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A REVIEW ON DRIED NANOSUSPENSIONS- A NOVEL FORMULATION TO ENHANCE SOLUBILITY OF POORLY AQUEOUS SOLUBLE DRUGS

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ABSTRACT

Solubility is most important and crucial factor for drug effectiveness. Large proportions of newly discovered drugs are water insoluble, and therefore poorly bioavailable. Nanosuspensions are one of the promising drug delivery systems proved to be very effective in eliminating the solubility problems and increasing the bioavailability of poorly soluble drugs. Nanosuspensions are very finely colloid, biphasic, dispersed, solid drug particles in an aqeous vehicle. These are prepared by using wet mill, high pressure homogenizer, emulsion-solvent evaporation, melt emulsification method and super critical fluid techniques. The most recent advancement in Nanosuspensions is Dried Nanosuspension which is prepared by freeze drying or spray drying of the formulated Nanosuspensions. It has higher stability and solubility properties than nanosuspensions. These can be delivered by oral, parenteral, pulmonary and ocular routes. Nanosuspensions can also be used for targeted drug delivery when incorporated in the ocular inserts and mucoadhesive hydrogels.

Key Words: Nanosuspensions, High Pressure Homogenizer, bioavailability, freeze drying.

INTRODUCTION

More than 40 percent of the drugs coming from High-throughput screening are poorly soluble in water. Obviously poorly water-soluble drugs show many problems in formulating them in conventional dosage forms. One of the critical problems associated with poorly soluble drugs is too low bioavailability and or erratic absorption. Nanosuspensions are promising strategy for the efficient delivery of hydrophobic drugs. To date, nanoscale systems for drug delivery have gained much interest as a way to improve the solubility problems. The reduction of drug particles into the sub-micron range leads to a significant increase in the dissolution rate and therefore enhances bioavailability. Nanosuspensions are promising candidates that can be used for enhancing the dissolution of poorly water soluble drugs. Nanosuspensions contain submicron colloidal dispersion of pharmaceutical active ingredient particles in a liquid phase stabilized by surfactants [1]. Present review is emphasised on dried nanosuspensions. Nanosuspensions of a poorly soluble drug could be spray dried or lyophilised to obtain flowable powders that could be easily redispersed. These optimized powders significantly improve dissolution rates as compared to the micronized drug, or unoptimized nanosuspensions[2].

Potential Benefits of Nanosuspension Technology for Poorly Soluble Drugs

- Reduced particle size, increased drug dissolution rate, increased rate and extent of absorption, increased bioavailability of drug, onset time, peak drug level, reduced variability and reduced fed/fasted effects.
- Nanosuspensions can be used for compounds that are water insoluble but which are soluble in oil. On the other hand, Nanosuspensions can be used

in contrast with lipidic systems, successfully formulate compounds that are insoluble in both water and oils.

- Nanoparticles can adhere to the gastrointestinal mucosa, prolonging the contact time of the drug and thereby enhancing its absorption.
- A pronounced advantage of Nanosuspension is that there are many administration routes for Nanosuspensions, such as oral, parenteral, pulmonary, dermal and ocular.
- Nanosuspensions overcome delivery issues for the compounds by obviating the need to dissolve them, and by maintaining the drug in a preferred crystalline state of size sufficiently small for pharmaceutical acceptability.
- Nanosuspension of nanoparticles (NPs) offers various advantages over conventional ocular dosage forms, including reduction in the amount of dose, maintenance of drug release over a prolonged period of time, reduction in systemic toxicity of drug, enhanced drug absorption due to longer residence time of nanoparticles on the corneal surface, higher drug concentrations in the infected tissue, suitability for poorly water-soluble drugs and smaller particles are better tolerated by patients than larger particles, therefore increased resistance to hydrolysis and oxidation, increased physical stability to settling.
- Nanosuspension has low incidence of side effects by the excipients.
- Reduced administration volumes, essential for intramuscular, subcutaneous, ophthalmic use. Finally, Nanosuspensions can provide the passive targeting[3].

PREPARATION METHODS OF NANOSUSPENSION:

Preparation of nanosuspensions were reported to be a more cost effective and technically more simpler alternative than liposomes and other conventional colloidal drug carriers, particularly for poorly soluble drugs and yield a physically more stable product.

Mainly there are two methods for preparation of Nanosuspensions namely Bottom-up technology and Top-down technology. The conventional methods of precipitation (Hydrosols) are called 'Bottom up technology'. The bottom-up technology is an assembling method from molecules to nano-sized particles, including microprecipitation, microemulsion, melt emulsification method and so on 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 (Nanoedege) [4].

1. **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 antisolvent. Mixing processes vary considerably. Precipitation has also been coupled with high shear processing[5].

2. **Lipid Emulsion/ Microemulsion Template:** Lipid emulsions as templates are applicable for drugs that are soluble in either volatile organic solvents or partially water miscible solvents. In this method the drug will be dissolved in the suitable organic solvent and then emulsified in aqueous phase using suitable surfactants. Then the organic solvent will be slowly evaporated under reduced pressure to form drug particles precipitating in the aqueous phase forming the aqueous suspension of the drug in the required particle size.

3. **Melt emulsification method:** Solid lipid nanoparticles are mainly prepared by melt emulsification method. Kipp and co workers firstly prepare nanosuspensions of ibuprofen by using melt emulsification method. It is a four-step procedure. Drug is first added to aqueous solution having stabilizer. The solution is heated at temperature higher than the melting point of the drug and then homogenized by high-speed homogenizer for the formation of emulsion. The temperature is maintained above the melting point of the drug during overall process. Finally, the emulsion is cooled to precipitate the particles. The particle size of nanosuspension mainly depends on parameters like drug concentration, concentration and type of stabilizers used, cooling temperature, and homogenization process.

4. **High Pressure Homogenization:** It is the most widely used method for the preparation of the nanosuspensions of many poorly water soluble drugs .The principle of this method is based on cavitation in the aqueous phase. The particles cavitations forces are sufficiently high to convert the drug microparticles into nanoparticles. The concern with this method is the need for small sample particles before loading and the fact that many cycles of homogenization are required [6].

5. **Milling Techniques:**

Media milling: In this technique, the nanosuspensions are produced using high-shear media mills or pearl mills. The media mill consists of

a milling chamber, a milling shaft and a recirculation chamber. 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 with the drug provide the necessary energy input to disintegrate the microparticulate drug into nanosized particles. The milling medium is usually composed of glass, zirconium oxide or highly cross-linked polystyrene resin.

Dry Cogrinding: Since many years, nanosuspensions are prepared through wet grinding processes by using pearl ball mill. Nowadays, nanosuspensions can be prepared by dry milling methods. Stable nanosuspensions are prepared by using dry grinding of poorly soluble drug with soluble polymers and copolymers after dispersing in liquid medium. Itoh *et al*. have described the colloidal particles formation of many poorly water-soluble drugs like nifedipine, griseofulvin, and glibenclamide with sodium dodecyl sulfate and polyvinylpyrrolidone as stabilizer.

6. **Microprecipitation – High-Pressure Homogenization (Nanoedge):** Nanoedge is a combination of microprecipitation and high-pressure homogenization techniques. Method includes precipitation of friable materials followed by fragmentation under high shear and/or thermal energy.

7. **Nanojet Technology:** This technique is also called opposite stream technology, uses a chamber where a stream of suspension is divided into two or more parts. Both streams are colloid with each other at high pressure. The high shear force produced during the process results in particle size reduction. Dearns had prepared nanosuspensions of atovaquone using the microfluidization process. The major disadvantage of this technique is the high number of passes through the microfluidizer and that the product obtained contains a relatively larger fraction of microparticles.

8. **Supercritical Fluid Methods:** Various methods like rapid expansion of supercritical solution (RESS) process, supercritical antisolvent process, and precipitation with compressed antisolvent (PCA) process are used to produce nanoparticles. In RESS technique, drug solution is expanded through a nozzle into supercritical fluid, resulting in precipitation of the drug as fine particles by loss of solvent power of the supercritical fluid. By using RESS method, Young *et al*. prepared cyclosporine nanoparticles having diameter of 400 to 700 nm. In the PCA method, the drug solution is atomized into the CO_2 compressed chamber. As the removal of solvent occurs, the solution gets supersaturated and finally precipitation occurs. In supercritical antisolvent process, drug solution is injected into the supercritical fluid and the solvent gets extracted as well as the drug solution becomes supersaturated.

POST-PRODUCTION PROCESSING

Post-production processing of Nanosuspensions becomes essential when the drug candidate is highly susceptible to hydrolytic cleavage or chemical degradation. Processing may also be required when the best possible stabilizer is not able to stabilize the Nanosuspension for a longer period of time or there are acceptability restrictions with respect to the desired route. Considering these aspects, techniques such as lyophilization or spray drying may be employed to produce a dry powder of nano-sized drug particles. Rational selection has to be made in these unit operations considering the drug properties and economic aspects. Generally, spray drying is more economical and convenient than lyophilization. The effect of postproduction processing on the particle size of the nanosuspension and moisture content of dried nanosized drug should be given due consideration. [7]

EVALUATION OF NANOSUSPENSIONS:

- Particle size and size distribution
- Particle charge (Zeta Potential)
- Crystalline state and morphology
- Saturation solubility and dissolution velocity
- Stability
- In-Vitro Evaluations:

1. Particle Size and Size Distribution:

It is the most important parameter in the evaluation of the suspensions as it is having the direct effect on the solubility and dissolution rate and the physical stability of the formulation. The mean particle size and the width of particle size can be determined by Photon Correlation Spectroscopy (PCS), laser diffraction and coulter current multisizer[8].

2. Particle Charge (Zeta Potential):

The particle charge is of importance in the study of the stability of the suspensions. Usually the zeta potential of more than ±40mV will be considered to be required for the stabilisation of the dispersions. For electrostatically stabilized nanosuspension a minimum zeta potential of ±30mV is required and in case of combined steric and electrostatic stabilization it should be a minimum of ±20mV of zeta potential is required.

3. Crystalline Sate and Particle Morphology: It is of importance as there are chances of the polymorphism during the storage of the nanosuspensions. Hence it is necessary to study the crystal morphology of the drug in suspension. Differential Scanning Calorimetry (DSC) is most commonly used for such studies.

4. Saturation Solubility And Dissolution Velocity: The main advantage associated with the nanosuspensions is improved saturation solubility as well as dissolution velocity. These are studied in different physiological solutions at 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.

5. Stability of Nanosuspensions:
Stability of the suspensions is dependent on the particle size. As the particle size reduces to the nanosize the surface energy of the particles will be increased and they tend to agglomerate. So stabilizers are used which will decrease the chances of Ostwald ripening and improving the stability of the suspension by providing a steric or ionic barrier[9].

APPLICATION OF NANOSUSPENSIONS:

Bioavailability Enhancement:
Bioavailability enhancement Drug with poor solubility, poor permeability or poor solubility in gastrointestinal tract will leads to poor oral bioavailability. Nanosuspension resolves the problem of poor bioavailability bysolving the problem of poor solubility, and poor permeability across the membranes[10].

Ocular Administration:
For delivery of poorly soluble drug in cul-de-sac suspensions and ointments are recommended. Suspensions have advantages of prolonged residual time in cul-de-sac and avoidance of higher tonicity produced by water soluble drugs. The ocular bioavailability of suspensions depends on the dissolution rate of the drug in lachrymal fluid.

Pulmonary administration:
Aqueous nanosuspension can be nebulized using mechanical or ultrasonic nebulizer for lung delivery. 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. This ability of nanosuspensions to offer quick onset of action initially and then controlled release of the active moiety is highly beneficial and is required by most pulmonarydiseases.

Targeted drug delivery:
Nanosuspensions can also be used as targeted drug delivery. The targeted drug delivery can be designed by incorporating the drug into the mononuclear phagocytic system. Targeted drug delivery can be used for the anti-mycobacterial, fungal or leishmanial drugs to macrophages if the infectious pathogen is persisting intracellular[11].

Mucoadhesion of the Nanoparticles:
Nanoparticles orally administered in the form of a suspension diffuse into the liquid media and rapidly encounter the mucosal surface. The particles are immobilized at the intestinal surface by an adhesion mechanism referred to as "bioadhesion." From this moment on, the concentrated suspension acts as a reservoir of particles and an adsorption process takes place very rapidly. The direct contact of the particles with the intestinal cells through a bioadhesive phase is the first step before particle absorption[12-14].

CONCLUSION:
Nanosuspensions are considered as the most promising delivery system for poorly soluble drugs, due to high bioavailability and less inter- and intra-subjects variances. Productions techniques such as media milling and high pressure homogenizer are used for large scale production of Nanosuspensions. Nanosuspensions can be administered through oral, parenteral, pulmonary, ocular and topical routes. Since nanotechnique is simple, less requirements of excipients, increased dissolution velocity and saturation solubility many poor bioavailability drugs are formulated in nanosuspension form. Post production techniques like freeze drying or spray drying of the nanosuspensions gives dry powder of nano size particles which show improved stability.

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