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NANOSUSPENSION TECHNOLOGY: A PROMISING APPROACH FOR ENHANCING DRUG SOLUBILITY AND BIOAVAILABILITY

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ABSTRACT

Pharmaceutical advancements have shown significant improvement through the innovation of nanosuspensions, colloidal dispersions, and biphasic drug particle systems in water with diameters smaller than 1 µm. Increased surface area and saturation solubility of nanoscale drug particles lead to enhanced dissolution rates and bioavailability, especially for medications with low solubility in water or both water and fat. This review examines how nanosuspensions are made, their various applications, and their advantages, with a focus on their ability to be used for different methods of drug delivery like inhalation, eye drops, injections, and oral ingestion. New chemical entities (NCEs) with high log P values and melting points frequently present solubility challenges that cannot be adequately addressed by conventional techniques like micronization and co-solvent solubilization. On the other hand, nanosuspension technology provides a reliable solution using methods like emulsion diffusion, media milling, and high-pressure homogenization. The study compares the "top-down" and "bottom-up" methods in technology, highlighting the advantages of using high-pressure homogenization to create concentrated, stable nanosuspensions for different medical uses. Furthermore, an investigation is underway regarding the impact of stabilizers, surfactants, and co-surfactants on improving the physical stability and effectiveness of nanosuspensions. Factors like saturation solubility, zeta potential, crystalline state, and particle size distribution play a critical role in assessing the efficacy and stability of nanosuspension formulations. in conclusion, the development of new medications may find that using nanosuspensions is a feasible way to address problems with drug delivery, specifically those related to solubility and bioavailability. Their potential as a game-changing technology in the pharmaceutical sector is highlighted by their capacity to improve therapeutic efficacy and drug absorption.

Key Words: Nanosuspension, bioavailability, poorly soluble drugs, nanotechnology

1. INTRODUCTION

Nanosuspensions are biphasic systems that are colloidal dispersions consisting of drug particles that are dispersed in an aqueous medium, all having a diameter smaller than 1 µm. Drug particles that have been decreased to the nanometer scale exhibit a quicker dissolution rate because of their enhanced surface area and higher saturation solubility. Nanosuspensions have been successful in addressing difficulties linked to administering medications with poor water solubility or solubility in both water and fat. Their simplicity and the benefits they offer set them apart from other methods.

This review primarily examines the different aspects of nanosuspensions and their potential for effective drug delivery . Utilizing nanosuspensions in different types of drug forms, such as mucoadhesive hydrogels, takes advantage of their distinct characteristics to improve drug delivery(1). Nanosuspension technology offers benefits primarily due to its ease of use and ability to be applied to many pharmaceutical compounds. Nanosuspensions offer a simple method of preparing water-insoluble drugs to improve their solubility. Nanosuspensions are prepared using emulsion solvent evaporation, melt emulsification, high-pressure homogenizer, wet mill, and supercritical fluid techniques. Nano-suspensions can be administered through the parenteral, pulmonary, ocular, and oral routes. Nanosuspensions are also applicable for delivering drugs specifically to the eyes through ocular inserts and mucoadhesive hydrogels. Micronization, adding co-solvents, using salt forms, dispersing with surfactants, precipitation techniques, and employing oily solutions are some of the traditional approaches to enhance the solubility of poorly soluble products. Although beneficial, certain drug delivery techniques (such as liposomes, emulsions, microemulsions, solid dispersions, and cyclodextrin inclusion complexation) may not be appropriate for every drug use. These techniques cannot be used for medications that are not soluble in organic or aqueous solvents. Applying nanotechnology can resolve the problems associated with traditional methods of addressing and improving bioavailability. Compounds that are most suitable for nanosuspension are those with high log P values, high melting points, high doses, and solubility in oil but not in water.

Insoluble drugs in organic solvents and water can also be treated with nanosuspension technology. Many hydrophobic medications, including spironolactone, amphotericin B, mitotane, clofazomine, bupravaquone, and nimesulide, are prepared as nanosuspensions(2).

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In today's scientific landscape, nanotechnology is a valuable component of nanoscience, a field that is considered as one of the most promising, rewarding, and challenging areas of research. It is a field of science that examines how specific characteristics of tiny particles change based on their size. The pharmaceutical sector is constantly seeking new techniques to achieve adequate oral bioavailability because most NCEs display low water solubility. The pharmaceutical industry is facing a major challenge with the increasing number of poorly soluble and poorly permeable lead compounds in drug formulations, which is hindering the development of new molecular entities. Lately, the rapid development of nanoscale systems with a size below 1 μm has emerged as a novel drug delivery approach. The main characteristic of these systems is their rapid dissolution rate, which enhances bioavailability after being taken orally(3).

CHARACTERISTICS OF NANOSUSPENSION

STRUCTURAL INTEGRITY

Ostwald ripening causes scattered systems to exhibit physical instability and crystal growth, resulting in microparticle formation. Ostwald ripening happens because there are differences There is a difference in both saturation solubility and dissolution rate between small and large particles. Due to the consistent size of all particles in nanosuspensions, there is uniformity in the saturation solubility of the drug particles., thus inhibiting Ostwald ripening (4).

NANOSTRUCTURE

The intense energy input alters the structure of drug particles during the disintegration process. During high-pressure homogenization, the drug particles change from crystalline to amorphous states. Factors such as the number of homogenization cycles, the drug's chemical makeup, hardness, and the power density of the homogenizer all influence the drug's transformation process(5).

STICKINESS

Finely ground powders have higher adhesion levels than coarsely ground powders. The adhesion of small drug nanoparticles can enhance the oral administration of drugs that have poor solubility(6).

STATE OF CRYSTALLIZATION AND SHAPE OF PARTICLES

When a drug undergoes nanosizing, its crystal form and particle shape are examined together to better grasp any polymorphic or morphological alterations that might take place. Due to high-pressure homogenization, nanosuspensions could alter the crystalline structure resulting in a disordered state or various polymorphic structures. is a technique that can be used to assess changes in the solid state of drug particles and the amount of amorphous material present. can be used in addition to differential scanning calorimetry to further examine the alterations in the drug particles'solid state7)

NANOPARTICLES ENABLE PASSIVE TARGETING IN SUSPENSION

Most drugs have not been effective as they are unable to get to the target location for action Serious adverse reactions often occur when a significant amount of medication is distributed to healthy tissues or organs not related to the disease. A feasible answer to this crucial issue is developing specialized medication delivery systems. The adaptability of nanosuspensions is shown through their capability of being easily adjusted in terms of particle size and surface properties, as well as their convenience in editing and finalizing the work after production is done. This flexibility allows them to be utilized in a variety of dosage forms, including tablets, pellets, suppositories, and hydrogels, for diverse modes of administration(6).

METHODS OF NANOSUSPENSION(8,9)

Nanosuspensions can be prepared in two main methods. "Inductive approach" is a term used for conventional precipitation methods, like hydrosols. Methods of precipitation are not as favored as methods of disintegration, commonly referred to as "top-down technologies." Instances of "stepwise design" consist of media milling for Nanocrystals, high-pressure homogenization in water for Dissocubes, high-pressure homogenization in non-aqueous media for Nanopure, and the amalgamation of precipitation and high-pressure homogenization for Nanoedege.

INDUCTIVE APPROACH

The inductive approach begins with molecules and advances to the creation of solid particles through molecular bonding. This indicates that we are having a conversation. classic techniques for precipitation that decrease the solvent's effectiveness, such as introducing a nonsolvent, changing the temperature, or both. A traditional approach in chemistry and technology in the pharmaceutical industry involves precipitation.

Benefit

1. Utilization of basic and inexpensive tools
2. The advantage of using precipitation for nanosuspension preparation is its superior saturation solubility compared to other methods.

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Drawback

1. The medication must dissolve in at least one solvent; this rule eliminates any novel medications exhibiting poor solubility in organic and aqueous media
2. The solvent needs to be able to mix with at least one nonsolvent
3. Eliminating leftover solvents raises the costs of production.

Keeping the characteristics of the particles, especially their size and amorphous component, can pose some difficulties. Typically, it is recommended to conduct spray drying or lyophilization as a follow up step in the particle preservation process.

High-Pressure Homogenization- o achieve uniformity, the suspension must be pushed through a valve with a small opening while being pressurized. Muller et al. created dissocubes in 1999. In this scenario, the medication is passed through a tiny opening, decreasing the static pressure sufficiently for the liquid to vaporize and form bubbles. As the bubbles burst, the drug particles move towards the center, colliding and reducing in size as the suspension exits the gap and goes back to normal air pressure. The homogenizer typically needs to be operated multiple times because of the drug's level of hardness uniformity and specified average particle size. Pre-milling is an effective technique for beginning the process of homogenization by using extremely small drug particles to develop a Nanosuspension containing a higher concentration of solids. High-pressure homogenization offers several benefits compared to media milling, notably its capability to create sterile products and its effectiveness with both concentrated and diluted suspensions..

Nanopure- Nanopure refers to suspensions in water-free or water-mixture media that are homogenized. The operation of the Dissocubes technology relies on cavitation for its effectiveness. Nevertheless, oils and fatty acids with an oily texture have a greater boiling point and much lower vapor pressure in comparison to water. As a result, cavitation cannot be caused by the static pressure drop alone. According to patents on the breakdown of polymeric material using high-pressure homogenization, disintegration was enhanced by temperatures up to 800C, which thermolabile compounds cannot tolerate. The drug suspensions were mixed evenly in non-aqueous substances using nanopure technology at temperatures near 00C, or possibly even below freezing; this method is known as "deep-freeze" homogenization. Since the results matched those of Dissocubes, thermolabile substances can be effectively used under milder conditions.

Nanoedge- This method will resemble the precipitation method or homogenization method. It is thought that better stability and bioavailability result from combining these two techniques. In order to lower the particle size and stop crystal growth, the suspension made using this method will be homogenized once more. There is a risk of crystal growth and long-term stability issues with the precipitation method. These issues will be resolved by nanotechnology.

The nano-edge technology also incorporates an evaporation technique to improve the production of nanosuspension, which will yield the modified starting solvent-free material.

Emulsion Diffusion Method- Emulsions can serve as templates for creating nanosuspensions as well as functioning as carriers for drug delivery. Drugs that can dissolve in partly water-miscible solvents or volatile organic solvents may serve as templates when in emulsion form. These kinds of Solvents are applicable to the dispersed phase of the emulsion. An emulsion forms by mixing a drug-containing organic solvent or solvent blend into an aqueous phase with appropriate surfactants under agitation. The emulsion that was created went through further homogenization via high-pressure homogenization. The emulsion was thinned out through the use of the subsequent homogenization rounds. A homogenizer is used to mix the water and organic solvent, forming solid particles from the droplets. Because every emulsion droplet corresponds to one particle, Controlling the emulsion size enables accurate regulation of the particle size in the nanosuspension. This results in greater absorption of the organic phase which leads to an escalation in the drug content in the emulsion. At first, organic solvents like methanol, ethanol, ethyl acetate and chloroform were used.

APPLICATIONS (10,11)

There are many pharmaceutical and biopharmaceutical uses for nanosuspensions; a few are listed below.
1. Making the medication into nanosuspensions improves the drug's bioavailability, saturable concentration, and rate of dissolution.

2. Nanosuspensions may be very helpful for medications that don't dissolve well in lachrymal fluids. Suggestions have been made for using suspensions and ointments to deliver these drugs.

3. Various drug delivery methods, such as pulmonary, mucoadhesive topical, for use in the eyes, oral, and targeted, utilize these nanosuspensions.

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Small drug nanoparticles are more easily absorbed through the mouth leading to increased availability in the body. Improved bioavailability is achieved as a result of drug nanoparticles having an increased capacity to stick to the mucosa and a higher solubility level. which enhances the concentration gradient between the blood and the gastrointestinal system's lumen. Aqueous nanosuspensions can be directly used with both liquid and solid forms like tabletsor hard gelatin capsules containing pellets. Another way to produce granules is by spray drying nanosuspensions.

PARENTERAL DRUG DELIVERY

Developing substances for intravenous administration is a primary application of nanosuspension technology. There are numerous advantages to IV administration, such as the ability to deliver medications with poor solubility without the use of additional toxic co-solvents, improve the effectiveness of medications that come in conventional spoken formats, and deliver drugs directly to macrophages and the harmful microorganisms they hold. Nanosuspensions containing the low-solubility medication tarazepide were developed for injection to improve the moderate effectiveness of traditional solubilization methods like surfactants and cyclodextrins in enhancing bioavailability.

DELIVERY OF DRUGS TO THE LUNGS

Mechanical and ultrasonic nebulizers are viable options for turning nanosuspensions into aerosols for pulmonary administration. Every single aerosol droplet contains Nanoparticles of drugs are used frequently due to the large number of small particles available. Because the drug's particles are so small, nebulizing and administering aqueous suspensions through the pulmonary pathways is quite simple. Some medicines that have shown good results tried via the pulmonary route include Fluconazole, Fluticasone, Cetirizine, Acetaminophen, Diclofenac, and Amlodipine.

FORMULATION OF NANOSUSPENSION (12,13)

STABILITY

The development of nanosuspensions relies heavily on stability. The drug crystals can clump together or group inappropriately due to the significant surface energy of nanoparticles.Stability's primary objective is to thoroughly wet the drug particles, thus preventing Ostwald's ripening. nanosuspension accumulation through steric or ionic barriers, resulting in a formulation that is physically stable due to the type and quantity of stabilizer used. play a major role in the in vivo performance and physical stability of nanosuspensions. Sometimes, it may be necessary to use a blend of stabilizing agents to create a steady nanosuspension.. Examining the proportion of drug to stabilizer in the mixture is recommended. for a particular situation, as it can range from 1:20 to 20:1. Thus far, cellulosic, poloxamers, polysorbates, lecithins, and povidones 21 have all been investigated as stabilizers.The stabilizer of choice for creating an autoclavable and parenterally acceptable nanosuspension is lecit-hin. The primary roles of a stabilizer include ensuring drug particles are wetted sufficiently and preventing Ostwald's ripening and agglomeration are utilized to develop a physically stable formulation of nanosuspensions. through the use of steric or ionic barriers. The stability and conduct of the body of nanosuspensions in vivo are significantly influenced by the type and quantity of stabilizer used. Sometimes a mix of stabilizing agents is necessary to achieve stability in nanosuspensions. The ratio of drug to stabilizer in the formula can range from 1:20 to 20:1 and needs to be studied for each individual situation. Examples of stabilizers that have been investigated up to this point are cellulosic, poloxamers, polysorbates, lecithins, and povidones 21. When aiming to create a nanosuspension that is suitable for injection and can withstand autoclaving, lecithin is the preferred stabilizer.

ORGANIC SOLVENTS

When preparing nanosuspensions with an emulsion or microemulsion as a guide, the formulation procedure might necessitate the use of organic solvents.

There is limited information on formulation considerations due to the early stage of development of these techniques. In creating nanosuspensions with emulsions or microemulsions as guides, factors like the toxicity of organic solvents, their removal from the formulation, and their suitability in the pharmaceutical sector need to be considered.

When formulating, it is better to utilize solvents like Butyl Acetate that are somewhat compatible with water,, Methyl Acetate, Ethyl Lactate, Glycerin, Dimethyl Carbonate, and Phenethyl Alcohol instead of the usual harmful solvents like dichloromethane. These solvents, such as ethanol and isopropanol, are less dangerous and suitable for pharmaceutical use. Additionally, if a microemulsion is going to be utilized as a guide for creating nanosuspensions, Partially water-soluble organic solvents can serve as the internal phase of the microemulsion.

SURFACTANTS

A surfactant is included in the formulation to reduce the dispersion, serving as a wetting agent or deflocculant to decrease tension at interfaces. Mono- and Diglycerides, Hydroxypropyl Methylcellulose, Xanthan Gum, Polysorbates, and Sodium Lauryl Sulfate (Tween/Span series) are some surfactants that are frequently utilized.

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CO-SURFACTANTS

different solubilizers - such as Ethyl Oleate, Propylene Glycol, Methanol, and Hexylene Glycol- are able to be utilized as co-surfactants without any safety concerns during the creation of microemulsions. While the literature discusses utilizing Phospholipid and Polysorbatesas co-surfactants, selecting the appropriate co-surfactant is essential for formulating nanosus pensi ons with microemulsions, as it can significantly impact phase behavior.

OTHER ADDITIVES

Nanosuspensions can contain buffers, salts, polyols, osmogents, and cryoprotectants based on the characteristics of the drug or the route of administration.

.EVALUATION OF NANOSUSPENSION (14,15)

ORGANOLEPTIC PROPERTIES

These qualities are crucial for formulas made for ingestion. Changes in taste, especially related to active ingredients, may be due to differences in particle size, crystal shape, and eventual particle breakdown. Modifications in flavor, scent, and hue may also indicate chemical instability.

PARTICLE SIZE DISTRIBUTION

Particle size distribution, variation in size among particles, and size of particles all affect properties of nanosuspension such as solubility, dissolution rate, stability, and *in vivo* performance. Different methods such as laser diffraction, photon correlation spectroscopy, microscopy, and Coulter counter can be employed for measuring particle size.

The level of PI will determine To maintain long-term stability, it is important to minimize the physical instability of nanosuspensions.

A PI value below 0.25 suggests a relatively tight size distribution, whereas a PI value exceeding 0.5 indicates a significantly wide distribution. LD is capable of detecting and measuring manufacturing drug microparticles. Additionally, it provides a range of volume size distribution and can examine particles ranging from 0.05 to 2000 μm. These traits are highly crucial for formulations meant to be taken by mouth. Changes in flavor, particularly in relation to the presence of active components, may be credited to alterations in particle size, crystal structure, and subsequent particle degradation.In comparison to LD, it is more efficient and suitable for assessing the contamination of nanosuspensions.

ZETA POTENTIAL

The zeta potential of a nanosuspension determines its physical stability by indicating the thickness of the diffusion layer, serving as an indicator for its long-term stability. For a nanosuspension held together by electrostatic forces, a zeta potential of at least ± 30 mV is required to remain stable, whereas a zeta potential of at least ± 20 mV is recommended for combined electrostatic and stericstabilization.

CRYSTALLINE STATE AND PARTICLE MORPHOLOGY

The crystalline state and shape of particles can be examined to confirm any changes in nanoparticles' polymorphism or morphology.

Nanosuspension involves using high-pressure homogenization to change the crystal structure of the formulation, enabling it to take on amorphous or various polymorphic forms. X-ray diffraction analysis is used to identify changes in the crystalline state of drug particles and the size of the non-crystalline component. Differential scanning calorimetry analysis is also used to validate these findings.

SATURATION SOLUBILITY AND DISSOLUTION VELOCITY

The nanosuspension technique is unique in its ability to improve the rate of dissolution and maximum solubility, which is consistent for each compound but changes with temperature and the characteristics of the solvent. The rise in saturation solubility can be clarified by the Ostwald-Freundlich and Kelvin equations.

2. CONCLUSION

Nanosuspension technology provides a creative solution to the solubility and bioavailability problems experienced by many pharmaceutical compounds. Nanosuspensions greatly increase surface area and saturation solubility by reducing drug particles to the nanometer size.

This enhances the speed at which the substance dissolves and boosts its ability to be absorbed by the body. Nanosuspensions are a versatile option for various therapeutic drugs, suitable for different delivery methods consisting of oral, injectable, respiratory, and eye-related methods.

The article spotlights on high-pressure homogenization and media milling.as more effective techniques for enhancing solubility compared to traditional methods. These techniques offer advantages in terms of ease, cost-effectiveness, and ability to expand, while also ensuring the development of reliable nanosuspensions. Stabilizers and Surfactants play a

crucial role in preserving the stability and efficacy of nanosuspensions. by preventing aggregation and ensuring even distribution of drug particles. Nanosuspensions have the potential to revolutionize drug delivery systems, particularly for medications with low solubility. Great potential is held in the pharmaceutical industry because of their ability to enhance drug absorption and increase efficiency.

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