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NANOSUSPENSION- A REVIEW

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ABSTRACT

Poorly soluble drugs are the drugs which have major problems related to their solubility profile. These drugs have low bioavailability as they belong to BCS class II and class IV of biopharmaceutical classification. The problem is more in cases of drugs such as Ketoconazole, Carbamazepine, Itraconazole, etc. as these drugs have low solubility in aqueous and non-aqueous media One of the major problems associated with poorly soluble drugs is very low bioavailability. To overcome such problems of bioavailability formulation of Nanosuspension is a promising approach and a best alternative. Nanosuspension consists of a poorly water soluble drug suspended in form of dispersion. Nanosuspension is applicable to all drugs which have low solubility problems as it alters the pharmacokinetic profile of the drug. This formulation also improves drug safety profile and efficacy. This review article describes Nanosuspension in details with methods of classification, Preparation, application and characterization.

KEYWORDS: Solubility enhancement, Low bioavilability, Nanosuspension technique, Target specific, Drug delivery, Dissolution.

INTRODUCTION

Many parameters such as solubility, permeability, dissociation and stability play an important role in drug formulations, and approximately 40% of new sites face low solubility or bioavailability issues.[1,8,12] Micronization, salt formation, dispersion, etc. are great techniques

but often suffer from low resolution and permeability. A system was developed to overcome the solubility and permeability problems of nanotechnological systems. Nanotechnology has solved the problems associated with this class of drugs and achieved incredible results. Nanotechnology is a process carried out at the nanoscale (e.g. 10-9m scale).[2] Drug delivery into nanoparticles using bottom-up and top-down methods. Nanosuspensions are submicron colloidal suspensions stabilized using surfactants.[1,2] They have poorly soluble substances that are not eliminated by the matrix process in the explosion. They are used to increase the solubility of drugs that are poorly soluble in aqueous and lipid environments.[1,8,12] Due to the strong solubility, the overflow rate of the active compound increases and the maximum plasma concentration is reached faster. This idea is useful for molecules with poor permeability, poor solubility or both, and pose significant challenges to formulators. The reduced size makes it possible to perform intravenous injection with low solubility without blocking capillaries.[9] The suspension can also be freeze-dried and formed into a solid matrix. In addition to their quality, liquid formulations also have advantages over other formulations. In this review, we will only focus on the advantages and disadvantages of different preparation methods and their application in terms of drug delivery.

ADVANTAGES OF NANOSUSPENSION[5,8,9,12]

- To increase bioavailability of drugs.
- To increase drug solubility.
- To increase drug permeability.
- Most suitable for hydrophilic drugs.
- High drug loading capacity.
- Doses can be reduced easily.
- Increase chemical and physical stability of drugs.
- Passive drug targeting can be achieved.

PREPARATION OF NANOSUSPENSION[6,7,8,12]

Stabilizer[5]

To wet the said drug; It prevents Ostwald maturation and aggregation of nanosuspensions and provides a spatial or ionic barrier.

For example

Lecithin, poloxamer, polysorbate, cellulose, povidone.

Co-surfactants[5]

Affect phase behavior when microemulsions are used to form nanosuspensions.

For example

Bile salts, dipotassium, glyceric acid, Transcutol, tetrahydrofuran, ethanol, isopropyl alcohol.

Organic solvents

Pharmaceutically acceptable, less harmful solvents used in the preparation.

For example

Methanol, ethanol, chloroform, isopropyl alcohol, ethyl acetate, ethyl formate, butyl lactate, triacetin, propylene carbonate, benzyl alcohol.

Other additives[5,14]

According to the requirements of the application method or the nature of the chemical components.

For example

Buffers, salts, polyols, penetrants, cryoprotectants.

TECHNIQUES OF PREPARING NANOSUSPENSION

Two methods are generally used in the preparation of nanosuspensions: "Bottom-up technology" and "Top-down technology", as shown in **FIGURE 1.** Bottom-up technology is a mechanism for the production of nanoparticles such as precipitation, microemulsion, melt emulsification and so on. Examples of surface technology, high-pressure homogenization and milling methods that involve breaking larger particles into nanoparticles.[6,7,8,12] The advantages and disadvantages of bottom-up technology" and top-down technology are given in **TABLE 1**. The principles of these methods are explained in detail and their Merits and Demerits are shown in **TABLE 2.**

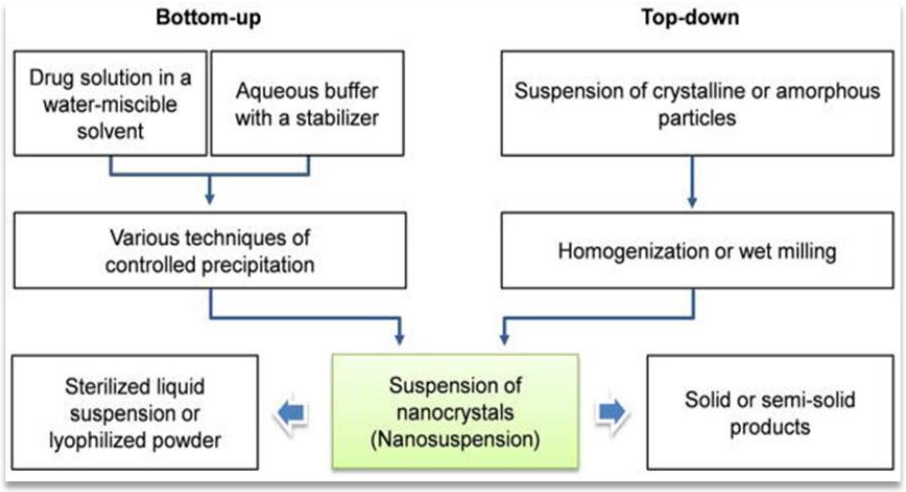

Figure 1: Methods of Preparing Nanosuspension.

Table 1: Nanosuspension Advantages and Disadvantages.

Preparation Method	Advantages	Limitations
Bottom-up technology	• Simple in principle and operation • No device requirement • Rapid preparation	• Poor reproducibility • Non-homogeneous particle size • Risk of toxic effects of the solvent • Difficult to scale up
Top-down technologies		
High-pressure homogenization method	• Easy to scale up • Easy to reproduce • Obtaining homogeneous particle size • Obtaining the desired particle size with process modifications • Decreasing for recrystallization	• Expensive equipment • Risk of heating in the device because of high pressure • Risk of clogging the chamber

Table 1: Nanosuspension Preparation Techniques Merits and Demerits.

Technique	Merits	Demerits
Precipitation	Simple process Stable products Low need of energy Low cost of equipment Ease of scale up	Growing of drug crystals needs to be limit by surfactant addition Drug must be soluble at least in one solvent Narrowly applying space, wide size distribution and potential toxicity of nonaqueous solvents
High-pressure homogenization	Simple technique General applicability to most drugs Useful for formation of very dilute as well as highly concentrate nanosuspension Aseptic production possible Low risk of product Contamination ease of scale-up	High number of homogenization cycles Pretreatment of micronized drug particles and presuspending materials before subjecting it to homogenization Possible contamination of product could occur from metal ions coming through wall of the homogenizer
Media milling	High flexibility in handling Very few batch to batch variation in particle size High flexibility in handling large quantities of drugs Ease of scale up	Possible erosion of material from the milling pearls Require milling process for hours to days Prolonged milling may induce the formation of amorphous lead to instability
Dry cogrinding	Easy process Require short grinding time No organic solvent	Generation of residue of milling media
Liquid emulsion/microemulsion template	Simple process Small size particles Stable products Low need of energy High drug solubilization Uniform particle distribution Ease of manufacture	Use of high amount of surfactant and stabilizers Use of hazardous solvent
Melt emulsification	Avoidance of organic solvents compared to the solvent diffusion	Formation of large particles Solvent diffusion

METHODS OF PREPARING NANOSUSPENSION[6,7,8.9,12]

Precipitation method

The precipitation method is a method for preparing slightly soluble substances related to the submicron. In this method, the drug is dissolved in a solvent and then the drug is mixed with a solvent in which the drug does not dissolve in the presence of a surfactant[5]. Rapid addition of the drug to a solvent such as water (usually water) causes the drug to rapidly supersaturate, forming an ultrafine amorphous or crystalline drug. This process involves nucleation and crystal growth depending on temperature. High nucleation rate and low crystal growth rate are the basic requirements for the preparation of stable suspensions with low particle size.

High pressure homogenization[13]

This machine includes the following three steps: first, the chemical powder is dispersed in the stabilizer solution to form a front beam; then the front beam is homogenized under low pressure with a high-pressure homogenizer and sometimes pre-ground; Finally, it is homogenized under high pressure for 10 to 25 minutes until the nanosuspension of the desired size is formed.

Aqueous Media Homogenization (Dissocubes)

Dissocubes technology was developed by Muller in 1999. The meter can operate at pressures from 100 to 1500 bar (2800 to 21300 psi) and up to 2000 bar with a volume of 40 ml. (for laboratory tests). To prepare nanosuspension, it is necessary to prepare micronized drug suspension in a surfactant solution using an accelerator. According to Bernoulli's law, the fluid flow in each section in a closed loop is constant. Reducing the diameter from 3 cm to 25 μm leads to an increase in dynamic pressure and a decrease in pressure below room temperature.[2] Therefore, room temperature water begins to boil and form bubbles; These bubbles burst when the suspension leaves the cavity and reaches high air pressure (called cavitation). The size of nanocrystals that can be processed depends on the temperature, number of homogenization cycles, power density of the homogenizer, and homogenization pressure. Pretreatments such as chemical micronization and costly metering increase the overall cost of paper dosing. Many drugs such as Amphotericin B, Ordinon, thimerosal, fenofibrate, Melarsoprol, Buparvaquone, prednisolone, carbamazepine and dexamethasone have been prepared in nanosuspensions using this method.

Homogenization in a non-aqueous environment (Nanopure)

Nanopure is a suspension homogenized in a non-aqueous environment. It is "deep freeze" homogenization in which the drug is suspended in a non-aqueous environment, homogenized at 0°C or sometimes below freezing. Since water, oil, and fatty acids have high boiling points and low vapor pressures, the drop in static pressure in nanopure technology is not sufficient to initiate cavitation.

Milling Technology media milling

Liversidge et al. It has a nanocrystal technology patent. In this technology, the drug is ground in the environment to produce nanoparticles. The effect of the collision medium and the drug provides the energy necessary for the disintegration of the micro particulate system into nanoparticles. In this process, a grinding chamber containing grinding media containing chemicals, stabilizers, and water or suitable buffers is rotated at a very high shear rate to create a suspension. Residue left in the finished product is a major problem related to this method.

Dry co-milling[18]

Nano suspensions have been prepared by wet grinding of pearl stones for many years. Nanosuspensions now can be prepared by dry milling method. Insoluble substances and soluble polymers and copolymers are dispersed in a liquid medium and then dry milled to prepare stable nanosuspensions. Bir et al. describes the production of colloidal particles using sodium lauryl sulfate and polyvinylpyrrolidone as stabilizers for various water-insoluble drugs such as nifedipine, griseofulvin, and glibenclamide.

Lipid emulsion/microemulsion

Nanosuspensions can also be prepared simply by diluting the formed emulsion using a water-miscible solvent as dispersed phase. Emulsification technology is designed for chemicals that are partially miscible with water or soluble in volatile organic solvents. Additionally, microemulsion samples can form nanosuspensions. Microemulsions are dispersions of two immiscible liquids (such as water and oil) that are thermodynamically stabilized by a surfactant or co-surfactant. The drug is transported in the preformed or internal phase of the microemulsion which can be saturated by mixing of drug. Griseofulvin nanosuspension is prepared by microemulsion technology using lecithin, butyl lactate, water and taurodeoxycholic acid sodium salt.

Micro precipitation → High pressure homogenization (Nanoedge)[19]

Nanoedge is a combination of micro precipitation and high pressure homogenization technology. The process involves precipitation of brittle materials and susbsequent separation under high shear and/or thermal forces.

Melt emulsification method[20]

Lipid nanoparticles are prepared by the melt emulsification method. Kipp et al. first prepared ibuprofen nanosuspension using the melt emulsification method. This is a four step process. The solution is first added to the aqueous solution containing the stabilizer. The solution is heated to a temperature higher than the melting point of the solution and then homogenized using a high speed homogenizer to form an emulsion. Throughout the process, the temperature is maintained above the melting point of the drug. Finally, the emulsion is cooled to precipitate the product. The size of nanosuspension mainly depends on parameters such as drug concentration, concentration and type of stabilizer used, cooling temperature and homogenization process.

Nanojet Technology

Also known as counterflow technology, this technology uses a baffle where the suspension flow is divided into two or more areas. Both streams are colloidal to each other under pressure. The high shear forces that occur during this process cause the particle size to decrease. Dearns used a microfluidization technique to prepare atovaquone nanosuspensions. The disadvantage of this method is that the amount passing through the microfluidizer and the product containing the majority of microparticles is greater.

Supercritical Fluid Methods

Various methods are used to produce nanoparticles, such as expansion of supercritical solution (RESS), supercritical antisolvent method, and compressed antisolvent precipitation method.In RESS technology, the chemical solution is expanded into a supercritical fluid through a nozzle the loss of solubility of the supercritical fluid causes the chemical to precipitate into fine particles using RESS method by Young ET al. Cyclosporine nanoparticle with diameter ranging from 400 to 700 nm were prepared. In the PCA method the solution is atomized in CO2 compression chamber. As the solvent is removed the solution becomes supersaturated and eventually precipitation occurs. In supercritical antisolvent process, the solution is injected into the supercritical fluid, the solvent is extracted and the solution becomes supersaturated.

APPLICATION OF NANOSUSPENSION

Drug Delivery[1,4,7,8]

Oral administration[1,4,7,8,9]

Due to its excellent results, the oral route is the preferred route of administration for many drugs, especially oral antibiotics such as atovaquone and bupraquinone. By bringing it to nano size, its solubility and bioavailability will increase.[13] Compared to naproxen nanosuspension and naproxen tablets, the area under the curve (AUC) of naproxen nanoparticles for oral administration (0-24 hours) is 97.5 mgh/l. In the case of danazol (a gonadotropin inhibitor), the actual bioavailability of the nanosuspension is 82.3 compared to only 5.2% for conventional dispersions.

Parental administration[1,7,8,11]

Clofazimine is administered intravenously and its concentrations in the liver, spleen and lungs reach high levels; For most strains of M. avium these concentrations are higher than the minimum inhibitory concentration. Tarazepide was designed as a nanosuspension to overcome the use of surfactants and cyclodextrins to increase bioavailability.

Pulmonary Drug Delivery[1,3,6,8,16]

Here we use nano formulation to treat drugs that have poor solubility in pulmonary secretions. Nebulization for children with lung cancer is done with a mechanical or ultrasonic nebulizer. For example: budesonide

Ocular drug delivery[1,8]

Also used for hydrophobic drugs. Increases the duration of the capsule. The best example of nanosuspension is ibuprofen. Ibuprofen increased anti-inflammatory activity compared to aqueous solution.

CONCLUSION[8]

Nanosuspension greatly solves solubility and dissolution problems and improves drug absorpion. It has the advantages of simple preparation, low amount of excipients, and increases the saturated solubility and dissolution rate of the drug. Many drug candidates have been identified in drug discovery programs, but most have poor solubility. This makes it difficult for pharmaceutical research to develop new ways to achieve high solubility, stability and bioavailability of drugs. Nanosuspensions are a commercial solution to the problems of poor drug solubility and bioavailability. High-pressure homogenization technology is widely

used for large scale production of nanosuspension formulations. Nanosuspension formulation solves the problem of poor solubility and also improves drug handling.

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