low temperatures, even below freezing, which makes it ideal for heat-sensitive substances. It gives similar results to Dissocubes but work under specific conditions.[53]

c) Nanojet

This method, also called "opposite stream technology," works by splitting the suspension into two or more streams, which collide at high pressure [about 1000 bar] and speed [1000 m/s].[54] The collision creates strong shear forces that break the particles down to the nanoscale. Equipment like the M110L and M110S micro fluidizers use this technology. It usually takes up to 75 passes to make a nanosuspension, but some microparticles may still remain in the final product.[55]

d) Nanoedge

It is the combination homogenization and precipitation techniques to obtain small size particle which promote stability. The limits in precipitation method are commonly associated with long term stability issues and the growth of crystals. Hence, the precipitated suspension is subjected for further homogenization to reduce the particle size and to inhibit crystal growth. Water miscible solvent which are tolerated in preparation of nanosuspension to approximate level, while it is required to absolutely eliminate them. Water miscible solvents like methanol, ethanol, and isopropanol.[56]

Other techniques

Dry co-grinding

For many years, nanosuspensions have been formulated using wet grinding techniques with a pearl sphere mill. However, currently, nanosuspensions can also be formulated by using dry milling methods and can also be formed by dry-grinding for poorly soluble drugs with soluble polymers and copolymers, which are then dispersed in a fluid medium. It has been defined that the formation of colloidal particles from poorly water-soluble drugs such as nifedipine, and griseofulvin use stabilizers like sodium dodecyl sulfate and Polyvinylpyrrolidone.[57-59]

Micro-emulsion template

Microemulsion is a biphasic dosage form that is thermodynamically stable. One of the advantages of the microemulsion method is that it can be utilized for formulating nanosuspensions. In this method, oil-in-water (O/W) microemulsion are preferred, with an organic solvent as the internal phase. The process starts by preparing the microemulsion, which is then diluted to create the nanosuspension. By adjusting the surfactant to co-surfactant ratio, the drug loading in the nanosuspension. This technique has potential for further research and development.[60]

Table 3: Marketed products.

Drug	Preparation method	Treatment
Gliclazide	Solvent -antisolvent precipitation	Antidiabetic
Ziprasidone	Micro fluidization	Antipsychotic
Cefixime (oral powder)	Co-spraying	Antibiotic

Doxazosin Mesylate	Emulsification solvent diffusion	Antihypertensive
Curcumin	Antisolvent precipitation	Anti-inflammatory, antiviral, antibacterial, and antitumor
Ibuprofen (Inhalable Powders)	Spray drying	Nonsteroidal anti-inflammatory drugs (NSAID)
Griseofulvin	Co-precipitation	Hypercholesterolemia
Aprepitant	Nanosystems	Antiemetic
Dexmethyl phenidate HCl	Nanosystems	CNS Stimulant
Tizanidine HCl	Nanosystems	Muscle Relaxant

Table 4: Over view of the technology and patents number.

Technology	Company	Patent Number
Dissocubes	Skype Pharma	US 5, 858, 410
Nanopure	Pharma Sol	PCT/EP00/063
Nanoedge TM	Baxter	US 6, 884, 436
Nanocrystal TM	Elan Nanosystems	US 5, 145, 684

PHARMACEUTICAL APPLICATIONS OF NANOSUSPENSIONS IN DRUG DELIVERY

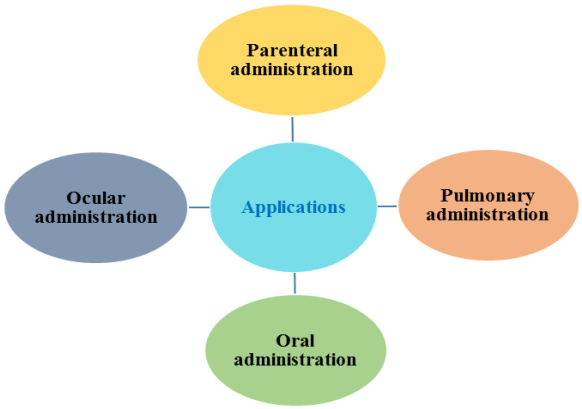

Figure 5: Administration of nanosuspension through different routes.

a) Parenteral administration

Current methods for paternal drug delivery, such as micellar solutions, cyclodextrin complexation, and liposome, have limitations like solubilization capacity and high costs. Nanosuspension improves drug delivery by increasing solubility and bioavailability. They can be administered intravenously (IV), enhancing efficacy. For instance, paclitaxel and clofazimine nanosuspensions show better therapeutic effects and itraconazole nanosuspensions offer increased antifungal activity.

b) Pulmonary Drug Delivery

In this method, nanosuspension can be administrated by nebulization of nano-sized particles using either mechanical or ultrasonic nebulizers. Various tiny particles in aerosol droplets contain drugs in the form of nanoparticles. Aqueous suspensions of the medicine can be easily nebulized and administered through the respiratory route due to their very small particle size. Examples: budesonide, ketotifen, ibuprofen, indomethacin, and nifedipine.

c) Ocular Drug Delivery

Nanosuspensions can prove to be an advantage for drugs that show poor solubility in lachrymal fluids. It can be designed as sustain drug release for effective results. Due to its nano sized formulation the dosing frequency get reduced with minimum toxicity.

d) Oral administration

The oral administration of medicine is the most convenient and easiest method for patients in which the nano-sized drug particles enhance oral absorption along with bioavailability.

CHARACTERIZATION

Characterizing nanosuspensions is vital for understanding their properties, stability, and performance in drug delivery and other applications. Key methods for evaluating aspects like size distribution, morphology, and surface properties include as shown in **fig s6.**

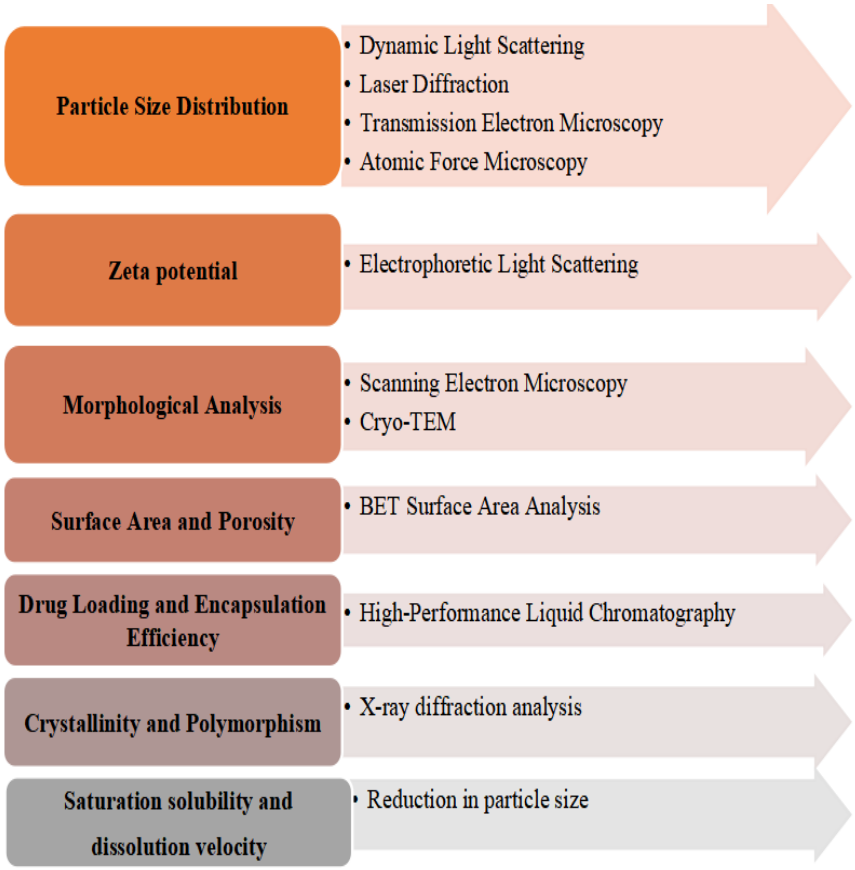

Figure 6: Characterization of nanosuspension.

1. Particle Size Distribution

a) Dynamic Light Scattering (DLS)

Principle: This method measures the hydrodynamic diameter of particles by analysing their Brownian motion.

Limitations

- This method may be inaccurate for polydisperse samples or aggregates.
- It measures hydrodynamic size, which can be influenced by surface coatings or agglomeration.
- Best for particles sized between 1 nm and 10 µm.

b) Laser Diffraction

Principle: This method effectively measures light scattering from suspended particles, allowing for accurate particle size estimation.

Limitations

- Less effective for particles smaller than 0.1 µm or larger than 100 µm.
- Assumes particles are spherical, which can cause inaccuracies for non-spherical shapes.

c) Transmission Electron Microscopy (TEM)

Principle: Provides high-resolution images of individual nano-particles.

Limitations

- Requires sample preparation, which can alter particle morphology.
- Limited to relatively dry or frozen samples.
- Size determination is often done manually and can be subject to observer bias.
- Best suited for particles **1 nm to ~1 µm** in size.

d) Atomic Force Microscopy (AFM)

Principle: Measures the surface topography of nanoparticles by scanning a sharp probe.

Limitations

- Cannot easily provide size distribution for bulk samples.
- Limited scanning area and slower acquisition time.
- Requires dry or very low moisture samples for optimal imaging.
- It is best suited for particles in the range of **1 nm to ~1 µm**.

2. Zeta potential

a) Electrophoretic Light Scattering (ELS)

Principle: This method measures the electrophoretic mobility of nanoparticles to determine their (zeta potential) surface charge.

Limitations

Zeta potential is affected by sample concentration and ionic strength.

A zeta potential above ±30 mV usually indicates good stability due to electrostatic repulsion, though this may vary by formulation.
Measurements are not reliable for highly concentrated samples or those with high poly disparity.

3. Morphological Analysis
a) Scanning Electron Microscopy (SEM)
Principle: Uses electron beams to scan particle surfaces and generate high-resolution images.

Limitations
- Requires sample preparation that can alter particle shape and size.
- Best for particles larger than 50 nm (smaller ones may be hard to detect).

b) Cryo-TEM
Principle: This provides high-resolution images of nanoparticles in their natural, frozen state.

Limitations
Requires specialized equipment and expertise. Sample preparation can be time-consuming, especially for small quantities, and is ideal for particles between 1 nm and 100 nm.

4. Surface Area and Porosity
a) BET Surface Area Analysis
Principle: Determines the specific surface area of nanoparticles through nitrogen adsorption and desorption methods.

Limitations
- Not suitable for large particles (>1 µm) or agglomerated samples.
- Measurements may be inclined by sample preparation and surface properties.
- Only external surface area is assessed, not internal surface area or porosity.

5. Drug Loading and Encapsulation Efficiency
a) High-Performance Liquid Chromatography (HPLC)
Principle: Separates and quantifies drug content from the nanosuspension.

Limitations
- Needs accurate calibration and validation of the chromatographic method.
- Sensitivity may be an issue for very low drug concentrations, typically requiring levels from ng/mL to µg/mL.
- Sample preparation can be time-consuming.

6. Crystallinity and Polymorphism
X-ray diffraction analysis, combined with differential scanning calorimetry and scanning electron microscopy, is utilized to determine the polymorphic changes in the crystalline structure of a drug resulting from high-pressure homogenization. During this process, a nanosuspension may experience changes in its crystalline structure, potentially transforming into an amorphous form or other polymorphic variations due to the high pressure. An increased amount of amorphous drug can lead to higher saturation.

7. Saturation solubility and dissolution velocity
Nanosuspension improves dissolution velocity and saturation solubility by reducing particle size, which increases dissolution pressure. Even slight reductions in particle size can enhance solubility due to changes in surface tension.

CONCLUSION
Nano-suspension represent a groundbreaking approach to addressing the challenges associated with the solubility of poorly water-soluble drug. Reduction in particle size to nanometer range, such type of formulation significantly enhances drug dissolution, absorption and bioavailability. In large scale production of nanosuspension, media milling and high-pressure homogenization technology has been successfully employed. This technology advancement allows for improved drug delivery through various route like oral, parental, pulmonary and ocular. However, the use of nanosuspensions in nasal, buccal, and topical drug delivery remains largely unexplored, presenting an exciting opportunity for further research and development in these areas.

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