A Brief Review On Nanosuspensions

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ABSTRACT

Nanotechnology has emerged as an tremendous field in the medicine. Nano refers to particles size range of 1-1000nm.Nanosuspensions are part of nanotechnology. Many of the drug candidates are exhibiting poor aqueous solubility. The use of drug nanosuspension is an universal formulation approach to increase the therapeutic performance of these drugs in any route of administration. A pharmaceutical nanosuspension is defined as very finely colloid, biphasic ,dispersed, solid drug particles in an aqeous vehicle , size below 1*m ,without any matrix material , stabilized by surfactants andpolymers, prepared by suitable methods for Drug Delivery applications, through various routes of administration like oral ,topical ,parenteral ,ocular and pulmanary routes. This review article describes the preparation methods,characterization and applications of the nanosuspensions.

Keywords: Nanotechnology, Nanosuspension, Matrix, Drug Delivery.

INTRODUCTION

A nanosuspension is a submicron colloidal dispersion of drug particles which are stabilized by surfactants. A pharmaceutical nanosuspension is defined as very finely dispersed solid drug particles in an aqueous vehicle for either oral and topical use or parenteral and pulmonary administration. The particle size distribution of the solid particles in nanosuspensions is usually less than one micron with an average particle size ranging between 200 and 600 nm. Nanosuspensions differ from nanoparticles. Nanoparticles are commonly polymeric colloidal carriers of drugs whereas solid lipid nanoparticles are lipidic carriers of drugs. In nanosuspension technology, the drug is maintained in the required crystalline state with reduced particle size, leading to an increased dissolution rate and therefore improved bioavailability. An increase in the dissolution rate of micronized particles (particle size < 10 μm) is related to an increase in the surface area and consequently the dissolution velocity. Nanosized particles can increase solution velocity and saturation solubility because of the vapor pressure effect.

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 programmes are poorly water-soluble.The problem is even more intense for drugs such as itraconazole and carbamazepine as they are poorly soluble in both aqueous and organic media, and for drugs having a log P value of 2. Such drugs often have an erratic absorption profile and highly variable bioavailability because their performance is dissolution-rate limited and is affected by the fed/fasted state of the patient.

TYPES OF NANOSUSPENSION METHODS

(1) micronization by colloid or jet milling, 2) high pressure homogenization,(3) emulsion and milling techniques

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.

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.

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.

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.

Lipid emulsion/microemulsion template:

Nanosuspensions are also obtained by just diluting the emulsion, formed by using a partially water-miscible solvent as the dispersed phase. The emulsion technique is applicable for drugs which are either partially water miscible or soluble in volatile organic solvents. Additionally, microemulsion templates can also produce nanosuspensions. Microemulsions are dispersions of two immiscible liquids like water and oil and stabilized thermodynamically by surfactant or cosurfactant. The drug is either loaded into preformed or internal phase of microemulsion and can be saturated by intimate mixing of drugs. Griseofulvin nanosuspension is prepared by the microemulsion technique by using water, butyl lactate, lecithin, and the sodium salt of taurodeoxycholate.

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.

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.

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.

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.

FORMULATION OF NANOSUSPENSION:

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.

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

watermiscible 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. Co-surfactants

The choice of co-surfactant is critical when using microemulsions formulate nanosuspensions. Since cosurfactants 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 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.

4. Other additives

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

Evaluation of Nanosuspensions :

In-Vitro Evaluations:

* Particle size and size distribution

* Particle charge (Zeta Potential)

* Crystalline state and morphology

* Saturation solubility and dissolution velocity

* Stability

* In-vivo evaluation:

* In-Vitro Evaluations:

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.

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.

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 .

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.

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.

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 behaviour 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-vitro drug release studies

Dissolution tests were performed in a USP typeII (paddle method - TDT-08 L, Electro lab, Mumbai, India) at 370C ± 0.50C and paddle was rotated at a speed of 100 rpm. Open ended tube was tightened with semipermeable membrane at one end and 8.5ml of CMNS was added into it. This setup was immersed on the dissolution medium (see fig.1). Samples of 5ml were collected at intervals 10, 30, 60, 90, 120, 150, 180, 210, 240, 300, 330 and 360mins and required dilution with dissolution medium then detected at 425nm using UVspectrophotometer. The peak area of standard solution and sample collected at intervals 10, 30, 60, 90, 120, 150, 180, 210, 240, 300, 330 and 360mins was recorded and the percentage drug release was calculated.

Applications of nanosuspensions in drug
Delivery Target drug delivery

Nanosuspensions can also be used for targeted delivery as their surface properties and in vivo behavior can easily be altered by changing either the stabilizer or the milieu. Their versatility, ease of scale up and commercial product enable the development of commercial viable nanosuspensions for targeted delivery. The engineering of stealth nanosuspensions by using various surface coatings for active or passive targeting of the desired site is the future of targeted drug delivery systems. Targeting of Cryptosporidium parvum, the organism responsible for cryptosporidiosis, was achieved by using surface modified mucoadhesive nanosuspensions of bupravaquone. Similarly, conditions such as pulmonary

aspergillosis can easily be targeted by using suitable drug candidates, such as amphotericin B, in the form of pulmonary nanosuspensions instead of using stealth liposomes.

Oral drug delivery

The oral route is the preferred route for drug delivery because of its numerous well-known advantages. The efficacy or performance of the orally administered drug generally depends on its solubility and absorption through the gastrointestinal tract. Hence, a drug candidate that exhibits poor aqueous solubility and/or dissolution-rate limited absorption is believed to possess low and/or highly variable oral bioavailability. Owing to low oral bioavailability, such a drug candidate would have to be administered in a larger excess than actually required if it were completely bioavailable in order to achieve a therapeutically active concentration, thus making the therapy costly. Orally administered antibiotics such as atovaquone and bupravaquone reflect this problem very well.Nanosizing of such drugs can lead to a dramatic increase in their oral absorption and subsequently bioavailability.

Parenteral drug delivery

Nanosuspensions can be administered via different parenteral administration routes ranging from intra-articular via intraperitonal to intravenous injection. For administration by the parenteral route, the drug either has to be solubilized or has particle/globule size below 5µm to avoid capillary blockage. The current approaches for parenteral delivery include salt formation, solubilization using co-solvents, micellar solutions, complexation with cyclodextrin and recently liposomes. However, there are limitations on the use of these approaches because of the limitations on their solubilization capacity and parenteral acceptability The parenteral route is an invasive route. Parenteral administration of drugs is critical and often associated with the problems such as the limited number of acceptable excipients, restrictions on the quantities of excipients approved for parenteral use, the stringent requirements of the aseptic production process, safety issues, patient noncompliance and biological problems such as allergic reactions
and thrombophlebitis. Despite all these limitations, the parenteral route still retains its value because of its special advantages, such as quick onset of action in case of emergency, reduction in dose of the drug and the ability to target the drug quickly to the desired site of action, especially in the case of severe infections. The parenteral route is often employed as an alternative when the drug is either not absorbed through the gastrointestinal tract or undergoes extensive first-pass metabolism.

Ocular drug delivery

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. Although suspensions offer advantages such as prolonged residence time in a cul-desac (which is desirable for most ocular diseases for effective treatment) and avoidance of the high tonicity created by water-soluble drugs, their actual performance depends on the intrinsic solubility of the drug in lachrymal fluids.Thus, the intrinsic dissolution rate of the drug in lachrymal fluid governs its release and ocular bioavailability. However, the intrinsic dissolution rate of the drug will vary because of the constant inflow and outflow of lachrymal fluids. Hence, suspensions may fail to give consistent performance. However, nanosuspensions, by their inherent ability to improve the saturation solubility of the drug, represent an ideal approach for ocular delivery of hydrophobic drugs. Moreover, the nanoparticulate nature of the drug allows its
prolonged residence in the cul-de-sac, giving sustained release of the drug. To achieve sustained release of the drug for a stipulated time period, nanosuspensions can be incorporated in a suitable hydrogel base or mucoadhesive base or even in ocular inserts. An approach that has recently been investigated to

achieve the desired duration of action of the drug is the formulation of polymeric nanosuspensions loaded with the drug.

Pulmonary drug delivery

Aqueous nanosuspensions can be nebulized using mechanical or ultrasonic nebulizers for lung delivery. Basically the nanosuspensions can be used in all nebulizers.The dispersions can be relatively high concentrated. Due to the presence of many small particles instead of a few large microparticles, all aerosol droplets are likely to contain drug nanoparticles. Budesonide, a poorly water-soluble corticosteroid, has been successfully prepared as a nanosuspension for pulmonary delivery. A good relationship was obtained between increasing the drug concentration in the formulation and the number of micrograms of drug delivered per actuation. In addition, bupravaquone nanosuspensions were formulated for treatment of lung infections by using nebulization.

Topical formulations

Drug nanoparticles can be incorporated into creams and water-free ointments. The nanocrystalline form leads to an increased saturation solubility of the drug in the topical dosage form, thus enhancing the diffusion of the drug into the skin.

CONCLUSION

Nanosuspensions appear to be a unique and yet commercially viable approach to combating problems such as poor bioavailability that are associated with the delivery of hydrophobic drugs, including those that are poorly soluble in aqueous as well as organic media. The dissolution problems of poorly water soluble drugs have been largely solved to improve drug absorption and bioavailability. Nanosuspension formulations are promising candidates for enhancing the solubility of poorly water soluble drugs. Nanosuspension technology can be combined with traditional dosage forms: tablets, 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.

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