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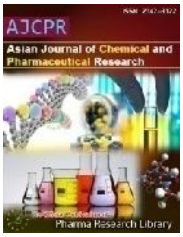

Review Article Open Access

Review on Nanosuspensions

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A B S T R A C T

Solubility is the crucial factor for drug effectiveness, independence of the route of administration. Large proportions of newly discovered drugs are water insoluble, and therefore poorly bioavailable contributing to deserted development effort. These so-called 'Brickellia' candidates can now be delivered by formulating them into Nanosuspension. Nanosuspension technology solved the problem of drugs which are poorly aqueous soluble and less bioavailability. Stability and bioavailability of the drugs can be improved by the Nanosuspension technology. Preparation of Nanosuspension is simple and applicable to all drugs which are aqueous insoluble. Nanosuspensions are prepared by using wet mill, high pressure homogenizer, emulsion-solvent evaporation, melt emulsification method and super critical fluid techniques. Nanosuspension can be prepared by using stabilizers, organic solvents and other additives such as buffers, salts, polyols, osmogent and cryoprotectant. Nanosuspensions 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.

Keywords: Dissolution, Nanosuspension, Saturation solubility, Solubility enhancement, Surfactant.

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1. Introduction

Definition of Nanosuspension: More than 40% of the new chemical entities being generated through drug discovery programmes are poorly water-soluble or lipophilic compounds. Formulating a poorly water-soluble drug has always been a challenging problem conformed by the pharmaceutical scientist. The usage of nano-sized particles

can be implemented to all drug compounds belonging to biopharmaceutical classification system (BCS) classes II and IV to increase the solubility and hence partition into gastrointestinal barrier. Nanotechnology can be used to solve the problems associated with these conventional approaches for solubility and bioavailability enhancement. Nanosuspension technology can also be used for drugs which are insoluble in both water and organic solvents, hydrophobic drugs such as Famitidine, Atorvastatin, Revaprazan, and Acelofenac are formulated as nanosuspension.

Nanosuspensions are colloidal dispersions of nano sized drug particles stabilized by surfactant. They can also be defined as biphasic system consisting of pure drug particles dispersed in an aqueous vehicle in which the diameter of the suspended particle is less than 1 µm in size. Nano is a Greek word which means 'dwarf'. Nano means it is the factor of 10^{-9} or one billionth. Some comparisons of nano scale are given below

0.1 nm = Diameter of one Hydrogen atom.
2.5 nm = Width of a DNA molecule
1 µm = 1000 nm.
1 nm = 10^{-9}m = 10^{-7} cm = 10^{-6} mm.
Micron = 10^{-6}m = 10^{-4}cm = 10^{-}3mm.

Advantages

- Enhance the solubility and bioavailability of drugs
- Suitable for hydrophilic drugs
- Higher drug loading can be achieved
- Dose reduction is possible
- Enhance the physical and chemical stability of drugs
- Provides a passive drug targeting
- Can be applied for poorly water soluble drugs.
- Can be given by any route
- Reduced tissue irritation in case of subcutaneous

Disadvantages

- Physical stability, sedimentation & compaction can cause problems.
- It is bulky sufficient care must be taken during handling & transport.
- Improper dose.
- Uniform & accurate dose cannot be achieved System.

2. Method of Preparation of Nano Suspensions

Mainly there are two methods for preparations of nanosuspensions .The conventional methods of precipitation are called 'bottom up technology'. The 'top down technologies' are the disintegration methods and are preferred over the precipitation methods. The 'top down water (Dissocubes), High pressure homogenization in non aqueous media (Nanopure) and combination of precipitation and high pressure Homogenization.

- Bottom up technology
- Top down technology

Bottom UP Technology

The term "Bottom up technology" means that one starts from the molecular level, and goes via molecular association to the formulation of a solid partical.That means that we are discussing classical precipitation techniques by reducing the solvent quality, for example, by pouring the solvent into a non solvent or changing the temperature or a combination of both Precipitation is a classical technique in pharmaceutical chemistry and technology.

Advantages

- Use of simple and low cost equipment.
- Higher saturation solubility is the advantage for precipitation compare to other methods of Nanosuspension preparation.

Disadvantages

- The drug needs to be soluble in at least one solvent (Thus excluding all new drugs that are simultaneousle poorly soluble in aqueous ad in orgaic media.
- The solvent needs to be missible to with atleast one nonsolvent.
- Solvent residues need to be removed, thus increase production costs.

Top down Technology

The top down technologies include

- Media milling
- High pressure homogenization

Media Milling

Nano suspensions are produced by using high shear media mills or pearl 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 mil containing small grinding balls/perals. As these balls rotate at a very high shear rate under control temperature, they fly through the grinding jar interior and impact against to the sample on the oppisite grinding jar wall. The milling media or balls are made of ceramic sintered aluminium oxide or zirconium oxide or highly cross linked polystyrene resin with high abrasion resistance .planetary ball mills(PM100 and PM200;Retsch Gmbh and co., KG ,Han ,Germany) is one example of an equipment that can be used to achieve a grind size below 0.1µm.The major drawbacks of this technology include the erosion of balls/pearls that can leave residues as contaminants in the final product , degradation of the thermolabile drugs due to heat generated during the process and presence of relatively high proportions of particles ≥5µm.

Advantages:

- Simple technology .Low cost process regarding the milling itself.
- Large scale production possible to some extent (batch process).

Disadvantages:

- Potential erosion from the milling material leading to product contamination.
- Duration of the process not being very production friendly.
- Potential growth of germs in water phase when milling for a long time.
- Time and cost associated with the separation milling material from the drug nanoparticle suspension,

especially when producing parenteral sterile products.

Formulation consideration

Stabilizer

The main function of a stabilizer is 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 barrier. The type and amount of stabilize has a amount of stabilize has a pronounced effect on the physical stability and in vivo pronounced effect on the physical stability and in vivo pronounced effect on the physical stability and in vivo pronounced effect on the physical stability and in vivo behavior of Nanosuspension. Stabilizers that have been used so far are poloxomers, polysorbate, cellulosic's Lecithin is the stabilizer of choice if one intends to develop a parentally acceptable and autoclavable, nanosuspension.

Organic Solvent

Organic solvents are used in the formulation of Nanosuspension if emulsions or micro emulsions are used as a template. The pharmaceutically acceptable less hazardous water miscible solvent, such as methanol, ethanol, chloroform, ispropanol, and partially water miscible solvents ethyl acetate, ethyl formate, butyl lactate, triacetin, propylene carbonate, benzyl alcohol, are preferent in the formulation over the conventional hazardous solvents, such as *Co-Surfactants* Nanosuspensions. Since cosurfactants dichloromethane.52,53 can greatly influence phase behaviour, the effect of co-surfactant on uptake of the internal phase for selected micro emulsion 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.

Other Additives: Nanosuspensions may contain additives such as buffers, salts, polyols, osmogent and cryoprotectant.

3. Evaluations of nanosuspensions

In-vitro evaluations

Color, Odor, Taste

These characteristics are especially important in orally administered formulation. Variations in taste, especially of active constituents, can offered be attributed to changes in particle size, crystal habit and subsequent particle dissolution. Changes in color, odor and taste can also indicate chemical instability.

Particle Size Distribution

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. The PCS method can measure particles in the size range of 3 nm to 3μm and the LD method has a measuring range of 0.05-80μm. The coulter counter multisizer gives the absolute number of particles, in contrast to the LD method, which gives only a relative size distribution. For IV use, particles should be less than 5μm, considering that the smallest size of the capillaries is 5-6μm and hence a higher particle size can lead to capillary blockade and embolism.

Zeta Potential

Zeta potential is an indication of the stability of the suspension. 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 steric stabilizer, a zeta potential of ±20 mV would be sufficient.

Crystal Morphology

To characterize the polymorphic changes due to the impact of high-pressure homogenization in the crystalline structure of the drug, techniques like X-ray diffraction analysis in combination with differential scanning calorimetry or differential thermal analysis can be utilized. 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.

Dissolution Velocity And Saturation Solubility

Nanosuspensions have an important advantage over other techniques, that it can increase the dissolution other techniques, that it can increase the dissolution velocity as well as the saturation solubility. These two parameters should be determined in various physiological solutions. The assessment of saturation solubility and dissolution velocity helps in determining the in vitro behavior of the formulation. Böhm et al. reported an increase in the dissolution pressure as well as dissolution velocity with a reduction in the particle size to the nanometer range. Size reduction leads to an increase in the dissolution pressure.

Density

Specific gravity or density of the formulation is an important parameter. A decrease in density often indicates the presence of entrapped air within the structure of the formulation. Density measurements at a given temperature should be made using well mixed, uniform formulation; precision hydrometer facilitate such measurements.

pH Value

The pH value of aqueous formulation should be taken at a given temperature and only after settling equilibrium has been reached, to minimize "pH drift" and electrode surface coating with suspended particles. Electrolyte should not be added to the external phase of the formulation to stabilize the pH.

Droplet Size

The droplet size distribution of micro emulsion vesicles can be determined by either light scattering technique or electron microscopy. Dynamic light scattering electron microscopy. Dynamic light scattering spectrophotometer which uses a neon laser of wavelength 632 nm.

Viscosity Measurement

The viscosity of lipid based formulations of several compositions can be measured at different shear rates at different temperatures using Brookfield type rotary viscometer. The sample room of the instrument must be maintained at 370C by a thermo bath and the samples, for the measurement are to be immersed in it.

Stability of Nanosuspension

The high surface energy of nanosized particles induces agglomeration of the drug crystals. The main function of the stabilizer is to wet the drug particles thoroughly to prevent Ostwald ripening and agglomeration of the Nanosuspension and form a physically stable formulation by providing a steric or an ionic barrier. Typical examples of stabilizers used in Nanosuspensions are cellulosic's, poloxamer, polysorbates, lecithin, polyoleate and povidones. Lecithin may be preferred in developing parenteral Nanosuspensions.

***In-Vivo* Biological Performance**

The establishment of an in-vitro/in-vivo correlation and the monitoring of the in-vivo performance of the drug is an essential part of the study, irrespective of the route and the delivery system employed. It is of the utmost importance in the case of intravenously injected Nanosuspensions since the in-vivo behavior of the drug depends on the organ distribution, which in turn depends on its surface properties, such as surface hydrophobicity and interactions with plasma proteins In fact, the qualitative and quantitative composition of the protein absorption pattern observed after the intravenous injection of nanoparticles is recognized as the essential factor for organ distribution. Hence, suitable techniques have to be used in order to evaluate the surface properties and protein interactions to get an idea of In-vivo behavior. Techniques such as hydrophobic interaction surface hydrophobicity, whereas 2-D PAGE can be employed for the quantitative and qualitative measurement of protein adsorption after intravenous injection of drug nanosuspensions in animals.

4. Applications of Nanosuspensions

ORAL: Oral drug delivery is the most widely preferred route of administration of drugs. But, some drugs possess the problem of limited bioavailability due to poor solubility and absorption which ultimately reduces its efficacy. In such cases, Nanosuspension can solve the problem as it helps in improving the dissolution rate and absorption due to increased surface area and enhanced adhesiveness. Nanosuspension can lead to increased mucoadhesion which can increase gastrointestinal transit time and lead to increased bioavailability. The enhancement in oral bioavailability can be attributed to increased surface area, saturation solubility and the adhesiveness of the drug Nanosuspension. Taste masking of particulate system is also easily possible.

Parenteral: Nanosuspensions can be used to transform poorly soluble non-injectable drugs into a formulation suitable for intravenous administration. Although the production of Nanosuspension for parenteral use is critical, current injectable formulations. The methods used for preparation of Nanosuspension are now precisely controlled, and are able to produce uniform particles with better control over maximum particle size. Various research reports are available which emphasize the applicability of Nanosuspensions for parenteral administration.

Ocular Delivery

Nanosuspension can prove to be a boon for drugs that exhibit poor solubility in lachrymal fluids. Nanosuspensions represent an ideal approach for ocular delivery of hydrophobic drugs due to their inherent ability to improve saturation solubility of drugs. Kassem et al., have developed Nanosuspension delivery system for certain glucocorticoid drugs

Pulmonary

Nanosuspensions can be advantageous for delivering drugs that exhibit poor solubility in pulmonary secretion. Currently available approaches for pulmonary delivery such as aerosols or dry powder inhalers possess certain disadvantages such as limited diffusion at required site, less residence time etc, which can be overcome by Nanosuspensions. Fluticasone and budesonide have been successfully formulated as Nanosuspension for pulmonary Delivery.

Dermal

The nanocrystalline form possesses increased saturation solubility resulting in enhanced diffusion of the drug into the skin. Nanocrystals also exhibit various properties such as increased penetration into a membrane, enhanced permeation and bioadhesiveness which could be very useful for dermal application.

Targeting

The uptake of drug nanoparticles depends on their particle size. By changing the surface properties of the nanoparticles, their in vivo behavior can be altered and Can be used as targeted delivery system. The phagocytotic uptake of nanocrystals can be avoided by preparing stealth nanocrystals or by preparing smart crystals i.e. drug particles below particle size of 100nm, which can be used as a targeted drug delivery system. Due to method simplicity, development of nanosuspension is a commercially viable option for targeted delivery. Mucoadhesive nanosuspension was reported for targeting of Cryptosporidium parvum. The surface properties of particles such as surface hydrophobicity, charge, presence and concentration of certain functional groups determine its organ distribution. Thus, Tween 80 coated nanocrystals can be used for brain targeting. Atovaquone nanocrystals coated with Tween80 were used to treat toxoplasmosis; the parasites could be efficiently eradicated in brain.

Mucoadhesion of the Nanoparticle

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.

5. Future Prospects

Nanosuspension technology is a unique and novel approach to overcome drug problems such as poor bioavailability that are related with the delivery of hydrophobic drugs, including those that are poorly soluble in aqueous as well as organic media. Production methods like media milling and high-pressure homogenization have been successfully

employed for large scale production of Nanosuspensions. Nanosuspension technology can be combined with dosage forms: tablets, traditional capsules, pellets, and can be used for parenteral products. To take advantage of Nanosuspension drug delivery, simple formation technologies and variety applications, Nanosuspensions will continue to be of interest as oral formulations and non-oral administration develop in the future. In consideration to data available Nanosuspensions can be considered as renaissance in formulation technologies for coming years.

6. Conclusion

Nanosuspension solved poor bioavailability problem of hydrophobic drugs and drugs which are poorly soluble in aqueous and organic solutions. 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.

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