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A Review on Nanosuspension Technology in Drug Delivery System

Praveen K Gaddam *, Srinath Balkundhi, Sowmya Cherukuri, Suryaprakash R Chappidi.

Department of Pharmaceutics, Raghavendra Institute of Pharmaceutical Education and Research, Anantapuramu-515721, Andhra Pradesh, India.

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*Corresponding author:

Praveen K Gaddam

Email:

g.praveenkumar51@gmail.com

Tel.: +91-9985889182.

ABSTRACT

Nanosuspension technology can be used to improve the stability as well as bioavailability of poorly soluble drugs. Nano refers to particles size range 1-1000nm. A pharmaceutical Nanosuspension is defined as very finely collide, biphasic, dispersed, solid drug particles in an aqueous vehicle, size below μm , without any matrix material which are stabilized by surfactants and polymer. Nanosuspensions are prepared by using wet mill, high pressure homogenizer, and emulsion solvent evaporation techniques. Nanosuspension can be delivered by oral, parental, pulmonary and ocular routes. The study is focused on the various method of preparation of Nanosuspension with their advantages and disadvantages, properties *In vivo-in vitro* evaluation method of Nanosuspension and their application drug delivery system. Nanosuspension not only solves the problem of poor solubility and bioavailability but also alter the pharmacokinetics of the drug and thus improving safety efficacy.

Key words: Bioavailability, solubility, Nanosuspension

INTRODUCTION

Nanosuspension can be defined as colloidal dispersions of Nano-sized drug particles that are produced by a suitable method and stabilized by a suitable stabilizer. They can also define as the biphasic system consisting of pure drug particle dispersed in an aqueous vehicle in which the diameter of the suspended particle is less than $1\mu\text{m}$ in size. Techniques of drug Nanosuspension preparation can be categorized into two principle classes; Top-down and bottom-up technologies. The top-down technologies are the mechanical communication processes of larger drug particles, as in milling and homogenization. The bottom-up technologies begin with the molecules which are dissolved and then precipitated through on solvent addition a in supercritical fluid technology, spray freezing in to liquid process, evaporative precipitation into aqueous solution and liquid solvent change process. Although top-down approaches are widely employed, the drawbacks associated with mechanical attritions processes, such as time consumption, intensive energy use, inadequate control of particles

size and electrostatic effects, promote greater interest toward bottom up creation of nanoparticles. Nano means it is the factor of 10^{-9} . The particle size distribution ranges from $0.1\mu\text{m}$ to $25\mu\text{m}$, only negligible amount being below $1\mu\text{m}$ in the manometer range. For a long duration of time micronization of poorly soluble drugs by colloidal mills was prepared.

Different Methods for Preparation of Nanosuspension [1]

Mainly there are two methods for preparation of Nanosuspension. The conventional methods of precipitation are called Bottom up Technology. In Bottom up Technology the drug is dissolved in a solvent, which is then added to non-solvent to precipitate the crystal. This technique is that during the precipitation procedure the growing of the drug crystals need to be controlled by addition of surfactant to avoid formation of micro particles. The top down Technologies are the disintegration methods and are preferred over the precipitation methods. The top

down Technologies include Media milling (Nano crystals), High pressure homogenization, Nanoedgs, Nanopure.

A. High Pressure Homogenization [2]:

It is most widely used method for preparing Nanosuspension of many poorly aqueous soluble drugs [2]. It involves three steps. First drug powders are dispersed in stabilizer solution to form pre suspension, and then the pre suspension is homogenized in high pressure homogenizer at low pressure for pre milling, and finally homogenized at high pressure for 10 to 25 cycles until the Nanosuspension of desired size are formed. Different methods are developed based on this principle for preparations of Nanosuspension are Disso cubes, Nanopure, Nanoedge [3].

Homogenization in aqueous media (Disso cubes):

This technology was developed by R.H. Muller using a piston-gap type high pressure homogenizer [4]. In this method, the suspension containing a drug and surfactant is forced under pressure through a Nanosized aperture valve of a high pressure homogenizer.

PRINCIPLE:

This method based on cavitation principle. The dispersion present in 3cm diameter cylinder is suddenly passed through a very narrow gap of 25 μ m. According to Bernoulli's law the flow volume of liquid in a closed system per cross section is constant. It leads to increase in dynamic pressure and decrease of static pressure below the boiling point of water at room temperature due to reduction in diameter from 3cm to 25 μ m. Then water starts boiling at room temperature and forms gas bubbles, which implode when the suspension leaves the gap (called cavitation) and normal air pressure is reached. The particles cavitation forces are sufficiently high to convert the drug micro particles into nanoparticles.

Advantages

1. It does not cause the erosion of processed materials.
2. It is applicable to the drugs that are poorly soluble in both aqueous and organic media.

Disadvantages

1. Pre-processing like micronization of drug is required.
2. High cost instruments are required that increases the cost of dosage form.

Homogenization in nonaqueous media (Nanopure):

Nanopure is suspensions homogenized in water-free media or water mixtures like PEG 400, PEG 1000 etc.

The homogenization can be done at room temperature, 0°C and below freezing point (-200C), hence it is known as "deep freeze" homogenization [5].

Nanoedgs:

Nanoedgs technology is the combination of both precipitation and homogenization. The principle is same as that of precipitation and homogenization. The major disadvantage of precipitation technique such as crystal growth and long term stability can be overcome by using the Nanoedgs technology. Particles of smaller size and better stability in short time can be achieved.

Nanojet:

It is also called as opposite stream technology, uses a chamber where a stream of suspension is divided into two or more parts, which colloid with each other at high pressure, due to the high shear forces produced during the process particle size is reduced.

B. Milling Methods

1. Media Milling:

The Nanosuspension by this method is prepared by high shear media mill. The milling chamber was charged with the milling media, water, drug and stabilizer and rotated at a very high shear rate under controlled temperature at least 2-7 days. The milling medium is composed of glass, Zirconium oxide or highly cross linked polystyrene resin. The high energy shear forces are formed as a result of impaction of milling media with the drug which results in breaking of drug micro particles to Nanosized particles.

Advantages

1. Very dilute as well as highly concentrated Nanosuspension can be prepared by handling 1 mg/ml to 400 mg/ml drug quantity.
2. Nanosized distribution of final Nanosized product.

Disadvantages

1. The media milling technique is time consuming.
2. Some fractions of particles are in the micrometer range.
3. Scale up is not easy due to mill size and weight.

2. Dry-co-grinding:

Recently many Nanosuspensions are prepared by dry milling technique. Dry- co grinding can be carried out easily and economically and can be conducted without organic solvents. Physicochemical properties and dissolution of poorly water soluble drugs are improved by Co-grinding because of an improvement in the surface polarity and transformation from a crystalline to an amorphous drug.

Advantages

1. Easy process and no organic solvent required.
2. Require short grinding time.

Disadvantages

1. Generation of residue from milling components.

C. Precipitation:

Within the last decade, precipitation has been applied to prepare submicron particles, especially for the poorly soluble drugs. The drug is first dissolved in a solvent, and then this solution is mixed with a miscible anti solvent in the presence of surfactants. Rapid addition of a drug solution to the anti solvent leads to sudden super saturation of drug and formation of ultrafine crystalline or amorphous drug solids [7].

Advantages

1. Simple process, Ease of scale up and Economical production.

Disadvantages

1. Growing of crystals needs to be limit by surfactant addition. Drug must be soluble at least in one solvent.

D. Emulsification-Solvent Evaporation Technique:

This technique involves preparing a solution of drug followed by its emulsification in another liquid that is a non solvent for the drug. Evaporation of the solvent leads to precipitation of the drug. Crystal growth and particle aggregation can be controlled by creating high shear forces using a high-speed stirrer.

E. Supercritical Fluid Process:

The particle size reduction was achieved more by the solubilisation and Nano sizing technologies through the super critical fluid process. Super critical fluids (SCF) are noncondensable dense fluids whose temperature and pressure are greater than its critical temperature (T_c) and critical pressure (T_p). This process allows the micronization of drug particles to submicron level. Recent advances in SCF process are to create Nano particulate suspension of particle size of 5 to 2000nm in diameter. The low solubility of poorly water-soluble drugs and surfactants in supercritical CO₂ and the high

pressure required for these processes restrict the utility of this technology in the pharmaceutical industry.

F. Solvent Evaporation:

In the solvent evaporation method, the solutions of polymer are prepared in volatile solvents and emulsions. But from the past years dichloromethane and chloroform were used which was now replaced by ethyl acetate which has a better profile of toxicology. The emulsion is converted into a nanoparticles suspension on evaporation of the solvent for the polymer, which is allowed to diffuse through the continuous phase of the emulsion. In the conventional methods, two main strategies are being used for the formation of emulsions, the preparation of single-emulsions, e.g., oil-in-water (o/w) or double-emulsions, e.g., (water-in-oil)-in-water, (w/o)/w. These methods require high-speed homogenization or ultrasonication, followed by evaporation of the solvent, either by continuous magnetic stirring at room temperature or under reduced pressure. By ultracentrifugation the solidified nanoparticles are collected which was washed with distilled water to remove the additives like surfactants, and then it was lyophilized. The particle size was influenced by the concentration of polymer, stabilizer and the speed of homogenizer.

Formulation of Nanosuspension [4, 8]:

Stabilizer

Stabilizer plays an important role in the formulation of Nanosuspension. In the absence of an appropriate stabilizer, the high surface energy of Nano-sized particles can induce agglomeration or aggregation of the drug crystals. The main functions of a stabilizer are to wet the drug particles thoroughly, and to prevent Ostwald's ripening and agglomeration of Nanosuspension in order to yield a physically stable formulation by providing steric or ionic barriers. The type and amount of stabilizer has a pronounced effect on the physical stability and in-vivo behaviour of Nanosuspension. In some cases, a mixture of stabilizers is required to obtain a stable Nanosuspension.

Organic solvents

Organic solvents may be required in the formulation of Nanosuspension if they are to be prepared using an emulsion or micro emulsion as a template. As these techniques are still in their infancy, elaborate information on formulation considerations is not available. The acceptability of the organic solvents in the pharmaceutical area, their toxicity potential and the ease of their removal from the formulation need to be considered when formulating a no suspensions using emulsions or micro emulsions as templates. The pharmaceutically acceptable and less hazardous water miscible solvents, such as ethanol and isopropanol, and partially water-miscible solvents, such as ethyl acetate, ethyl format, butyl lactate, triacetin, propylene carbonate and benzyl alcohol.

Co-surfactants

The choice of co-surfactant is critical when using micro emulsions formulate Nanosuspension. Since co surfactants can greatly influence phase behaviour, the effect of co-surfactant on uptake of the internal phase for selected micro emulsions composition and on drug loading should be investigated. Although the literature describes the use of bile salts and dipotassium glycerrhizinate as co-surfactants, various solubilizers, such as Transcutol, glycofurol, ethanol and isopropanol, can be safely used as co-surfactants in the formulation of microemulsions [8, 9].

Other additives

Formulation considerations Nanosuspension may contain additives such as buffers, salts, polyols, osmogent and cryoprotectant, depending on either the route of administration or the properties of the drug moiety [10].

Advantages of Nanosuspension Drug Delivery System [6]:

1. Its general applicability to most drugs and simplicity.
2. Can be applied for poorly water soluble drugs.
3. Can be given by any route.
4. Reduced tissue irritation in case of subcutaneous/intramuscular administration.
5. Oral administration of Nanosuspension provide rapid onset, reduced fed/fasted ration, and improved bioavailability.
6. Nanosuspension can be incorporated in tablets, pellets, hydro gel; suppositories are suitable for various route of administration.
7. Improvement in biological performance due to high dissolution rate and saturation solubility of the drugs.

8. Possibility of large scale production the pre requisite for the introduction of delivery system to the market [11].

Disadvantages for Nanosuspension Drug Delivery System [10]:

1. Physical stability, sedimentation and compaction can cause problems.
2. Improper dose.
3. Uniform and accurate dose cannot be achieved [12].

Evaluation of Nanosuspension [9]

1. In-vitro evaluations
2. Particle size and size distribution
3. Particle charge (Zeta Potential)
4. Crystalline state and morphology.
5. In-vivo evaluation
6. Evaluation for surface-modified Nanosuspension
7. Surface hydrophilicity [11]
8. Adhesion properties
9. Interaction with body proteins

In-vitro evaluation

Mean particle size and size distribution [12]

The mean particle size and the width of particle size distribution (called Polydispersity Index) are determined by Photon Correlation Spectroscopy (PCS). Particle size and Polydispersity index (PI) governs the saturation solubility; dissolution velocity and biological performance. It is proved that change in particle size changes saturation solubility and dissolution velocity. PCS measures the particle size in the range of 3 nm- 3 μ m only. PCS is a versatile technique but has low measuring range. In addition to PCS analysis Nanosuspension are analyzed by Laser Diffractometry (LD).

Particle charge (zeta potential)

The determination of the zeta potential of a Nanosuspension is essential as it gives an idea about the physical stability of the Nanosuspension. The zeta potential of a Nanosuspension is governed by both the stabilizer and the drug itself. In order to obtain a Nanosuspension exhibiting good stability, for an electro statically stabilized Nanosuspension minimum zeta potential of 30mV is required whereas in the case of a combined electrostatic and 20 mV is desirable.

Crystalline state and particle morphology

The X-Ray Diffraction (XRD) is also used for determining change in physical state and extent of amorphous drug. Differential Scanning Calorimetry (DSC) determines the crystalline structure.

When Nanosuspension is prepared drug particles get converted to amorphous form hence it is essential to measure the extent of amorphous drug generated during the production of Nanosuspension.

In-vivo evaluation

The in vivo evaluation of the Nanosuspension is specific to drug and route of administration. Most commonly the formulation was given by required route of administration and the plasma drug levels were estimated using HPLC-UV visible Spectrophotometers.

Application of Nanosuspension [13]

Nanosuspension has various pharmaceutical and biopharmaceutical application a few of them highlighted here are:

1. Formulating the drug as Nanosuspension increases the satiable concentration, dissolution rate as well as bioavailability of the drug.
2. Nanosuspension can prove to be a boon for drugs that exhibit poor solubility in lachrymal fluids. For delivery of such drugs, approaches such as suspensions and ointments have been recommended.
3. These Nanosuspension are having application in different routes of administrations like oral, Parenteral, topical, ophthalmic, mucoadhesive, pulmonary and targeted drug delivery.

CONCLUSION:

The main goal of this review was to describe the various preparation techniques for production of Nanosuspension. It was observed that preparing Nanosuspension is a suitable technique among the various possible methods. Production techniques such as high pressure homogenization media milling have been successfully employed for large scale production. Nanosuspension are administering poorly water soluble drugs have been largely solved the dissolution problems to improve drug absorption and bioavailability. The applications of Nanosuspension in parental and oral routes have been very well investigated and applications in pulmonary and ocular delivery have been realized.

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