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Review Article

Nanosuspension in Drug Delivery

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ABSTRACT

The science of nanotechnology studies processes at the molecular level and at sizes smaller than a nanometer. The term "nano" describes the particle size range of 1–1000 nm. Nanotechnology includes nanosuspensions. An item of pharmaceutical A very finely colloid, biphasic, dispersed solid drug particle in an aqueous vehicle, with a size below 1 µm stabilized by surfactants and polymers created using appropriate techniques for drug delivery applications is known as a nanosuspension. It boosts the bioavailability and delivers hydrophobic medications effectively. An appealing and promising technique to increase the medications' poor solubility and bioavailability is nanosuspension. The preparation procedures and uses of nanosuspensions in the pharmaceutical sciences are covered in this review article.

INTRODUCTION

The management of material on a nuclear, molecular, and supramolecular scale is known as *nanotechnology*. The most basic and comprehensive explanation of nanotechnology. Referred to as molecular nanotechnology,

which is the current term for the specific technological goal of using atoms and molecules to build macroscale goods. The National Nanotechnology Initiative, which defines nanotechnology as the management of matter with at least one measurement scaled from 1 to 100 nanometers, later acknowledged a wider application. The significance of mechanical belongings at this quantum-realm scale is reflected in this meaning, which changed from being a specific technological objective to a research category encompassing all kinds of research and technologies dealing with the unique properties of matter that exist below the specified size threshold.

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Submicron-sized (usually 10-1000 nanometers) solid drug particles stabilized in a liquid medium, usually water or a buffer solution, make up nanosuspension, a colloidal dispersion system. The drug particles can be crystalline or amorphous, and they are dispersed in the liquid phase using surfactants, polymers, or other stabilizing agents.

There are various reasons why nanosuspensions are made:

1. Improved solubility : To make medications that are poorly soluble more soluble and therefore more bioavailable.

2. Enhanced bioavailability: To promote the absorption and usage of medications, resulting to better therapeutic benefits.

3. Targeted delivery: To reduce adverse effects and increase efficacy by focusing on particular body regions.

4. Increased stability: To shield delicate medications from deterioration and increase their stability. 5. Controlled release: To provide a prolonged or postponed release of medication.

6. Improved safety: By administering medications directly to the target spot, toxicity and adverse effects are decreased.

7. Enhanced patient compliance: By lowering dosage frequency and enhancing administration simplicity, this strategy aims to increase patient compliance.

8. Overcoming crystal lattice energy: To overcome the crystal.

> *Benefits of Nanosuspension :*

-Enhanced absorption capacity
– Increased solubility
– Targeted distribution
– Release under control
– Security and steadiness
– Adaptability and versatility
– Enhanced therapeutic efficacy
– Better patient compliance

> Limitations of Nanosuspension :

– Formulation complexity
– Stability issues
– Safety and toxicity issues
– Poor comprehension
– Sterilization difficulties

Nanosizing of API :

The term "nanosizing" refers to the pharmaceutical procedure of bringing the active ingredient's particle size down to the nanometer size Achieving a particle size less than 1 μm, or below the sub-micron range, is what it refers to Because nanosizing procedures can be used to most substances with poor solubility difficulties, they have gained increased popularity. "Non-specific techniques" are the methods used to increase the bioavailability of poorly soluble medications.

Drugs can be nanosized using a variety of methods, which are divided into top-down synthesis and bottom-up method.

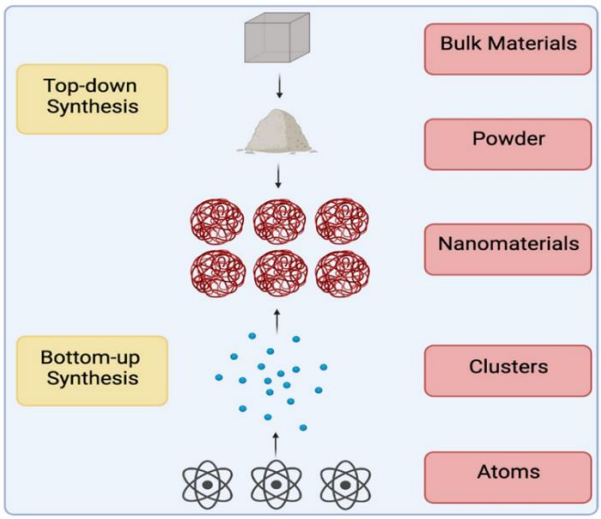
➢ Top-Down synthesis:

Typical solid-state processing of the materials includes top-down pathways. This method starts with the bulk material and uses physical procedures like crushing, milling, or grinding to reduce it in size and break up larger particles. This method is typically not appropriate for creating materials with regular shapes, and even with significant energy consumption, it is very difficult to achieve very fine particles. The primary issue with the top-down technique is the surface structure's imperfection. Such an imperfection would significantly affect the surface chemistry and physical characteristics of nanomaterials and nanostructures. The traditional top-down method is known to seriously harm processed patterns' crystallographic integrity. 'Force' (e.g., mechanical force, laser) is used in top-down approaches to break down bulk materials into nanoparticles. 'Ball milling' is a widely used technique that mechanically breaks down bulk

materials into nanoparticles. Additionally, a target (solid) can be ablated using short pulse lasers, such as femtosecond lasers, to create nanoparticles.

➢ Bottom Up Method:

Atoms or molecules are assembled into nanostructured arrays using bottom-up techniques. These techniques can use solids, liquids, or gasses as their raw materials. They need to be disassembled in some way before being incorporated into a nanostructure. There are two main types of bottom-up methods: regulated and anarchic. Elevating the component atoms or molecules to a chaotic state and then abruptly altering the environment to render that state unstable are the hallmarks of chaotic processes. Products arise primarily from the ensuring kinetics by the creative management of numerous parameters. The ensuing size distribution and average size are typically determined by ensemble statistics because the collapse from the chaotic stage can be hard or impossible to manage. Accordingly, controlling the final condition of the products allows for the control of nanoparticle formation. Laser ablation, exploding wires, arcs, flame pyrolysis, combustion, and precipitation synthesis procedures are a few instances of chaotic processes. Regulated procedures entail the regulated delivery of the constituent atoms or molecules to the site of nanoparticle formation such that the nanoparticle can grow to a defined size in a controlled way. In general, the constituent molecules or atoms are always in a condition close to What is required for the production of nanoparticles. As a result, controlling the reactant's state controls the production of nanoparticles. Self-limiting growth solutions, self-limited chemical vapour deposition, shaped pulse femtosecond laser method, and molecular beam epitaxy are a few examples of regulated processes.



➢ Precipitation Method :

A common technique for creating submicron particles of poorly soluble medications is precipitation.This approach involves dissolving the drug in a solvent, mixing the solution with a solvent that contains a surfactant, making the drug insoluble. Fast supersaturation of the drug in the solution and the creation of ultrafine amorphous or crystalline drug result from the quick addition of solution to such solvent (usually water). This process involves the creation of nuclei and the development of crystals, both of which are temperature-dependent. The preparation of a stable suspension with the smallest possible particle size primarily requires a high nucleation rate and a low crystal growth rate.

➢ Supercritical Fluid Techniques :

A variety of techniques are employed to produce nanoparticles, including the rapid expansion of supercritical solution (RESS) process, the

supercritical antisolvent process, and the precipitation with compressed antisolvent (PCA) process. The RESS technique involves expanding a drug solution through a nozzle into a supercritical fluid, which leads to the drug precipitating as fine particles by loss of solvent power of the supercritical fluid. Young et al. prepared cyclosporine nanoparticles with a diameter of 400 to 700 nm using the RESS method. The PCA method involves atomizing the drug solution into a CO2 compressed chamber, which leads to the solution becoming supersaturated and ultimately precipitation. The supercritical antisolvent process involves injecting drug solution into the supercritical fluid and extracting the solvent as well as the drug solution becomes saturated.

- Melt emulsification method :

Melt emulsification is the primary process used to generate solid lipid nanoparticles. Using the melt emulsification approach, Kipp and colleagues first create ibuprofen nanosuspensions. It follows a four-step process. The drug is first mixed with 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 entire operation keeps the temperature above the drug's melting point. In order to precipitate the particles, the emulsion is finally chilled. The key factors influencing the size of the nanosuspension's particles are the drug concentration, the kind and concentration of stabilizers used, the cooling temperature, and the homogenization procedure.

- High pressure Homogenization :

The three phases involved in this technique are as follows: To create presuspension, drug powders are first dispersed in a stabilizing solution. Presuspension is then homogenized using a high pressure homogenizer at low pressure occasionally for premilling. Finally, high pressure homogenization is performed for 10 to 25 cycles to create nanosuspensions of the desired size.

A. Homogenization in non- aqueous media (Nanopure) :

A water-free medium is used to homogenize the suspension of nanopure. The drug suspensions in nonaqueous media are homogenized using a process known as “deep-freeze,” which involves freezing the mixture at or below 0°C. Water, oils, and fatty acids have relatively high boiling points and low vapor pressures, hence in nanopure technology, a static pressure reduction is insufficient to trigger cavitation.

B. Homogenization in aqueous Media (Dissocubes) :

Muller created the Dissocubes technology in 1999. The instrument can be operated at pressure varied from 100 to 1 500 bars (2 800 – 21 300 psi) and up to 2 000 bars with volume capacity of 40 ml (for laboratory scale). Using a high-speed stirrer, prepare a presuspension of the micronized medication in a surfactant solution before proceeding with the creation of the nanosuspension. The liquid flow volume per cross section in a closed system is constant, according to Bernoulli’s Law. Below the room temperature water boiling point, the reduction in diameter from 3 cm to 25 μm results in an increase in dynamic pressure and a decrease in static pressure.Because of this, water begins to boil at room temperature and produces gas bubbles that implode as the suspension (also known as cavitation) departs the gap and the air pressure returns to normal. The temperature, the number of homogenization cycles, the homogenizer’s power density, and the homogenization pressure are the primary determinants of the size of drug nanocrystals that can be produced. Preprocessing, such as medication micronization and the use of expensive equipment, raises the dosage form’s overall cost. This technique was used to manufacture a number of medications as nanosuspensions, including

Amphotericin B, Ordinon, Thiomerasol, Fenofibrate, Melarsoprol, Buparvaquone, Prednisolone, Carbamazepine, and Dexamethasone.

Making of Nanosuspension Formulation:

Stabilizer:

A stabilizer's main function is to guarantee that drug particles are thoroughly wetted, which inhibits Ostwald's ripening and accumulation of nanosuspensions and increases the formulation's physical stability. By acting as an ionic or steric barrier, this is attained.7, 13, 22, The kind and amount of stabilizer used significantly affect the nanosuspension's in vivo behavior as well as its physical stability. To date, lecithins, povidones, cellulosics, polysorbates, and poloxamers have all been employed as stabilizers in the production of nanosuspensions. Lecithin has been the go-to stabilizer in the attempt to create a nanosuspension that can withstand autoclaving and be administered parenterally. Other Examples_ such cellulose, hydroxypropyl methylcellulose, gelatin, sodium alginate, polyvinyl alcohol, are used.

Organic Solvent :

In the formulation of the nanosuspension, organic solvents is necessary when emulsions or microemulsions are used as templates. In these kinds of situations, it's best to use water-miscible, less dangerous, pharmaceutical-grade solvents like methanol, ethanol, chloroform, and isopropanol. In the formulation process, partially water-miscible solvents such benzyl alcohol, propylene carbonate, butyl lactate, triacetin, ethyl acetate, and ethyl formate are also chosen over traditional toxic solvents like dichloromethane.

1. Co- surfactants :

Choosing an appropriate co-surfactant becomes crucial while creating nanosuspensions with the help of microemulsions. This is due to the fact that the selection of co-surfactants can have a substantial impact on drug loading and internal phase uptake within a particular microemulsion composition, which in turn can affect phase behavior. While bile salts and dipotassium glycyrrhizinate are frequently mentioned as possible co-surfactants in literature references, alternative solubilizers, including transcutol, glycofurol, ethanol, and isopropanol, can be used in the formation of microemulsions without creating significant hazards.

2. Other additives:

Additives that can be added to nanosuspensions include buffers, salts, polyols, osmotic agents, and cryoprotectants. The previously mentioned additions serve various purposes with the goal of improving the nanosuspension's stability and effectiveness. While salts provide ionic strength and buffers are essential for maintaining exact pH values, salts also contribute to system stability. Conversely, polyols function as stabilizers, halting the accumulation of particles. The job of osmotic agents is to control the pH of the solution in order to make it compatible with cellular structures. To protect the nanosuspension during the heating and cooling processes, freezing agents are the last step.

Assessment criteria for Nanosuspension :

1.Organoleptic features:

Taste, Color, and Odour - Before initiating the process of formulating oral dosage forms, specific factors must be taken into account. Flavor variations may result from variations in particle size, crystal structure, and the ensuing changes in particle dissolution, especially when it comes to active substances. A chemical instability may also be shown by changes in color, taste, or Odour.

2. Particle size distribution :

Particle size distribution is a major determinant of the formulation's physicochemical properties, which include saturation solubility, dissolving rate, and physical stability. There are various techniques available to evaluate the particle size distribution, such as the Coulter Counter Multisizer, laser diffraction (LD), and photon correlation spectroscopy.

3. Zeta potential:

A key indicator of suspension stability is the zeta potential. For situations when electrostatic repulsion is the only source of stability, a zeta potential of ±30 mV is necessary. However, a zeta potential of ±20 mV might be sufficient when using both steric and electrostatic stabilization.

4. Solubility and Dissolution:

Because they improve saturation solubility and dissolution rate at the same time, nanosuspensions have a major advantage over other techniques. To determine these two vital factors, different physiological solutions need to be used.30, 35 Evaluations of the dissolving rate and saturation solubility are useful for forecasting the composition's in vitro behavior. Particle size decrease raises the rate of dissolution, which raises the dissolution pressure.

5. pH value:

According to Shrestha et al. (2014), it is crucial to measure the pH of an aqueous formulation at a specific temperature in order to reduce "pH drift" and the coating of electrode surfaces with suspended particles. However, this measurement should only be carried out after equilibrium has been reached after settling. To preserve pH stability, electrolytes must not be added to the formulation's exterior phase.

6. Density:

The specific gravity, or density, of the formulation is an important factor to take into consideration. Over time, a reduction in density usually indicates the presence of trapped air inside the structure of the formulation. For accurate measurements of density at a given temperature, a homogeneous, well-mixed formulation should be used, and precision hydrometers should be used.

7. Crystal Morphology:

To investigate how high-pressure homogenization affects the drug's crystalline structure, methods such as differential scanning calorimetry or X-ray diffraction analysis in conjunction with differential thermal analysis can be utilized. The appearance of amorphous or other polymorphic morphologies in nanosuspensions can be one of the crystalline structural modifications brought about by high-pressure homogenization.

8. Droplets size :

The light scattering method or electron microscopy can be used to evaluate the droplet size distribution of nanosuspension and microemulsion vesicles, two colloidal systems employed in the pharmaceutical and other sectors for drug administration and formulation. Using a neon laser with a wavelength of 632 nm, a spectrophotometer is utilized for dynamic light scattering.

9. Biological Performance:

Creating an in vitro/in vivo correlation and closely observing the drug's in vivo performance are essential elements of some drug delivery systems, regardless of the route and mode of administration that is used. Given the significant implications for the drug's in vivo behavior, they may not be as relevant or simple for intravenous formulations because of the drug's quick and direct entry into the systemic circulation, which bypasses many of the factors that make IVIVC relevant for oral formulations. methods like 2-D PAGE can be used to quantify and qualitatively evaluate protein adsorption after intravenous administration of drug nanosuspensions in animals, and hydrophobic interaction chromatography can be utilized to determine surface hydrophobicity.

Stability Study :

>stabilizers that are usually employed*:*

In order to stop agglomeration and aggregation, stabilisers are essential in nanosuspension formulations. Common stabilizers for nanosuspensions are polymers, such as polyvinyl pyrrolidone (PVP), and hydroxypropyl methyl cellulose (HPMCs).

>Aggregation:

During storage or the solidification process, nanosuspensions that are not permanently

stabilized or that are stabilized with unsuitable stabilizers may coalesce. Because of the Ostwald ripening phenomena, improper stabilizers cause smaller particles to aggregate in the nanosuspensions. When Ostwald ripening occurs, fine particles dissolve more quickly than coarse particles do. Because larger nanocrystals are less soluble than smaller ones.

>High-pressure homogenization method:

The previous few decades have seen significant advancements in nanosuspension preparation technology. For the manufacture of nanosuspensions, the technologies that are currently available or actively being developed include milling, high-pressure homogenization (HPH), impinging jet, electro-spraying, liquid-based approaches, and supercritical fluid procedures.

>Spray Drying:

The solidified form is preferable over aqueous nanosuspensions due to the large decrease in aggregation and other instability issues. As a result, produced nanosuspensions are frequently turned into solid forms. The powder that has solidified is subsequently prepared into several dosage forms, including injection-grade sterile powder, nebulized powder for pulmonary administration, and tablets and capsules for oral administration.

Issue	Reason	Solution
Agglomeration	large surface area of nanoparticles → high total surface energy → thermodynamically unfavourable → particles tend to agglomerate to minimize the surface energy.	Stabilizers: Ionic (electrostatic) – SDS, SLS, Lecithin Non-ionic (steric) – Poloxamer, PEG, HPMC, PVA
Sedimentation (rare due to small particle-size)	Mainly due to agglomeration	Prevent agglomeration, **Open-flocs**
Change in crystalline state	Due to high-energy top-down processes	Stabilizers depending on suspension
Stability during solidification (spray/freeze-drying)	drug nanocrystal growth or agglomeration during drying process	matrix formers, such as mannitol, sucrose and cellulose, into nanosuspensions prior to drying

Applications

- Parentral Formulation:

The drug must be solubilized or have a particle/globule size smaller than Sum when administered parenterally in order to prevent capillary blockage. Parenteral administration is now accomplished by complexing with cyclodextrins, liposomes, micellar solutions, solubilization with co-solvents, and salt formation. Nevertheless, these methods' parenteral acceptability and solubilization capability are limited, which places restrictions on their application. When it comes to parenteral distribution, liposomes are far more palatable and adaptable; nonetheless, they frequently have issues including physical instability, high manufacturing costs, and scaling up challenges.

- Topical Formulation:

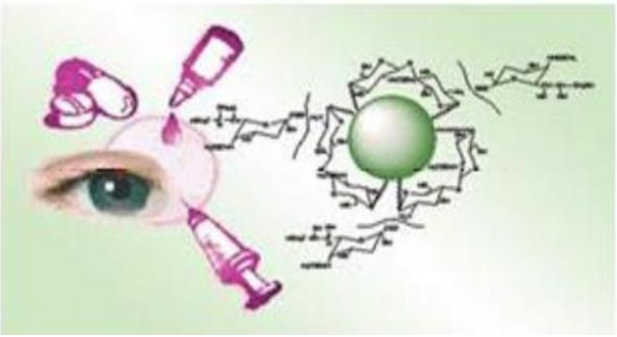
The use of nanosuspensions in topical formulations results in supersaturated systems, or increased solubility at saturation. Higher drug diffusion pressure in the skin.

- Paste, gel, and patch treatments for oral cavities:

Small particles enhanced adherence and sustained residence for medications whose typical oral formulations did not have a high enough bioavailability.

- Ocular Formulation:

For medications that don't dissolve well in lachrymal fluids, nanosuspensions may be a great help. Techniques including ointments and suspensions have been suggested for the delivery of such medications. Also, it is possible to reduce copying.



- Targeted drug delivery:

Since it is simple to modify the surface characteristics and in-vivo behavior of nanosuspensions by adjusting the milieu or stabilizer, they can be employed for targeted distribution. The creation of economically viable nanosuspensions for targeted distribution is made possible by their diversity and ease of scale-up and commercial production.

CONCLUSION :

Drugs with low bioavailability and issues with solubility in both organic and aqueous solutions have been treated with nanosuspensions. High-pressure homogenization and media milling are two techniques that can be used to produce nanosuspensions on a large scale. One can apply nanosuspensions parenterally, topically, ocularly, or orally. Nanosuspensions have become the preferred formulation for drugs with restricted bioavailability because of their ease of use, lower requirement for excipients, quicker rate of dissolution, and saturation solubility.

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