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Nanosuspension An Innovative Approach For Poorly Soluble Drug

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Abstract

More than 40% of newly developed chemical compounds exhibit poor water solubility or lipophilic characteristics, posing a significant challenge in formulating suitable dosage forms. While various conventional techniques have been explored, nanotechnology, particularly nanosuspensions, offers a promising solution to enhance the solubility and absorption of poorly soluble drugs. A nanosuspension is a colloidal dispersion of drug particles, typically ranging from 10 to 1,000 nanometers, stabilized by surfactants. This reduction in particle size dramatically increases the surface area, leading to improved dissolution rates and enhanced bioavailability, as explained by the Noyes-Whitney equation. Nanosuspension technology not only addresses solubility and bioavailability issues but also modifies drug pharmacokinetics, improving safety and efficacy. This review article discusses the advantages, drug selection criteria, formulation considerations (including stabilizers, surfactants, and co-surfactants), and preparation techniques such as bottom-up (precipitation) and top-down (media milling, high-pressure homogenization, melt emulsification, emulsification solvent evaporation, wet milling, supercritical fluid process, and dry co-grinding) approaches. Furthermore, it details the characterization methods for nanosuspensions, including particle size, zeta potential, in vitro drug release, crystalline state, pH, and stability. The diverse applications of nanosuspensions in oral, parenteral, dermal, targeted, ocular, and pulmonary drug delivery are also highlighted, demonstrating their versatility and potential to revolutionize drug delivery systems.

Keyword - Nanosuspension, Poorly soluble drugs, Bioavailability, Particle size reduction

Introduction

More than 40%, of newly identified chemical compounds in drug development process show either poor water solubility or lipophilic characteristics. Drugs were classified on the basis of there BCS classification and the majority of drugs are BCS class II and IV drugs which posses poor solubility which is the major issue face by the researcher in formulating drugs into sutaible dosage form. It has posed a complicated challenge for pharmaceutical researchers to formulate poorly soluble drug into suitable dosage form. Various conventional techniques have been employed to enhance the solubility of poorly soluble drugs such as micronization, solubilization with cosolvents, formation of salts, surfactant dispersions, precipitation methods, and oily solutions but none of approach were able to resolve the problem but one of the approach to improve solubility and enhancement of absorption is the utilization of nanosized particles, to formulate therapeutic agents.[1-4]

Although other techniques such as cyclodextrin-based inclusion complexation, liposomes, solid dispersions, emulsions, and microemulsions have shown promising results, they are not suitable for all medications. Furthermore, these methods don't work for medications that don't dissolve in organic or aqueous solvents. The shortcomings of conventional techniques for improving solubility and bioavailability may be addressed by nanotechnology. Specifically, substances with high log P and melting point values that are insoluble in water but dissolve in oil are well suited for nanosuspensions.[5–7]

A nanosuspension constitutes a colloidal dispersion of nanosized drug particles that are stabilized by surfactants. Such suspensions are employed to enhance the solubility and bioavailability of drugs with limited aqueous solubility. The dimensions of the particles within a nanosuspension generally range from 10 to 1,000 nanometers, and their diminutive size facilitates improved dissolution rates and, consequently, enhanced absorption within the biological system.[8,9]

The reduction of drug particle size results in an augmentation of surface area and, thus, an increase in the dissolution rate, as articulated by the Noyes-Whitney equation.[10] In the context of nanosuspension technology, the drug is preserved in the requisite crystalline form while exhibiting diminished particle size, which culminates in an increased dissolution rate. Nanosuspensions not only address the challenges of inadequate solubility and bioavailability but also modify the pharmacokinetics of the drug, thereby enhancing its safety and efficacy.[11]

Nanosuspension technology represents a highly promising approach for the enhancement of drug delivery systems relevant to alopecia treatment, with the potential to augment therapeutic outcomes while alleviating adverse effects commonly associated with conventional therapeutic approaches. This innovative technique employs nanoencapsulation to facilitate targeted drug delivery, thereby increasing local bioavailability and potentially reducing side effects associated with traditional treatment modalities.[12]

Advantages [13,14,15]

- They are cost-effective and useful for poorly soluble drugs.
- They are physically more stable than liposome.
- Provide ease of manufacture and scale-up for large-scale production.
- Rapid dissolution and tissue targeting.
- Higher bioavailability especially in ocular and inhalational drug delivery.
- Improved dose proportionality.

SELECTION OF DRUG FOR NANOSUSPENSION [16]

- Water-insoluble but which are soluble in oil.
- Drugs have High log P or API that is insoluble in both water and oils.
- Drugs with a reduced tendency of the crystal to dissolve, regardless of the solvent.
- API with a very large dose.

FORMULATION CONSIDERATIONS IN NANOSUSPENSION [16,17,18]

TABLE NO. 1: FORMULATION CONSIDERATIONS

Excipient	Function	Example
Stabilizers	Moisten the pharmaceutical particulates comprehensively, inhibit Ostwald ripening and the agglomeration of nanosuspensions, thereby establishing a steric or ionic barrier.	Poloxamers, SLS, Lecithins, Povidone
Surfactants	lessen the interfacial tension in order to enhance dispersion. They serve as a foaming or wetting agent.	Tween 80 or span
Co- surfactants	Influence phase behavior when creating nanosuspension using microemulsions.	Bile salts, Dipotassium glycyrrhizinate, Transcutol, Ethanol, Isopropanol
Organic Solvent	Use of solvent that is less harmful and suitable for use in pharmaceutical formulations.	Methanol, Ethanol, Chloroform, Isopropanol, Ethyl acetate, etc.
Other Additives	Based on the characteristics of the medication moiety or the requirements of the delivery route	Buffers, salts, polyols, osmogens, cryoprotectants, etc.

PREPARATION TECHNIQUES

To prepare nanosuspension, two methods are employed:

- Bottom-up technology
- Top-down technology

Using a variety of techniques, including solvent addition, spray freezing, evaporative precipitation, and liquid solvent change process, molecules are dissolved in a solvent and precipitated in the bottom-up manner. Homogenization and milling are examples of top-down mechanical processes. Top-down methods are frequently employed. Time expenditure, increased energy usage, the possibility of contaminants, and insufficient particle size control are some disadvantages of mechanical processes.[19]

1) Bottom-up technology

"Bottom-up technology" refers to a method that begins at the molecular level and progresses through molecule association to the creation of a solid particle.By lowering the solvent quality—for instance, by transferring the solvent into a nonsolvent, altering the temperature, or a combination of both we are talking about traditional precipitation approaches. In pharmaceutical chemistry and technology, precipitation is a traditional method.

Advantages

- Precipitation has a higher saturation solubility than other techniques for creating nanosuspensions.
- One benefit is the use of inexpensive and basic equipment.

Disadvantages

- The medication must dissolve in at least one solvent; this rule eliminates any novel medications that are insoluble in both organic and aqueous media at the same time.
- A minimum of one nonslovent must be miscible with the solvent.
- Removing solvent residues raises production expenses.
- Maintaining the particle nature (i.e., size, particularly the amorphous portion) is a little bit difficult. For particle preservation, a second sequential procedure, such as spray drying or lyophilization, is generally advised.

2) Top-Down Technology

The top down technologies include
a) Media milling
b) High pressure homogenization

a) Media milling technique: Pearl mills or high shear media mills are used to create nanosuspensions. A milling chamber, recirculation chamber, and milling shaft make up this apparatus. Balls or pearls composed of ceramic sintered aluminum oxide or zirconium oxide make up milling medium. Water, medication, stabilizer, and milling media are all charged in the milling chamber. The sample is affected by balls that rotate at a high shear rate at a regulated temperature. Particle size decreases and nanosized particles are produced as a result of both impact and friction forces.**[20]**

Advantages

- Simple technology; low cost of the milling process itself; and the possibility of some large-scale production (batch process).

Disadvantages

- The process's duration is not conducive to productivity.
- Long-term grinding may result in the development of germs in the water phase.
- The process of separating the milling material from the medication nanoparticle suspension, particularly when creating parenteral sterile products, takes time and money.
- The potential for product contamination as a result of erosion from the milling material is one disadvantage.

b) High pressure homogenization : The process of homogenization entails pushing the suspension via a narrow-adjustment valve while under pressure. This technique uses a nanosized aperture value of high-pressure homogenization to focus the medication and surfactant under pressure. Cavitations in the aqueous phase form the basis of the principle. The drug microparticles can be transformed into nanoparticles because the particle cavitation force is high enough. Using high-speed stirrers to create a presuspension of the micronized drug in a surfactant solution is crucial prior to the drug going through the homogenization process.[21]

- **Nanopure:** Nanopure is a method of homogenization that employs media or mixtures without water. Although cavitation is essential in Dissocube technology, the drop in static pressure is insufficient to cause cavitation when non-aqueous liquids are used. Because Nanopure can homogenize materials at lower temperatures—even below the freezing point—it can be used with thermolabile materials. In milder settings, it produces outcomes that are comparable to those of Dissocubes. [22,23]

- **Dissocubes:** This method uses high pressure to push the suspension through a tiny valve using a pressure plunger pump. The static pressure will drop below the boiling pressure of water when the suspension is allowed to pass through the orifice, causing the water to boil and gas bubbles to develop. Bubbles will burst and the pressure will return to normal after it exits the orifice. As a result, nearby particles will rush onto the surface, reducing its size.

- **Nanoedge:** This process is comparable to the precipitation or homogenization methods. Better stability and bioavailability are thought to result from combining these two techniques. To lessen the particle size and stop crystal development, the suspension made using this technique will be homogenized once more. The nano edge technology also incorporates an evaporation process to improve the formation of nanosuspension, which will yield a modified beginning material free of solvents.

- **Nanojet:** This technology is primarily used to reduce particle size by applying high pressure and force to a suspension that is divided into at least two sections that are affected by one another due to the high shear forces created throughout the process.

c) Melt emulsification method: This approach involves dispersing the medication in a stabilizer aqueous solution, heating it over the drug's melting temperature, and homogenizing the mixture to create an emulsion. The temperature of the emulsion was kept above the drug's melting point throughout this procedure by wrapping the sample holder in heating tape that was equipped with a temperature controller. After that, the emulsion was either allowed to cool gradually to room temperature or placed in an ice bath. This method's primary benefit is that organic solvents are completely avoided throughout the production process.

d) Emulsification solvent evaporation technique: This method entails making a drug solution and then emulsifying it in a different liquid that isn't a solvent for the medication. The substance precipitates when the solvent evaporates. A high-speed stirrer can be used to generate high shear forces, which will control crystal development and particle aggregation. Solvent evaporation: This technique involves creating polymer solutions in volatile solvents and emulsions. When the solvent for the polymer evaporates and the polymer is let to diffuse into the continuous phase of the emulsion, the emulsion transforms into a suspension of nanoparticles. The stabilizer, polymer concentration, and homogenizer speed all had an impact on the particle size. The solvent must be evaporating using continuous magnetic stirring at room temperature or under decreased pressure after high-speed homogenization or ultrasonication.[24]

e) Wet milling: Pearl mills or high shear media mills are used to create nanosuspensions. The mill is made up of a recirculation chamber, a milling chamber, and a milling shaft. The drug's aqueous suspension is then fed into a mill that has tiny grinding balls or pearls in it. These balls fly through the inside of the grinding jar and strike the sample on the other grinding jar wall as they rotate at a very high shear rate at a regulated temperature. There is a significant reduction in particle size due to the combined effects of collision and friction. Ceramic-sintered aluminum oxide, zirconium oxide, or strongly cross-linked polystyrene resin with great abrasion resistance are the materials used to make the milling media or balls. The PM100 and PM200 planetary ball mills (Retsch GmbH and Co., KG, Haan, Germany) are one type of equipment that can be used to grind materials down to 0.1 μm. Wet milling was used to create a Zn-insulin nanosuspension with a mean particle size of 150 nm. The main disadvantages of this technology include the existence of relatively high proportions of particles ≥5 μm, the erosion of balls or pearls that may leave residues as contaminants in the finished product, and the degradation of thermolabile pharmaceuticals due to heat created during the process.[25]

f) Supercritical fluid process: This method uses a dense noncondensable fluid to minimize particle size. Both the temperature and the pressure of this fluid are higher than their critical values. Its procedures enable medication particles to be micronized within a specific range of particle sizes, frequently below the micron level. It has been shown that this method can produce nanoparticulate. Particles in nanosuspension range in diameter from 5 to 2000 nm. The industry's ability to use technology is limited by the high pressure and poorly soluble medication and surfactant in supercritical CO2.

g) Dry co-grinding: After dispersing in liquid medium, a weakly soluble medication is dry ground with soluble polymers and copolymers including PVP, PEG, and HPMC to create a nanosuspension. Because co-grinding increased surface polarity and changed the drug from crystalline to amorphous, it improved the

physicochemical characteristics and dissolving of the poorly soluble medication. It is simple to perform dry co-grinding without the need of organic solvent. The particle size is decreased.[26]

Characterization of nanosuspension

Nanosuspensions are characterized using a variety of techniques and a range of criteria, such as particle size, particle size distribution, and zeta potential, as these factors primarily impact formulation stability, safety, and efficacy.

1) Particle size: Photon correlation spectroscopy (PCS), laser diffraction (LD), and a Coulter counter multisizer can all be used to determine the particle size distribution. The LD method measures particles between 0.05 and 80µm, while the PCS method measures particles between 3 nm and 3µm. Unlike the LD method, which only provides a relative size distribution, the Coulter counter multisizer provide the absolute number of particles. The polydispersity index (PI) and particle size are two of the most important aspects of nanosuspensions. Many of the characteristics of nanosuspensions are controlled by the size of the particles.[27] PI gives nanosuspensions their physical stability. If the PI is low, the stability of nanosuspensions can be preserved for an extended amount of time. A size distribution that is somewhat tight is represented by a PI value between 0.1 and 0.25, whereas one that is very broad is indicated by a PI value greater than 0.5. Since capillaries are only 5–6 µm in size, particles used in intravenous (IV) administration should be smaller than 5µm. A larger particle size may result in embolism and capillary blockage.

i. The rate and extent of drug (bioavailability)
ii. Dissolution rate

According to the Noyes and Whitney equation, a drug's solubility, dissolving rate, and particle surface area will all rise as particle size decreases.[28]

2) Particle charge (zeta potential): The stability of nanosuspension is mostly dependent on particle size. In order to show the double electrical coating surrounding a charged particle, the electrical charge on its surface causes electrostatic repulsion between the nanoparticles and inhibits particle collection and precipitation. The opposing diffusion layer and the stern layer make up the double layer. A minimum zeta potential of ±30 mV is necessary for a stable suspension stabilized solely by electrostatic repulsion, while a zeta potential of ±20 mV would be adequate for a combination electrostatic and steric stabilizer. When an electric field is applied, electrophoretic mobility is measured, which is subsequently translated to zeta potential to calculate the charge of the particles.[29]

3) In vitro drug release: Drug release studies were conducted in a dissolving apparatus utilizing the paddle method at a rotational speed of 50 rpm.[30] The temperature and volume of the dissolving medium were 37.0±0.2 °C and 900 ml, respectively. Samples were gathered at predetermined intervals and filtered via a 0.45µm filter. Using HPLC or UV spectroscopy to measure absorbance, one can ascertain the amount of medication dissolved. The utility of an in vitro study is increased by the establishment of an IVIVC, which is defined as a correlation between in vitro release and in vivo behavior.[31] Water, buffer solutions (PH 6.8, 7.4), aqueous surfactant solutions, or other biologically-like fluids can be used as dissolving media.[32]

4) Crystalline state and particle morphology: Together, the evaluation of the crystalline state and particle morphology aids in comprehending the potential polymorphism or morphological alterations that a medicine may experience upon nanosizing. Furthermore, it is probable that amorphous drug particles will be produced during the preparation of nano suspensions. Therefore, it is crucial to look into the amount of amorphous drug nanoparticles produced when making nanosuspensions. The extent of the amorphous fraction and the changes in the physical state of the drug particles can be ascertained by X-ray diffraction analysis, which can be enhanced by differential scanning calorimetry. It is recommended to use scanning electron microscopy to obtain a true understanding of particle shape [33,34,35].

5) pH: The pH values were measured at 25°C using a digital pH meter set to 20±1 C. After coming into touch with the pH-meter electrode, the formulation was allowed to equilibrate for one minute. The mean and standard deviation were calculated using this approach, which was carried out in triplicate. [36]

6) Stability: Consistency in The number of unstable surface atoms and molecules increases as particle size decreases, leading to a rise in surface energy. The assessment of saturation solubility aids in the investigation of any alteration in the drug's in vivo performance (blood profiles, plasma peaks, and bioavailability). In

order to prevent particle clustering and lower the likelihood of Ostwald ripening, stabilizers are used.[37] For the long-term stability of nanosuspensions, the combination of polymers and surfactants is advantageous.[38]

Application of Nanosuspension

- **Oral Drug Delivery:** Oral administration is the preferred method for many medications, including antibiotics like atovaquone and buparvaquone, due to its numerous advantages. Making it nanoscale will improve its solubility and bioavailability. Comparing oral naproxen nanoparticle delivery to naproxen nanosuspension and tablet administration, the area below the curve (AUC) (0-24 h) is 97.5 mg-h/l [39]. The absolute bioavailability of danazol (a gonadotrophin inhibitor) in nanosuspension is 82.3, whereas the typical dispersion is just 5.2%. [40]

- **Parentral Drug Delivery:** Additionally, the parenteral drug delivery method makes use of nanotechnology. This method's benefit is that it requires far less hazardous cosolvent for medications that are poorly soluble. When compared to the traditional oral formulation, this will increase the drug's therapeutic impact and target the macrophages. Clofazimine is administered intravenously (IV), and for the majority of Mycobacterium avium strains, the concentration in the liver, spleen, and lungs reached an excessive level, or higher than the minimal inhibitory concentration. Tarazepide is made as a nanosuspension to increase its bioavailability without the need for cyclodextrins and surfactants [41].

- **Dermal application:** Nanocrystalline drugs have the ability to increase saturation solubility, which leads to improved drug penetration. Nanocrystals are ideal for cutaneous applications due to their increased membrane penetration, enhanced permeability, and adhesiveness.[42]

- **Targeted delivery:** The drug's absorption capacity is influenced by the size of its nanoparticles. Modifying the properties of nanoparticles, such as their surface, allows for targeted distribution by changing their in vivo behavior. Techniques such as the creation of stealth nanocrystals or smart crystals with particle sizes less than 100 nm can be used to construct targeted medication delivery systems. The development of nanosuspensions is a commercially viable method for targeted distribution because of its ease of use. The way the particles are transported throughout the body is influenced by their surface characteristics, including charge, surface hydrophobicity, and the presence or concentration of particular functional groups. The successful application of atovaquone nanocrystals coated with tween 80 for effective parasite removal in the brain during toxoplasmosis treatment demonstrates the capacity of tween 80-coated nanocrystals for brain targeting.[43]

- **Occular Drug Delivery:** Some medications are poorly soluble in the lachrymal fluid. Its bioavailability and saturation solubility will both rise if it is prepared as nanoparticles. mostly used for hydrophobic medications. It lengthens the time spent in the cul de sac. Ibuprofen is an excellent illustration of nanosuspension. When compared to the aqueous formulation, ibuprofen's anti-inflammatory efficacy increased.[44]

- **Pulmonary delivery:** Drugs with low solubility in pulmonary secretions may benefit from administration using nanosuspensions. Current pulmonary delivery methods, such aerosols and dry powder inhalers, have the drawbacks of short residence times and restricted diffusion at the targeted location. Nanosuspensions can be used to get around these limitations. Budesonide and fluticasone have been successfully formulated as nanosuspensions for pulmonary delivery, for instance.[45]

Future Perspectives

Nanosuspension technology represents a new and cutting-edge approach for overcoming difficulties with the administration of hydrophobic medications, particularly those with restricted solubility in both organic and aqueous environments. Methods like media milling have proven effective for producing nanosuspensions in large quantities, paving the way for their commercial viability. Beyond conventional dosage forms such as tablets, capsules, and pellets, nanosuspension technology also enables the development of improved parenteral products. The field of nanosuspension drug delivery is poised for continued expansion and will remain a significant area of interest for both oral and non-oral modes of administration, primarily due to its straightforward formulation processes and wide array of therapeutic applications. Further research will likely

focus on optimizing formulation parameters, exploring novel stabilizers, and developing advanced manufacturing techniques to ensure even greater stability, efficacy, and safety of nanosuspension-based drug products. The potential for targeted drug delivery and combination therapies utilizing nanosuspensions also presents exciting avenues for future development in pharmaceutical science.

Conclusion

Nanosuspensions have emerged as an effective solution for drugs facing challenges with poor bioavailability and solubility in both organic and aqueous solutions. The advancement of techniques like media milling and high-pressure homogenization has facilitated the commercial production of nanosuspensions, making them a practical and scalable pharmaceutical approach. Their versatility allows for administration through various routes, including oral, topical, parenteral, and ocular delivery.

Nanosuspensions have become the preferred formulation for drugs with low bioavailability due to their ease of use, reduced requirement for excipients, and ability to significantly enhance the rate of dissolution and saturation solubility. This innovative technology offers substantial benefits in improving drug efficacy and patient outcomes, positioning it as a vital tool in modern drug delivery systems.

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