Review Article

A COMPREHENSIVE REVIEW OF A NEW NANOSUSPENSION FOR IMPROVING THE ORAL BIOAVAILABILITY OF POORLY SOLUBLE DRUGS

ABSTRACT:

Nanosuspension is a novel drug formulation for the delivery of hydrophobic drugs. The problem of medications that are poorly water-soluble and have low bioavailability is countered by nanosuspension technology. Solubility is a significant physiochemical element that influences drug absorption and therapeutic effectiveness. Poor aqueous solubility has the potential to impair formulation development. Nanosuspension technology can improve the drug's stability and bioavailability. Nanosuspensions can be formulated for various routes of administration such as oral, parenteral, ocular, topical, and pulmonary routes. Nanosuspension can be used for targeted drug delivery also by mucoadhesive gels and ocular inserts. Recent studies were approached to develop nanosuspension on site-specific drug delivery.

Keywords: *Nanosuspension, oral bioavailability, solubility enhancement, particle size, drug delivery.*

INTRODUCTION

A nanoparticle is a tiny particle with a diameter of 1 to 100 nanometers. A sub - micron colloidal dispersion of drug particles is known as nanosuspension. Nanosuspension for the pharmaceutical formulations are generally biphasic [1], colloid particles that are dispersed in the aqueous vehicle with the size range of below 1µm and stabilized by the use of suitable surfactants and polymers [2]. By preparing the formulations on nanosuspension problems related to weakly water-soluble, poorly water, and lipid-soluble drugs [3] correlated with poor drug delivery can be overcome/avoided. It improves absorption and bioavailability thereby minimizing the dosage of traditional oral dosage forms. As a result, the active compound's saturation rate increases, and the maximum plasma level is achieved faster (for example, when the nanosuspension is administered orally or intravenously). According to the Noyes Whitney equation [4], reducing the size of drug particles increases the surface area and thus the rate of

dissolution. The majority of drugs with solubility and bioavailability challenges grow [5], this technique will become more important. Nanosuspension can also change the drug's pharmacokinetics, improving drug safety and efficacy. [6] In this article it is explained that formulating the drug in nanosuspension can improve the oral bioavailability of poorly soluble drug. The aim of the review is to discuss the methods which are available for the nanosuspension formulation.

Drug selection criteria for nanosuspensions

The API (Active Pharmaceutical Ingredient) which has the following characteristics can be formulated in nanosuspension, they are;

a.) Water-insoluble but are soluble in oil

b.) API (Active Pharmaceutical Ingredient) insoluble in both water and oil

c.) Drugs which have a lower tendency of a crystal to dissolve in any solvent

d.) API (Active Pharmaceutical Ingredient) with larger dosage

Advantages of nanosuspension [7]

- Enhance the solubility and bioavailability of drugs.
- The most cost-effective.
- They're more physically stable than liposomes.
- It is possible to acquire a higher drug loading.
- It is feasible to alter the dose.
- Rapid dissolution and tissue targeting.
- Tissue inflammation is avoided.
- Higher bioavailability in ocular and inhalational drug delivery.

PREPARATION OF NANOSUSPENSION:

There are two approaches for making nanosuspensions: "Top-down process technology" and "Bottom-up process technology."[8][9] From large particles to micro particles to nanosized particles, the top-down process follows a disintegration technique, as shown in Figure 1.

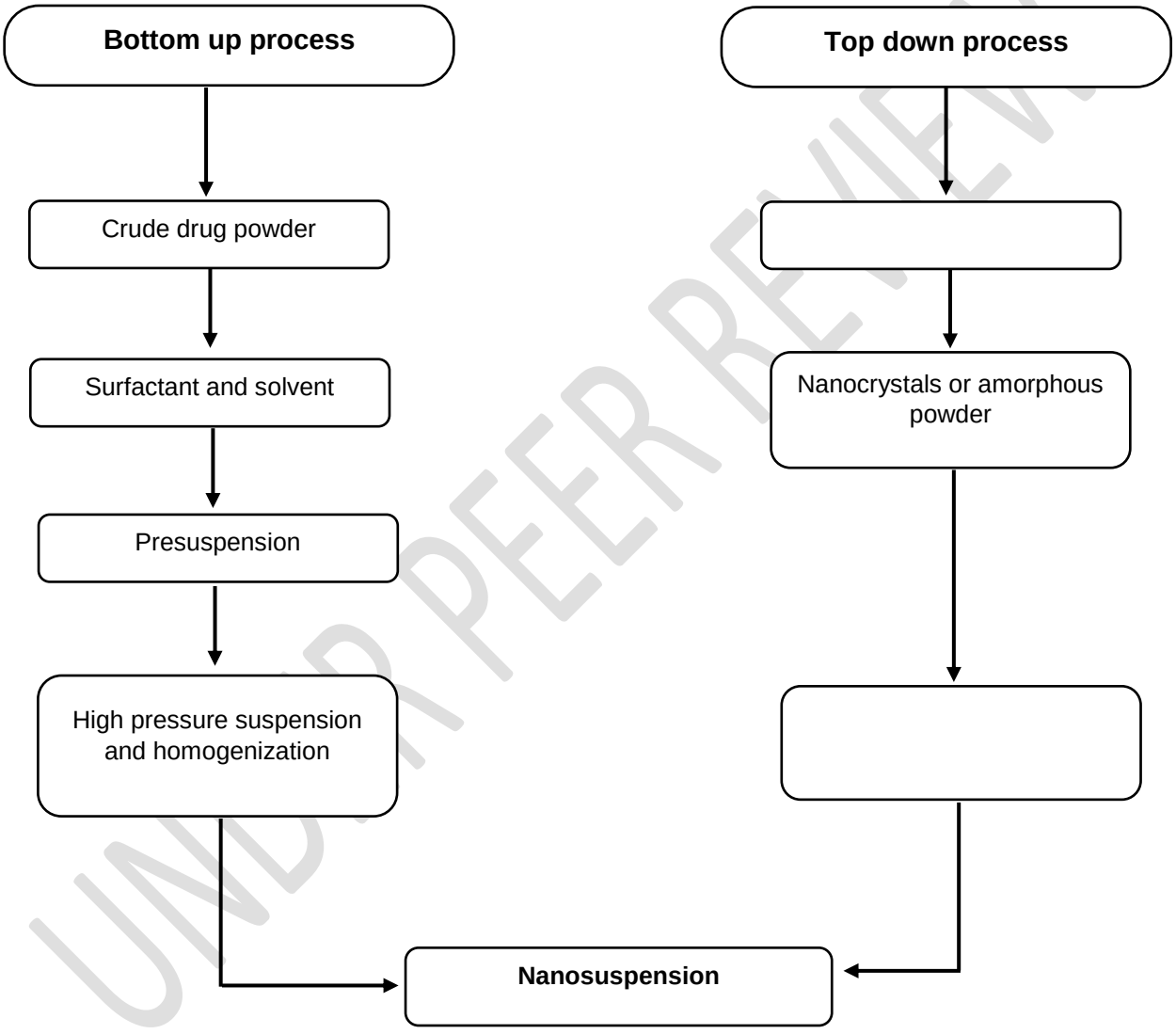

Figure 1. Preparation techniques for nanosuspensions

The most common methods for making nanosuspensions in recent years can be divided into the following categories.

Wet milling

High shear media mills or pearl mills are being used to produce nanosuspensions. The mill consists of a milling chamber, milling shaft, and recirculation chamber. The drug is then fed into a mill containing small grinding balls/pearls in an aqueous suspension. These balls fly through to the grinding jar interior and impact on the sample on the opposite grinding jar wall as they spin at a very high shear rate within controlled temperature. As a result of the combined forces of resistance and impact, particle size is significantly reduced. The milling media or spheres are made of highly cross-linked polystyrene polymer with exceptional abrasion resistance or ceramic-sintered aluminum oxide or zirconium oxide. A planetary ball is one example of equipment that can be used to achieve a grind size below 0.1 µm [10].

Homogenization Dissocubes

Homogenization involves pushing the suspension under force through a narrow-aperture valve. Dissocubes® was developed by Muller et al (1999). [11] In this situation, the drug suspension is forced to flow through a small opening, resulting in in a reduction of the static pressure below the boiling pressure of water which leads to boiling of water and the formation of gas bubbles. When the suspension leaves the gap and normal air pressure is reached again, the bubbles implode and the surrounding the section holding the drug particles flows to the core, and colloids reduce the particle size in the process. Most cases require several passes or repetitions through the homogenizer, depending on the condition. Depending on the drug's hardness, desired mean particle size, and homogeneity requirements.

Emulsification–solvent evaporation technique

This technique includes formulating a pharmaceutical solution and thereafter infusing the emulsification in another liquid that is a non-solvent for the drug. Precipitation of the drug is acquired by solvent evaporation technique. A high-speed stirrer can be used to control crystal formation and particle aggregation by providing high shear forces.

Nanoedge

Nanoedge is based on the same principles as precipitation and homogenization. A combination of these techniques results in smaller particle sizes and better stability in a shorter time [12]. The Nanoedge technology can solve the major drawbacks of the precipitation technology, such as crystal

development and long-term stability. The precipitate suspension is further disintegrated in this technique, resulting in a reduction in size of particles as well as the prevention of crystal formation. Water-miscible solvents including methanol, ethanol, and isopropanol are being used to precipitate in water. Even though such solvents can be treated to some level in the formulation, it is preferable to remove those completely. For effective production of nanosuspensions using the Nanoedge technology, an evaporation step can be used to produce a solvent-free improved starting material which is then homogenized under high pressure.

Nanoprecipitation method

In this method, drug nanoparticles are precipitated out by adding a solution of the drug into a non-solvent in presence of a stabilizer. The introduction of the drug solution to the anti-solvent generates high supersaturation which results in a fast nucleation rate and produces a large number of nuclei [13]. These nuclei further reduce the solute mass for subsequent growth. Submicron particles also can be obtained if the stabilizer limits the development of nucleating crystals [14].

Nanojet technology

This method, also known as opposite stream or nano jet technology, involves dividing a stream of suspension into two or more sections that interact with one other at high pressure in a chamber [15].

Supercritical fluid method

To make nanoparticles from medication solutions, supercritical fluid technology can be used. The various methods attempted are a rapid expansion of the supercritical solution process (RESS), supercritical anti-solvent process (SAS), and precipitation with the compressed anti-solvent process (PCA). The RESS contains a nozzle which expands the medication solution in supercritical. The medication precipitates as small particles as a result of the supercritical fluid's depreciation of solvent power. A supercritical fluid in which a drug is dissolved is used in the supercritical anti-solvent method poorly soluble and a solvent for the drug that is also miscible with the supercritical fluid [16]. The drug solution is injected into the supercritical fluid, which extracts the solvent and causes the drug solution to become supersaturated. The drug then crystallizes into fine crystals.

CHARACTERIZATION TECHNIQUES FOR NANOSUSPENSION:

Nanosuspensions are evaluated in the same way as conventional suspensions are, including appearance, color, odour, assay, related impurities, and so on. As a result, nanoparticle characterization is essential for determining the nano-drug delivery performance in the *invitro* and *invivo* studies.

Mean Particle size and particle size distribution

Particle size distribution and mean particle size alter the saturation solubility, dissolving rate, physical stability, and in vivo performance of nanosuspensions. Photon correlation spectroscopy (PCS), laser diffraction (LD), and the coulter counter multisizer can all be used to measure the particle size distribution of a nanosuspension. [17]. The PCS method can measure particles in the size range of 3 nm to 3 µm and the LD method has a measuring range of 0.05-80 µm. The coulter counter multisizer gives the absolute number of particles, in comparison to the LD method, which gives only a relative size distribution. For intravenous use, particles should be less than 5 µm, considering that the smallest size of the capillaries is 5-6 µm and hence a higher particle size can lead to capillary blockade and embolism.

Surface Charge (Zeta Potential)

The zeta potential is used to investigate the surface charge characteristics of nanosuspensions. The macroscopic stability of nanosuspensions is determined by the value of particle surface charge [18]. The zeta potential is useful for predicting the stability of systems with dispersed particles in this potential, rather than the Nernst potential, governs the degree of repulsion between the adjacent, similarly charged, dispersed particles. If the zeta potential decreases below a specific limit (which depends on the particular system being used), the attractive forces exceed the repulsive forces and the particles come together. This phenomenon is called flocculation.

Crystal morphology

To characterize the polymorphic variations in the drug's crystalline structure caused by the high homogenization X-ray diffraction analysis in combination with differential scanning calorimetry or differential thermal analysis are examples of techniques which can be used [19]. Because of high-pressure homogenization, nanosuspensions can transform their crystalline structure to an amorphous or other polymorphic state.

Dissolution velocity and saturation solubility:

Nanosuspensions have a significant advantage over different approaches in that they can speed up dissolution and increase saturation solubility**.** In various physiological solutions, these two parameters should be determined. Size reduction leads to an increase in the dissolution pressure. A change in surface tension resulting to higher saturation solubility may be the main cause of an increase in solubility that occurs with relatively moderate reduction of particles size.

APPLICATIONS OF NANOSUSPENSIONS

Nanosuspensions have a wide range of advantages, especially in the case of medications with low solubility and bioavailability. They are as follows,

Enhancement of Bioavailability

The drug's low bioavailability is caused primarily to its poor solubility, permeability, or solubility in the GIT (gastrointestinal tract). By formulating in nanosuspension these problems can be overcome through the membrane. The nanosuspension has advantages like improved absorption, dose proportionality, and low intersubject variability.

Oral Drug Delivery

Due to smaller particle sizes and much larger surface-to-volume ratio, Oral nanosuspensions are used to increase the rate of absorption and bioavailability of poorly soluble medicines [19].

Parenteral drug delivery

Nanotechnology is also used in the parenteral drug delivery system. For poorly soluble drugs, this method has the advantage of requiring less toxic co-solvent. This leads to an increase in the therapeutic of the drug compared to other oral conventional dosage forms [20].

Pulmonary drug delivery

For medications with low solubility in pulmonary secretions, we employ nanoformulations in pulmonary drug delivery. It is nebulized for lung delivery using a mechanical or ultrasonic nebulizer.

Uniform distribution of the drug is possible and each droplet contains at least a single drug particle. The drug's diffusion and solubility are improved by nanosizing. It enhances the adhesiveness of the drug to the mucosal surface and increased residence time at the site of absorption. Nanosuspensions have a rapid onset of action and then a controlled release of active moiety, which is essential for the majority of pulmonary diseases.

Targeted drug delivery

Nanosuspension can be employed for target drug delivery due to its surface properties and changing of stabilizer can easily alter the in vivo behavior. The drugs will be taken up by the mononuclear phagocytic system that will allow for regional delivery. This can be used for targeting anti-mycobacterial, fungal, or leishmanial drugs to the macrophages if the infectious pathogen is persisting intracellularly [21].

Mucoadhesion of nanoparticles:

In the case of oral administration of nanosuspension initially, it diffuses into the liquid medium and adheres to the mucosal surface before absorption. It improves the bioavailability and targeting to the parasite persisting the GIT [21].

CONCLUSION

Nanosuspensions are a novel and economically feasible solution to the issues associated with hydrophobic drugs, such as poor solubility and bioavailability**.** For larger-scale production of nanosuspension techniques like media milling and high-pressure homogenizer can be used. Nanosuspension can be administered by oral, parenteral, pulmonary, ocular, and topical routes. Striking characteristics, like improvement of dissolution velocity, increased saturation solubility, improved bioadhesive, and versatility in surface modification have widened the application of nanosuspension. A nanosuspension improves medication solubility and bioavailability while also altering drug pharmacokinetics, enhancing drug safety and efficacy.

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