



NANOSUSPENSION - A NEW APPROACH OF BIOAVAILABILITY ENHANCEMENT

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ABSTRACT

Solubility is essential factor for drug effectiveness, independent of the route of administration. Poorly soluble drug are formulated in industry. Nanosuspension technology can be used to improve the stability as well as bioavailability of poorly soluble drug. Nanosuspensions are also use in various dosage forms, including specialized drug delivery system such as mucoadhesive hydrogel. Nanosuspension have emerged as a promising strategy for the efficient delivery of hydrophobic drugs because of their versatile features and unique advantages. Recently, the engineering of nanosuspensions employing emulsions and micro-emulsions as templates has been addressed in the literature. The study is focused on the various method of preparation of nanosuspension with their advantages and disadvantages, formulation In vivo-in vitro evaluation method of nanosuspension and their application in drug delivery system.

Keywords: Nanosuspension, Saturation solubility, Solubility enhancement.

1. INTRODUCTION

The formulation of poorly water-soluble drugs has always been a challenging problem faced by pharmaceutical scientists and it is expected to increase because approximately 40% or more of the new chemical entities being generated through drug discovery programmers are poorly water-soluble.

Nanosuspensions 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 1µm in size¹. Techniques of drug nanosuspensions preparation can be categorized into two principle classes; top-down and bottom-up technologies. The "top-down" technologies are the mechanical comminution processes of larger drug particles, as in milling (jet mills and pear-ball mills) and homogenization (high-pressure homogenizers). The "bottom-up" technologies begin with the molecules which are dissolved and then precipitated through on-solvent addition as in supercritical fluid (SCF) technology, spray-freezing into liquid process, evaporative precipitation into aqueous solution (EPAS) 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, introduction of impurities, inadequate control of particles size and electrostatic effects, promote greater interest toward "bottom-up" creation of nanoparticles^{2,3}. Nano is a Greek word, which means 'dwarf'. Nano means it is the factor of 10⁻⁹ or one billionth. Some comparisons of nanoscale are given below,

0.1 nm = Diameter of one Hydrogen atom.

2.5 nm = Width of a DNA molecule

1 micron = 1000 nm.

1 nm = 10⁻⁹m = 10⁻⁷ cm = 10⁻⁶ mm.

Micron = 10⁻⁶m = 10⁻⁴ cm = 10⁻³mm⁴.

For a long duration of time micronization of poorly soluble drugs by colloid mills or jet mills was preferred. The overall particle size distribution ranges from 0.1 µm to approximately 25 µm, only negligible amount being below 1 µm in the nanometer range.

2. TECHNIQUE OF PREPARATION OF NANOSUSPENSION

Mainly there are two methods for preparation of nanosuspensions. The conventional methods of precipitation (Hydrosols) 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 crystals. This technique is that during the precipitation procedure the growing of the drug crystals needs to be controlled by addition of surfactant to avoid formation of microparticles⁷. The 'Top Down Technologies' are the disintegration methods and are preferred over the precipitation methods.

The 'Top Down Technologies' include Media Milling (Nanocrystals), High Pressure Homogenization in water (Dissocubes), High Pressure Homogenization in non aqueous media (Nanopure) and combination of Precipitation and High-Pressure Homogenization (Nanoedge)^{8,9}.

2.1. Media milling (nanocrystals or nanosystems)

The method is first developed and reported by Liversidge (1992). The nanosuspensions are prepared by using high-shear media mills. The milling chamber charged with milling media, water, drug and stabilizer is rotated at a



very high shear rate under controlled temperatures for several days (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 generated as a result of the impactation of the milling media with the drug resulting into breaking of microparticulate drug to nanosized particles¹⁰.

Advantages

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

Disadvantages

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

2.2 High pressure homogenization (Dissocubes)

It is the most widely used method for the preparation of nanosuspensions of many poorly water soluble drugs. Dissocubes are engineered using piston-gap-type high-pressure homogenizers. A commonly used homogenizer is the APV Micron LAB 40. However, other piston-gap homogenizers from Avestin and Stansted can also be used. A high-pressure homogenizer consists of a high-pressure plunger pump with a subsequent relief valve (homogenizing valve). The task of the plunger pump is to provide the energy level required for the relief. The relief valve consists of a fixed valve seat and an adjustable valve. These parts form an adjustable radial precision gap. The gap conditions, the resistance and thus the homogenizing pressure vary as a function of the force acting on the valve¹¹.

Principle

In piston gap homogenizer particle size reduction is based on the cavitations principle. Particles are also reduced due to high shear forces and the collision of the particles against each other. The dispersion contained in 3 cm diameter cylinder; suddenly passes through a very narrow gap of 25 μm . According to Bernoulli's Law the flow volume of liquid in a closed system per cross section is constant. The reduction in diameter from 3 cm to 25 μm leads to increase in dynamic pressure and decrease of static pressure below the boiling point of water at room temperature. Due to this water starts boiling at room temperature and forms gas bubbles, which implode when the suspension leaves the gap (called cavitations) and normal air pressure, are reached. The size of the drug nanocrystals that can be achieved mainly depends on factors like temperature, number of homogenization cycles, and power density of homogenizer and homogenization pressure¹².

Advantages

1. It does not cause the erosion of processed materials.
2. Very dilute as well as highly concentrated nanosuspensions can be prepared by handling 1mg/ml to 400mg/ml drug quantity.
3. It is applicable to the drugs that are poorly soluble in both aqueous and organic media.

Disadvantages

1. Preprocessing like micronization of drug is required.
2. High cost instruments are required that increases the cost of dosage form¹³.

2.3. Homogenisation in nonaqueous media (nanopure)

Nanopure is the water free media or water mixture. In nanopure technology the drug suspension in the non aqueous media when homonized at 0°C or even the freezing point and hence called as deep freeze homogenization¹⁴.

2.4. Nanoedge

The precipitated drug nanoparticles have tendency to continue crystal growth to the size of microcrystal. They need to be processed with high-energy forces (Homogenisation). They are in completely amorphous, partially amorphous or completely crystalline which create problems in long term stability as well as in bioavailability, so the precipitated particle suspension is subsequently homogenized which preserve the particle size obtained after the precipitation step¹⁵.

2.5. Co-grinding

Recently, nanosuspensions can be obtained by dry milling techniques. Successful work in preparing stable nanosuspensions using dry-grinding of poorly soluble drugs with soluble polymers and copolymers after dispersing in a liquid media has been reported. It the colloidal particles formation of many poorly water soluble drugs; griseofulvin glibenclamide and nifedipine obtained by grinding with polyvinylpyrrolidone (PVP) and sodiumdodecylsulfate (SDS)¹⁶. Many soluble polymers and co-polymers such as PVP, polyethylene glycol (PEG), hydroxypropyl methylcellulose (HPMC) and cyclodextrin derivatives have been used. Physicochemical properties and dissolution of poorly water soluble drugs were improved by co-grinding because of an improvement in the surface polarity and transformation from a crystalline to an amorphous drug. Dry co grinding can be carried out easily and economically and can be conducted without organic solvents¹⁷.

2.6. Precipitation

The most common method of precipitation used is anti solvent addition method in which the drug is dissolved in an organic solvent and this solution is mixed with a miscible anti solvent. Mixing processes vary considerably. Precipitation has also been coupled with high shear



processing. The NANOEDGE process relies on the precipitation of friable materials for subsequent fragmentation under conditions of high shear or thermal energy. Rapid addition of a drug solution to a solvent leads to sudden super saturation of the mixed solution, and generation of fine crystalline or amorphous solids¹⁸.

2.7. Emulsification – solvent evaporation technique

This technique involves the preparing the solution of drug by its emulsification in another liquid that is non-solvent for the drug. Evaporation of the solvent leads to precipitations of the drug. Crystal growth and particle aggregation can be controlled by creating high shear force using a high speed stirrer¹⁹.

2.8. Supercritical fluid process

Novel nanosizing and solubilization technology whose application has increased particle size reduction via supercritical fluid (SCF) processes. A supercritical fluid (SF) can be defined as a dense non condensable fluid. Supercritical fluids are fluids whose temperature and pressure are greater than its critical temperature (Tc) and critical pressure (Tp). A SCF process allows micronization of drug particles within narrow range of particle size, often to sub-micron levels. Current SCF processes have demonstrated the ability to create nanoparticulate suspensions of particles 5 to 2,000 nm 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^{20,21}.

3. FORMULATION OF NANOSUSPENSION

3.1. Stabilizer

Stabilizer plays an important role in the formulation of nanosuspensions. 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 nanosuspensions 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 behavior of nanosuspensions. In some cases, a mixture of stabilizers is required to obtain a stable Nanosuspension.

3.2. Organic solvents

Organic solvents may be required in the formulation of nanosuspensions if they are to be prepared using an emulsion or microemulsion 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 microemulsions 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..

3.3. Co-surfactants

The choice of co-surfactant is critical when using microemulsions formulate nanosuspensions. Since co-surfactants can greatly influence phase behavior, the effect of co-surfactant on uptake of the internal phase for selected microemulsions composition and on drug loading should be investigated. Although the literature describes the use of bile salts and dipotassium glycerolrhizinate as co-surfactants, various solubilizers, such as Transcutol, glycofurol, ethanol and isopropanol, can be safely used as co-surfactants in the formulation of microemulsions^{22,23}.

3.4. Other additives

Formulation considerations Nanosuspensions may contain additives such as buffers, salts, polyols, osmogen and cryoprotectant, depending on either the route of administration or the properties of the drug moiety²⁴.

4. EVALUATION OF NANOSUSPENSION

4.1. In-vitro evaluations

- 4.1.1. Particle size and size distribution
- 4.1.2. Particle charge (Zeta Potential)
- 4.1.3. Crystalline state and morphology
- 4.1.4. Saturation solubility and dissolution velocity²⁵.

4.2. In-vivo evaluation

4.3. Evaluation for surface-modified nanosuspension

- 4.3.1. Surface hydrophilicity
- 4.3.2. Adhesion properties
- 4.3.3. Interaction with body proteins²⁶

4.1. In-vitro evaluation

4.1.1. Mean particle size and size distribution

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 μm only. PCS is a versatile technique but has low measuring range. In addition to PCS analysis nanosuspensions are analyzed by Laser Diffraction (LD).

4.1.2. 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 nanosuspensions exhibiting good stability, for an electrostatically stabilized nanosuspensions minimum zeta potential of 30mV is required whereas in the case of a combined electrostatic and 20 mV is desirable.

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

4.1.4. Solubility and Dissolution velocity

The main advantage associated with then a nosuspensions is improved saturation Solubility as well as dissolution velocity. These are studied in different physiological solution sat different pH. Kelvin equation and the Ostwald-Freundlich equations can explain increase in saturation solubility. Determination of these parameters is useful to assess in vivo performance of the formulation.

4.2. In-vivo evaluation

The in vivo evaluation of the nanosuspensions 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 Spectrophotometry.

5. APPLICATIONS

- 1) Formulating the drug as nanosuspensions increases the saturable concentration, dissolution rate as well as bioavailability of the drug.
- 2) Nanosuspensions 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 nanosuspensions are having application in different routes of administrations like oral, parenteral, topical, ophthalmic, mucoadhesive, pulmonary and targeted drug delivery²⁶.

6. CONCLUSION

Nanosuspensions are administering poorly water soluble drugs have been largely solved the dissolution problems to improve drug absorption and bioavailability. Nanosuspension technology can be combined with traditional dosage forms: tablets, capsules, pellets, and can be used for parenteral products. They have recently received increasing attention as colloidal carriers for

targeted delivery of various anticancer drugs, photosensitizes, Production techniques such as media milling and high-pressure homogenization have been successfully employed for large-scale production of nanosuspensions. The applications of nanosuspensions in parenteral and oral routes have been very well investigated and applications in pulmonary and ocular delivery have been realized. The transformation of any drug to drug nanoparticles leading to an increase in saturation solubility, dissolution velocity, and providing the general feature of an increased adhesiveness to surfaces is one of the most important achievement.

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