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PHARMACEUTICAL NANOSUSPENSION: UNVEILING THE SYNERGY OF BOTTOM –UP AND TOP-DOWN FORMULATION STRATEGIES: A REVIEW

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ABSTRACT

Nanotechnology is the science that studies the process that occurs at molecular level and of nano length scale size. Nano refers to the particle size range of 1-1000 nm. Nanosuspensions are belongs to nanotechnology. A Drug nanosuspension is defined as perfectly colloidal, biphasic drug substances, dispersed solid drug particles in an aqueous vehicle, size of less than 1 µm stabilized by surfactants and polymers prepared by suitable methods for drug delivery applications. It ensures efficient delivery of hydrophobic drugs and increases the bioavailability. It is an attractive and promising tool to improve poor solubility and bioavailability of the drugs. It increase medication stability and can be easily prepared for water- insoluble drugs using techniques such as high-pressure homogenizers, wet mills and emulsion solvent evaporation. Additives like stabilizers, solvents, buffers, salts, and cryoprotectants can be used for this. Nanosuspensions can be administered orally, parenterally, intravenously, and can be combined with ocular inserts and mucoadhesive hydrogels for targeted drug delivery. This article describes the preparation of nanosuspensions and their application in pharmaceutical research.

KEYWORDS: Nanotechnology, Nanosuspensions, polymers, drugs. Bottom-up Technology, Top- Down Technology etc.

INTRODUCTION

In drug development, large portions (More than 40%) of newly discovered drugs are water- insoluble or lipophilic. The challenge of creating water soluble, nontoxic drugs has always been a difficult task for medical researchers One strategy to improve solubility and speed up absorption across the gastrointestinal barrier is to create therapeutic compounds that are categorized as BCS class II or IV using nanoparticles. Class II medications in the BCS, which have limited solubility but good permeability, are micronized. Drugs with low solubility have benefited from the use of a number of conventional techniques, such as oily solutions, salt creation, micronization, solubilization with cosolvents, and surfactant dispersions.[1-4] Alternative strategies include solid dispersion, liposomes, emulsions, microemulsions, and cyclodextrin-based inclusion complexation have demonstrated encouraging outcomes, although they are not always suitable for all medications. Moreover, these techniques don't work for medications that don't dissolve in organic or aqueous solvents.[5–7]

Considerations on the practical use of the nano suspensions method

1. When dealing with compounds characterized by a high log P value, indicating solubility in oil but insolubility in water, the preparation of nanosuspensions emerges as a favored method.
2. Nanosuspensions are the preferred choice for formulating drugs not soluble in both water and organic media, removing the need for lipidic systems.
3. When drugs show poor solubility in organic media or water, nanosuspensions provide an alternative formulation approach that surpasses the use of lipidic systems.
4. While liposomes or emulsions are commonly employed for drugs which arepoorly soluble in water but soluble in oil, these lipid-based methods may not be suitable for all the drugs. It is preferable touse nanosuspensions in suchsituations.[8,9]

Advantages of nanosuspension technology in increasing the solubility of drug with limited solubility

1. Nano suspensions are suitable for water- insoluble

compounds soluble in oil. They are also effective for formulating compounds insoluble in both water and oil, giving an alternative to lipidic systems.

2. The decrease in particle size attained through nanosuspension technology leads to an improved drug dissolution rate and enhanced drug absorption, resulting in increased bioavailability, faster onset of action, and higher peak drug levels.
3. In nanosuspensions the drug is in contact with the gastrointestinal mucosa for a longer period, stimulating better absorption.
4. Nanosuspensions offer adaptability in drug delivery and various routes can be used to administer them, including parenteral, oral, dermal, pulmonary and ocular routes, providing treatment options that are flexible.
5. Nanosuspensions offer important benefits for ocular applications. As a result, it is possible to administer drugs that are poorly water-soluble and to achieve minimal drug doses, sustained drug release, a reduction in systemic toxicity, a prolongation of corneal residence time, and higher drugconcentrations in infected tissues.
6. Utilising nanosuspensions improves the safety profile overall since they lessen the likelihood of side effects connected to theexcipients employed in the formulation.
7. Nanosuspensions do not require the dissolution of compounds and help preserve the crystalline state of drugs for pharmaceutical use.
8. Nanosuspensions have improved physical stability and decreased particle settling due to their increased resistance to oxidation and hydrolysis.
9. Nanosuspensions enable the administration of lower volumes of the drug, making them suitable for ophthalmic, intramuscular and subcutaneous applications.
10. Nanosuspensions possess the ability for passive targeting, allowing for the concentration of drugs at preciselocations within the body where theyexert their intended effects.[10,11]

Approaches for Nanosuspension preparation

There are primarily two methods for preparing nanosuspensions. The conventional approach, known as "bottom-up technology," relies on precipitation to create hydrosols. In contrast, "top- down technologies" are preferred over "precipitation techniques" due to their disintegration methods. These "top-down technologies' include media milling for nanocrystals, high- pressure homogenization in water for dissocubes, high-pressure homogenization in non-aqueous media for nanopures, and a combination of precipitation and high- pressure homogenization known as nano edge.

1. Bottom-up technology

Bottom-up technology begins at the molecule level and develops through association to produce solid particles. The method uses precipitation approaches, such as changing the temperature or adding a nonsolvent, to change the solvent's quality. precipitation is a well-known process in pharmaceutical chemistry and technology.[12,13]

Benefits

- Simple as well as cost-effectiveequipment can be used.
- Precipitation offers higher saturation solubility when compared with methods used in the preparation of nanosuspension.

Difficulties

- The drug must exhibit solubility in at leastone solvent, which excludes new drugs with poor solubility in both aqueous and organic media.
- At least one non-solvent must be misciblewith the solvent being utilised.
- Removal of residues of solvent increases production costs.
- Preserving the particle characteristics, particularly size and the amorphous fraction, can be challenging. To maintain particle integrity, a subsequent process such as lyophilization or spray drying is often recommended.[14,15]

2. Top-down technology

The top-down technologies encompass two methods:

a) Media milling

Pearl mills can be used for the preparation of nanomaterials. The process includes a recirculation chamber, a milling shaft and a milling chamber. The drug suspension is combined with pearls or small grinding balls in the mill. The size of the particles is reduced by the impact of the rotating balls within the grinding jar.[16] The milling media, typically made of durable materials such as zirconium oxide, demonstrate excellent resistance to wear andtear. Advanced equipment like planetary ball mills, such as the PM200, PM100 models can achieve particle sizes below 0.1 µm. In a specific study, researchers employed a wet milling technique to produce a nanosuspension that consists of Zn-Insulin, resulting in particle size that is about 150 nm. However, it's important to note that media milling has its limitations, including potential contamination from milling material erosion, the risk of thermolabile drug degradation due to heat generation, andthe occurrence of particles that are around 5 µm in size.[17]

Benefits

- Straight forward technology
- Milling process is cost-effective
- To a certain extent, achieving extensive manufacturing is possible through the utilization of batch processing.

Difficulties

- There is a credible possibility that the erosion of milling material could result in the contamination of the product.
- The process duration may not be optimal for

efficient production.

- Potential for microbial growth in the water phase during prolonged milling periods
- The duration and expenses related to the milling material's separation from the nanosuspension pose significant considerations, particularly in the production of sterile parenteral products.[18,19]

b) High pressure homogenization

This technique entails passing a liquid suspension through a narrow valve while applying pressure. This process employs the formation and collapse of gas bubbles to decrease the size of particles. It is advisable to pre-mill fine drug particles to achieve higher solid concentrations. High-pressure homogenization offers numerous advantages, such as its versatility in handling both diluted and concentrated suspensions and its ability to facilitate aseptic manufacturing processes.[20]

Nanopure

Nanopure is a technique used for homogenization that utilizes media or mixtures without the presence of water. In technology that utilizes dissocubes cavitation, it is essential, but when non- aqueous media are used, the reduction in static pressure is insufficient to cause cavitation. Nanopure is capable of achieving homogenization at lower temperatures, even below freezing, making it suitable for substances that are sensitive to heat. It yields similar outcomes to dissocubes in more moderate circumstances.[21,22]

Nanoedge™

NanoedgeTM combines homogenization and precipitation techniques to acquire smaller particle size that is small and effectively complements the stability. It addresses the constraints typically related to precipitation strategies, consisting of long-time period stability issues and crystal growth. To begin with here suspension this is brought on undergoes additional homogenization if you want to decrease size of particle and inhibit crystal improvement. Methanol, ethanol, and isopropanol are just a few examples of water- miscible solvents that can be used within the precipitation process. those solvents can be tolerated within the formula to a degree, whilst it's far proper to absolutely take away them.

An evaporation stage can be introduced to the Nanoedge TM nanosuspension production technique to provide a changed beginning fabric without solvent, whi ch is ultimately homogenised under excessive pressure.[23]

Emulsion diffusion method

This technique uses emulsions as templates to create nanosuspensions and as a medication delivery vehicle. This method works best when the medication dissolves in volatile organic solvents or solvents with a water solubility of just a small amount. These solvents, which transport the medication, are present in the emulsion's dispersed phase. An aqueous phase containing the proper surfactants is mixed with the solvent combination to create an emulsion, which is then agitated. The emulsion is then homogenized using high-pressure homogenization. Water is added to the emulsion to dilute it, and then it is homogenized again through repeated cycles so that the organic solvent diffuses and the droplets solidify into particles. The emulsion's size can be adjusted to control the particle size of the nanosuspension.[24,25]

Advantages

- It doesn't require any specialized equipment.
- By adjusting the emulsion's droplet size, itis easy to regulate the particle size.
- The formulation can be optimised toensure scalability.

Disadvantages

- Drugs whose solubility is limited in organic and aqueous media are not suitable for this method.
- Issues associated with safety may arise due to the use of hazardous solvents during the process. Purifying the drug nanosuspension through ultrafiltration may increase overall costs.
- Relatively larger amounts ofsurfactant/stabilizer are needed compared to other previously mentioned productiontechniques.[26,27]

Micro emulsion template

In order to create an emulsion, this procedure entails dispersing the medication in a mixture of organic and inorganic solvents, which must be combined with an aqueous phase and an aqueous phase that contains the necessary surfactants. As the organic phase evaporates, the drug's particles rapidly precipitate at low pressure, resulting in nanosuspension. The organic phase rapidly evaporates at lower pressure, causing the drug particles to precipitate and form the nanosuspension. The inclusion of surfactants ensures the stability of the nanosuspension. Among the solvents that can be utilized in the dispersion phase instead of hazardous solvents are triacetin, benzyl alcohol, and butyl lactate..[28]

Advantages

- It doesn't require any specialised equipment.
- By adjusting the emulsion's droplet size, itis simple to regulate the particle size.
- The scalability of the process is achievable with appropriate formulation optimisation.

Disadvantages

- Drugs that show low solubility in both media, i.e., organic and aqueous, are not suitable for this technique.
- The purification process of nanosuspension through diultrafiltration may lead to increased process costs.
- Compared to the other manufacturing methods previously described, more surfactant or stabiliser is needed.[29,30]

Supercritical fluid method

Supercritical fluid technique can be used to create drug nanoparticles from drug solutions. Several strategies have been tested, including precipitation utilizing the supercritical anti-solvent process, the rapid expansion of the supercritical solution process, and the compressed anti- solvent process (PCA). Using a nozzle and supercritical fluid, a pharmaceutical solution is expanded as part of the RESS process. Particles of the medication precipitate due to the loss of solvent power. The drug solution is atomized using compressed CO2 in the PCA process, which results in supersaturation and the precipitation of the drug as small crystals. A drug solvent that is miscible with the supercritical fluid and a supercritical fluid in which the medication is only weakly soluble are used in the supercritical anti-solvent approach.[31]

Disadvantages

- The use of toxic solvents and a larger quantity of stabilisers and surfactants compared to other procedures
- Potential particle nucleation overgrowth owing to temporary high supersaturation may lead to the creation of unwanted forms or polymorphs.[32]

Emulsification melt method

During the melt emulsification procedure, the medication is dissolved in an aqueous solution of a stabiliser while being heated above its melting point. After that, the mixture is homogenized to create an emulsion. Using a heating tape and temperature controller, the emulsion's temperature is kept above the medication's melting point during the procedure. After that, the emulsion is either quickly refrigerated in an ice bath or gradually cooled to room temperature.[33]

Advantage

- When employing the melt emulsification method, no organic solvents are used at all throughout the production process.[34]

Dry co-grinding

Recently, nanosuspensions have been made via dry milling processes. This method creates stable nanosuspensions by combining poorly soluble medications with soluble copolymers and polymers in a liquid medium. This method has been applied to numerous soluble polymers and copolymers, including PVP, polyethylene glycol (PEG), hydroxypropyl methylcellulose (HPMC), and derivatives of cyclodextrin.[35]

Considerations in formulating nanosuspensions

- **Stabilizer**

In nanosuspensions, a stabiliser's main job is to keep drug particles adequately hydrated while also inhibiting Ostwald's ripening and agglomeration. The inclusion of ionic or steric barriers preserves the formulation's physical stability. The kind and amount of stabiliser that is used has a significant impact on how physically stable and behaved nanosuspensions are. Lecithins, poloxomers, polysorbate, cellulosics, and povidones are examples of common stabilisers. In particular, lecithin is required to prepare nanosuspensions that can be autoclaved and administered parenterally.[36]

- **Organic solvent**

When emulsions or micro emulsions are used as templates for the formation of nanosuspensions, organic solvents are used. It is recommended to utilize water-miscible and less dangerous solvents, such as propylene carbonate, butyl lactate, ethyl acetate, and ethyl formate. Methanol, ethanol, isopropanol, and chloroform are some of these solvents. These substitutes are preferred over conventionally used toxic solvents such as dichloromethane.[37]

- **Co-surfactants**

When creating nanosuspensions using microemulsions, the appropriate co-surfactant needs to be selected. Co-surfactants have an important role in phase behavior because they influence the amount of medication added to the microemulsion and the absorption of the internal phase. Even though co-surfactants such bile salts and dipotassium glycyrrhizinate have been reported in the literature, other solubilizers including transcutol, glycofurol, ethanol, and isopropanol can be employed in microemulsion formulations without any problems.[38]

- **Other additives**

Depending on the needs, nanosuspensions may also include other additives such as buffers, salts, polyols, osmogents, and cryoprotectants.[39]

Post-production processing

For nanosuspensions, post-production processing is required if a treatment candidate is particularly susceptible to hydrolytic cleavage or chemical degradation. Processing may also be necessary if the suggested mode of administration has realistic restrictions or if the preferred stabiliser is not strong enough to keep the nanosuspension stable for an extended length of time. Using nanoscale drug particles, two methods for producing dry, powdery pharmaceuticals are spray drying and lyophilization. It is important to consider medication characteristics and cost while choosing between two-unit approaches. Generally speaking, spray drying is more practical and less costly than lyophilization.[40]

Nanosuspension characterization techniques

In-vitro Evaluations

- **Organoleptic properties**

Formulations that must be administered orally must take these characteristics into account. Taste variations can be explained by changes in particle size, crystal habit, and subsequent particle disintegration, especially for active chemicals. Changes in flavor, scent, and color can all be signs of chemical instability.

- **Particle size distribution**

The particle size has an impact on the physicochemical characteristics, such as dissolving rate, saturation solubility, and physical stability. Several techniques, including the Coulter counter multisizer, laser diffraction (LD), and photon correlation spectroscopy, can be used to determine the particle size distribution. In contrast to LD, which has a measuring range of 0.05–80 m, PCS can measure particles with a size range of 3 nm to 3 m. In contrast to LD, which offers a relative size distribution, the Coultercounter multisizer generates a set number ofparticles. In order to avoid issues like capillary obstruction and embolism, it is preferable for particles used for intravenous.

- **(IV) usage to be smaller than 5 m, given thatthe lowest capillary size is around 5–6 m. Zeta potential**

The suspension's stability can be measured using zeta potential. A stable suspension thatrelies only on electrostatic attraction needs azeta potential of at least 30 mV. However, it is believed that when both steric and electrostatic stabilising mechanisms are active, a zeta potential of 20 mV is enough.

- **Crystal morphology**

The effects of high-pressure homogenization on the drug's crystalline structure can be investigated using methods such as differential scanning calorimetry or X-ray diffraction analysis in conjunction with differential thermal analysis. High-pressure homogenization in nanosuspensions can lead to changes in the crystalline structure, such as the appearance of amorphous or other polymorphic morphologies.

- **Dissolution velocity and saturationsolubility**

Nanosuspensions offer a substantial advantage over other techniques since they can raise the rate of dissolving and saturation solubility. In order to fully understand the formulation's behavior in vitro, these characteristics need to be investigated in a range of physiological solutions. Böhm et al. claim that increasing the particle size to the nanoscale area may accelerate and increase the dissolving pressure. It has been shown that the pressure of dissolution rises with decreasing size.

- **Density**

An essential factor to take into account is a formulation's specific gravity, often known as density. If the density decreases, air that got stuck inside the formulation structuremay be the cause of the issue. It is suggestedto use a homogeneous, well-mixed mixture for determining density at a certaintemperature. Density can be measured usingprecision hydrometers.

- **pH Value**

An aqueous formulation's pH value must be determined at a certain temperature to avoid "pH drift" and electrode surface coating brought on by suspended particles, as well as to ensure equilibrium has been attained. For pH stability, it is suggested not to include electrolytes in the formulation's exterior phase.

- **Droplet size**

Electron microscopy can be used to discoverthe distribution of droplet sizes in microemulsion vesicles. In a dynamic light scattering spectrophotometer, a neon laser with a wavelength of 632 nm can be used forthis.

- **Measurement of viscosity**

Using a rotational viscometer of the Brookfield type, the viscosity of lipid-based formulations with varied compositions may be assessed at various shear rates and temperatures. The samples for measurement should be submerged in the thermobath- controlled sample chamber of the instrument, which should be kept at 37°C.

- **Stability of nanosuspension**

Drug crystals may assemble in nanosuspensions due to their high surface energies and small particle sizes. Stabilizers are necessary to completely moisten the drug particles, prevent agglomeration and Ostwald ripening, and provide a formulation that is physically stable because they create a steric or ionic barrier. Cellulosics, poloxamers, lecithin, polyoleate, and povidones are commonly used as stabilisers in nanosuspensions. Often times, lecithin is used as a component in parenteral nanosuspensions.

In-vivo biological performance: Regardless of the route and method of delivery, an in vitro/in vivo correlation needsto be developed in order to monitor a drug'seffectiveness in the body. It is significant inthe contextof intravenously delivered nanosuspensions since the organ distribution is reliant on the drug's surface properties, such as surface hydrophobicity and interactions with plasma proteins, which in turn are dependent on the in vivo behaviour of the drug. It is commonly accepted that significant factors influencing organ distribution include the size and kind of protein absorption pattern that is seen after intravenous injection of nanoparticles. It is crucial to employ the right methods to assess surface features and protein interactions in order to understand in vivo behaviour. One method for assessing surface hydrophobicity is hydrophobic interaction chromatography, while another method is 2-D PAGE for quantifying and evaluating the adsorption ofprotein in animals after administration through the intravenous route.[41–44]

Versatile implementations of nanosuspensions

- **Oral administration**

The recommended method of administration is oral. However, some medications have restricted absorption and solubility, which limits their bioavailability and decreases their effectiveness. When this happens, nanosuspensions can help by increasing surface area and adhesiveness, which improves the absorption and dissolution rate. By improving mucoadhesion, nanosuspensions can also lengthen the time that food

travels through the gastrointestinal tract, which increases bioavailability. Increases in the nanosuspension's adhesiveness, saturation solubility, and surface area are thought to be responsible for the improved oral bioavailability. Moreover, nanosuspensions make it simple to hide the flavor of particle systems.[45]

- **Parenteral administration**

Drugs that are not injectable and exhibit poor solubility must be transformed into formulations suitable for intravenous administration by the use of nanosuspensions. The creation of nanosuspensions for parenteral use is imperative, and recent advancements in this area have demonstrated their efficacy for injectable formulations. Today's highly regulated nanosuspension technologies allow for the production of homogeneous particles with superior control over the maximum particle size. Several research publications highlight the value of nanosuspensions for parenteral administration.[46]

- **Ocular delivery**

A potential method for administering drugs with low lachrymal fluid solubility is nanosuspensions. Given that they increase the saturation solubility of drugs that are hydrophobic in nature, they constitute the perfect technique for ocular drug administration. For some drugs, such as glucocorticoids, researchers have created effective nanosuspension delivery devices, including Kassem et al.

- **Pulmonary delivery**

Nanosuspensions may be an advantageous delivery method for medications with low solubility in pulmonary secretions. Current pulmonary delivery methods, such aerosols and dry powder inhalers, have two drawbacks: they have limited residence time and limited diffusion at the targeted location. Nanosuspensions provide a way around these limitations. As an illustration, consider the effective creation of nanosuspensions for pulmonary administration of fluticasone and budesonide.[47]

- **Dermal application**

Drugs in nanocrystalline form can enhance saturation solubility, which results in enhanced penetration of the drug. Because of their greater membrane penetration, improved permeability, and adhesiveness, nanocrystals are well suited for cutaneous applications.[48]

- **Targeted delivery**

The drug's nanoparticles' absorption efficiency is influenced by their size. Targeted delivery is achieved by modifying the in vivo behavior of nanoparticles by the modification of their surface properties. Strategies such as the development of stealth nanocrystals or smart crystals with particle sizes less than 100 nm can be used to produce targeted medication delivery systems. Making nanosuspensions is an economically viable method for targeted distribution because of its ease of use. The surface characteristics of the particles, including their hydrophobicity, charge, and the concentration or presence of particular functional groups, influence the distribution of the particles inside the body. The successful use of atovaquone nanocrystals coated with tween 80 for effective parasite control has revealed the potential of tween 80-coated nanocrystals for brain targeting.[49]

- **Mucoadhesion**

When administered as a suspension, the nanoparticles quickly make contact with the mucosal surface by dispersing in the liquid medium. The particles at the intestinal surface become immobile due to the process of "bioadhesion". This concentrated solution has a rapid adsorption process and functions as a particle reservoir. The initial step of particle absorption involves direct contact between the intestinal cells and the particles, which is made possible by the bioadhesive phase. [49–52]

Future perspectives

A unique and cutting-edge method for resolving issues with the delivery of hydrophobic medications, such as those with restricted solubility in both aqueous and organic environments, is nanosuspension technology. Methods like media milling have shown promise in producing nanosuspensions in large quantities. The use of parenteral products in addition to traditional dosage forms like pills, capsules, and pellets is made possible by nanosuspension technology. The field of nanosuspension drug delivery will keep expanding and be interesting for both oral and non-oral modes of administration because of its simple formulation processes and broad variety of applications.

CONCLUSION

Drugs with poor 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 now be used to produce nanosuspensions on an industrial scale. Oral, topically applied, ocular, and parenterally applied nanosuspensions can all be used. Nanosuspensions have become the preferred formulation for drugs with low bioavailability because of their ease of use, lower requirement for excipients, quicker rate of dissolution, and saturation solubility.

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