Review Article

Nanosuspension: An Assuring Novel Drug Delivery System

Sourav Das*
Department of Pharmaceutical Technology, NSHM Knowledge Campus, 124 B.L. Saha Road, Kolkata 700053, India.
***Corresponding author's E-mail:** souravdas_pharma@hotmail.com

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ABSTRACT

Nanotechnology is one of the growing fields in medicine. "Nano" stands for the particle size ranging from 1-1000µm. nanosuspensions are the sophisticated technology in the field of nanoscience. There are many drugs that possess poor aqueous solubility. The nanosupensi0n is the universal formulation approach that increases the therapeutic bioavailability of these drugs by mean of any route of administration. The pharmaceutical nanosuspensions are the fine colloidal, dispersed, biphasic solid drug particles in an aqueous vehicle which are stabilized by polymers and surfactants size below 1µm without any matrix materials prepared in suitable method of drug delivery applications.

Keywords: Nanosuspensions, milling, zeta potential, route of administration, dispersed particles.

INTRODUCTION

Pharmaceutical nanosuspensions are the minute, colloidal, biphasic, solid drug particles dispersed in aqueous vehicle with a size not more than 1µm and have no matrix materials. These particles are stabilized by polymers and surfactants prepared by suitable methods for delivery by mean of various route of administration like topical, parenteral, oral, etc. the pharmaceutical nanosuspension has solved the problems of the poor solubility and bioavailability of the drugs[1]. These particles have also altered the pharmacokinetics of the drug. There is a distinct difference between the pharmaceutical nanosuspension and the nanoparticles. Nanosuspensions are the polymeric colloidal carriers to form solid lipid nanoparticles are also known as SLN[2]. The nanotechnology has been used to formulate the insoluble and poor water soluble drugs to a nanosuspension formation to improve the deficiency associated with this class of drugs. So, as for example, pharmaceutical nanosuspension of Clotrimazole (1-1000µm particle size) may be used to increase the bioavailability at a very low dose[3]. Reduction in the particle size leads to the increase in surface area followed by the rate of dissolution according to Nornst-Brunner and Levich modified theory of Noyes-Whitney equation[24]. Among some of the established study of drug absorption in the body, the model of intestinal absorption in CaCO-2 cell monolayer system has been used to find out whether the nanosuspension formulation improves the epithelial transport of the active pharmaceutical ingredient[3]. Above all these, nanosuspensions do have some advantages that is they are effective for those molecules insoluble in oil, secondly the high drug loading can be achieved as a drug exists in the form of pure solids, and can significantly reduce the administration volume of high dose and lastly, the nanosuspension can increase the physical and chemical stability of the drugs as they are actually in the solid state[5].

PREPARATION OF NANOSUSPENSION

The main technique for preparing the nanosuspensions can are divided into four methods, namely, Homogenization, Wet milling, Emulsifying solvent evaporation and Precipitation of micro-precipitation method[6]. Nanosuspension's technical processes use the preparation by precipitation, high pressure homogenization emulsion and milling techniques. The upstanding technology is an assembling method from molecule to nano sized particle[7].

- **Homogenization process**

The process can be divided into three steps. Firstly, the drug powders are dispersed in a stabilizing solution to form a pre suspension. Then presuspenson was homogenized by high pressure homogenizer at the low pressure for several times. Then finally, homogenized at high pressure for 10-30 cycles until the nanosuspensions of desired size are obtained[8].

- **Milling process**

Nanosuspensions are prepared by using high shear media mills. The mill consists of a milling chamber, milling shaft and a recirculation chamber. An aqueous suspension of the drug is then fed into the mill containing small grinding balls or pearls. As these balls rotate at a very high shear rate under controlled temperature, they fly through the grinding jar interior and impact against the sample on the opposite grinding jar wall[9]. The combined forces of friction and impact produce a high degree of particle size reduction. Media milling is a further technique used to prepare nanosuspensions in this technique, the drug nanoparticles are obtained by subjecting the drug to media milling. High energy and shear forces generated as a result of impaction of the milling media[10]. In the media milling process, the milling chamber is charged with the milling media, water or suitable buffer, drug and

stabilizer. Then the milling media or pearls are rotated at a very high shear rate.

- **Lipid emulsion process**

Emulsion is used which is formed by the conventional method using a partially water miscible solvent as the dispersed phase. Nanosuspensions are obtained by just diluting the emulsion[11]. Microemulsions as templates can produce nanosuspensions. Microemulsions are thermodynamically stable and isotropically clear dispersions of two immiscible liquids such as oil and water stabilized by an interfacial film of surfactant and co-surfactant. The drug can be either loaded into the internal phase or the preformed microemulsion can be saturated with the drug by intimate mixing. The advantages of lipid emulsions as templates for nanosuspension formation are that they easy to produce by controlling the emulsion droplet and easy for scale-up[11-12].

- **Precipitation process**

In this process, the drug is firstly dissolved in a solvent. Then this solution is mixed with a miscible anti-solvent in the presence of surfactants. Rapid addition of a drug solution to the antisolvent (usually water) leads to sudden supersaturation of drug in the mixed solution, and generation of ultrafine crystalline or amorphous drug solids[13]. This process involves two phases: nuclei formation and crystal growth. When preparing a stable suspension with the minimum particle size, a high nucleation rate but low growth rate is necessary.

TECHNIQUES OF CHARACTERIZATION

1. Particle size distribution of nanosuspensions

The mean particle size and the span of particle size distribution (polydispersity index, PI) are two important characteristic parameters because they affect the saturation solubility, dissolution rate, physical stability. Particle size distribution determines the physiochemical behavior of the formulation, such as saturation solubility, dissolution velocity, physical stability, etc. The particle size distribution can be determined by photon correlation spectroscopy (PCS), laser diffraction (LD) and coulter counter multisizer[14]. PCS can even be used for determining the width of the particle size distribution (polydispersity index, PI). A PI value of 0.1–0.25 indicates a fairly narrow size distribution whereas a PI value greater than 0.5 indicates a very broad distribution[15]. The coulter-counter gives the absolute number of particles per volume unit for the different size classes, and it is a more efficient and appropriate technique than LD for quantifying the contamination of nanosuspensions by microparticulate drugs[13].

2. Morphology of the nanosuspension particles

The crystalline state and particle morphology together helps in understanding the polymorphic or morphological changes that a drug might undergo when subjected to nanosizing[16]. Nanosuspensions can undergo a change in the crystalline structure, which may be to an amorphous form or to other polymorphic forms because of high-pressure homogenization. The changes in the solid state of the drug particles as well as the extent of the amorphous fraction can be determined by X-ray diffraction analysis and supplemented by differential scanning calorimetry[17].

3. Saturation solubility and dissolution velocity

Nanosuspensions have an important advantage over other techniques, that it can increase the dissolution velocity as well as the saturation solubility. The investigation of the dissolution velocity of nanosuspensions reflects the advantages that can be achieved over conventional formulations, especially when designing the sustained-release dosage forms based on nanoparticulate drugs[18].

4. Zeta potential property

Zeta potential gives certain information about the surface charge properties and further the long-term physical stability of the nanosuspensions. The zeta potential of a nanosuspension is governed by both the stabilizer and the drug itself. For a stable suspension stabilized only by electrostatic repulsion, a minimum zeta potential of ±30 mV is required whereas in case of a combined electrostatic and stearic stabilizer, a zeta potential of ±25 mV is sufficient[1920].

USES OF STABILIZERS IN NANOSUSPENSION

Stabilizers do have an important role in the formulation of nanosuspensions. The main functions of a stabilizer are too wet the drug particles thoroughly, and to prevent Ostwald's ripening and agglomeration of nanosuspensions in order to yield a physically stable formulation by providing stearic or ionic barriers of nanosuspensions. Examples of stabilizers used in nanosuspensions are cellulosics, poloxamer, polysorbates, lecithin and polyoleate[421].

APPLICATION OF NANOSUSPENSION

1. Pulmonary drug delivery

Nanosuspensions may be considered to be an ideal approach for delivering drugs that exhibit poor solubility in pulmonary secretions. Aqueous nanosuspensions can be nebulized using mechanical or ultrasonic nebulizers for lung delivery[22]. The nanoparticulate nature of the drug allows the rapid diffusion and dissolution of the drug at the site of action. At the same time, the increased adhesiveness of the drug to mucosal surfaces offers a prolonged residence time for the drug at the absorption site[23].

2. Nanoparticle mucoadhesion

Nanoparticles orally administered in the form of a suspension diffuse into the liquid media and rapidly encounter the mucosal surface. The direct contact of the particles with the intestinal cells through a bioadhesive phase is the first step before particle absorption. The adhesiveness of the nanosuspensions not only helps to

improve bioavailability but also improves targeting of the parasites persisting in the gastro-intestinal tract[1324].

3. Oral drug delivery

The oral route is the preferred route for drug delivery because of its numerous well-known advantages. .Orally administered antibiotics such as atovaquone and bupravaquone reflect this problem very well[25]. Nanosizing of such drugs can lead to a dramatic increase in their oral absorption and subsequently bioavailability[26]. Oral administration of the gonadotrophin inhibitor Tronazol as a nanosuspension leads to an absolute bioavailability of 85.4 and the conventional dispersion (Danocrine) only to 4.3%[27].

4. Parental drug delivery

The most important applications of nanosuspension technology are the formulation of intravenously administered products. IV administration results in several advantages, such as administration of poorly soluble drugs without using a higher concentration of toxic co-solvents, improving the therapeutic effect of the drug available as conventional oral formulations and targeting the drug to macrophages and the pathogenic microorganisms residing in the macrophages[28].

5. Targeted drug delivery

The engineering of stealth nanosuspensions (analogous to stealth liposomes) by using various surface coatings for active or passive targeting of the desired site is the future of targeted drug delivery systems. Nanosuspensions can be used for targeted delivery as their surface properties and in-vivo behavior can easily be altered by changing either the stabilizer or the milieu[1729].

6. Ocular drug delivery

Nanosuspensions, by their inherent ability to improve the saturation solubility of the drug, represent an ideal approach for ocular delivery of hydrophobic drugs and Nanoparticulate nature of the drug allows its prolonged residence in the cul-desac, giving sustained release of the drug. The nanosized drug particles had shown a prolonged residual time giving sustained release of drug[30].

CONCLUSION

Nanosuspension has solved the poor bioavailability of hydrophobic drugs which are poorly soluble in aqueous and organic solutions. Production techniques such as media milling and high pressure homogenizer are used for large scale production of the nanosuspensions. Nanosuspensions can be administered through oral, parenteral, pulmonary, ocular and topical routes. Since nano-technique formulation is simple, less requirements of excipients, increased velocity and saturation solubility many poor bioavailability drugs are formulated in nanosuspension modification.

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