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NANOSUSPENSION: A NANOCARRIER DRUG DELIVERY SYSTEM

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ABSTRACT

Nanosuspensions are fine dispersion of uniform-sized solid particles in an aqueous vehicle. Many of the drug candidates are exhibiting poor aqueous solubility. The use of drug nanosuspension is a universal formulation approach to increase the therapeutic performance of these drugs in any route of administration. Nanosuspension consists of the pure poorly water-soluble drug without any matrix material suspended in dispersion. Preparation of nanosuspension is simple and applicable to all drugs which are water insoluble. A nanosuspension not only solves the problems of poor solubility and bioavailability, but also alters the pharmacokinetics of drug and thus improves drug safety and efficacy. This review article describes the preparation methods, characterization, and applications of the nanosuspension.

KEYWORDS: Nanosuspension, Bioavailability and Pharmacokinetics.

INTRODUCTION

A pharmaceutical nanosuspension is defined as a very finely colloid, biphasic, dispersed, solid drug particles in aqueous vehicle, size below 1µm, without any matrix material, stabilised by surfactants & polymers, prepared by suitable methods for drug delivery applications, through various routes of administration like oral, topical, parenteral, ocular & pulmonary routes. A nanosuspension not only solves the problem of poor solubility & bioavailability but also alters the pharmacokinetics of drug & that improves safety & efficacy. Nanosuspension formulation approach is most suitable for the compounds with high log P value, high melting point & dose. Nanosuspension has been reported to enhance adsorption & bioavailability it may help to reduce the dose of the convectional oral dosage forms. Drug particle size reduction leads to an increase in surface area & consequently in the rate of dissolution as described by Nernst-Brunner & Levich modification of the Noyes- Whitney equation. In addition, an increase in saturation solubility is postulated by particle size reduction due to an increase dissolution pressure explained by the Ostwald Freundlich equation. Depending on the production technique applied changes in crystalline structure of the drug particles may also occur. An increasing amount of amorphous drug fraction could induce higher saturation solubility (Nayak S & Panda D. *et al.*, 2010). Nanosuspensions differ from nanoparticles, Nanoparticles are commonly polymeric colloidal carrier of drugs whereas solid lipid nanoparticles are lipidic carriers of drugs. In nanosuspension technology, the drug is maintained in the crystalline state with reduced particle size, leading to increase dissolution rate & therefore improved bioavailability. Drugs encapsulated within nanosuspensions exist in pharmaceutically accepted crystalline or amorphous state. Nanaosuspensions can successfully formulate the brick dust molecules for improved dissolution & good absorption (Prabhakar C & Krishna K. *et al.*, 2011).

Advantages

1. Its general applicability to most drugs & simplicity
2. It can apply for poorly water soluble drugs
3. It can given by any route
4. Reduced tissue irritation in case of subcutaneous/intramuscular administration
5. Rapid dissolution & tissue targeting can be achieved by IV route of administration
6. Oral administration of nanosuspension provide rapid onset & improved bioavailability
7. The absorption form absorption window can be increased, due to reduction in the particle size
8. Drug with higher log P value can be formulated as nanosuspensions to increase the bioavailability
9. Long term physical stability
10. Possibility of large scale production

Disadvantages

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

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 ionicbarrier. The type and amount of stabilize has a pronounced effect on the physical stability and in vivo behavior of Nanosuspension. Stabilizers that have been used so far are poloxomers, polysorbate, cellulosics, povidones, and lecithins (Shaha T, Patel D, *et al.,* 2007). 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 dichloromethane (Patel M, Shaha A, *et al.,* 2011).

Co-Surfactants: The choice of co-surfactant is critical when using micro emulsions to formulate Nanosuspensions. Since cosurfactants can greatly influence phase behaviour, the effect of co-surfactant on uptake of the internal phase forselected micro emulsion composition and on drug loading should be investigated. Although the literature describesthe use of bile salts and dipotassium glycerrhizinate as cosurfactants, various solubilizers, such as Transcutol, glycofurol, ethanol and isopropanol, can be safely used as co-surfactants in the formulation of microemulsions (Patel M, Shaha A, *et al.,* 2011).

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

TECHNIQUES FOR NANOSUSPENSIONS

There are different methods for the preparation of nanosuspensions.

High pressure homogenization (Disso Cubes)

Disso cubes are engineered using piston-gap-type high pressure homogenizers (Patravale V, Date A. *et al.,* 2004). High pressure homogenization has been used to prepare nanosuspension of many poorly water soluble drugs. Homogenization involves the forcing of the suspension under pressure through a valve having a narrow aperture. The instrument can be operated at pressure varying from 100-1500 bars and upto 2000 bars with volume capacity of 40ml. The concern with this method is the need for small sample particles before loading &the fact that many cycles of homonization are required. Before subjecting the drug to the homogenization process, it is essential to form a pre suspension of the microsized drug in a surfactant solution using high speed stirrer. During the homogenization process, the drug suspension is pressed through the homogenization gap in order to achieve nanosizing of the drug. In piston gap homogenizer, particle size reduction is based on the cavitation principle. A piston-gap homogenizer like APV Gaulin type has been shown. Particles are also reduced due to high shear forces & the collision of the particles against each other. The dispersion contained in 3cm diameter cylinder, suddenly passes through a very narrow gap of 25µm. The reduction in diameter of 3cm to 25µm leads to increase in dynamic pressure &decrease of static pressure below the boiling point of water at room temperature. Due to this water startsboiling at room temperature & forms bubbles, which implode when the suspension leaves the gap & normalair pressure, are reached (Jagdale D, Kamble. *et al*., 2010).

Advantages

Both diluted and concentrated suspension can be formulated

Does not cause erosion of processed material

Applicable to the drugs which are poorly soluble in both aqueous and organic solvent

Disadvantages

Micronisation may occur

High cost of instrument

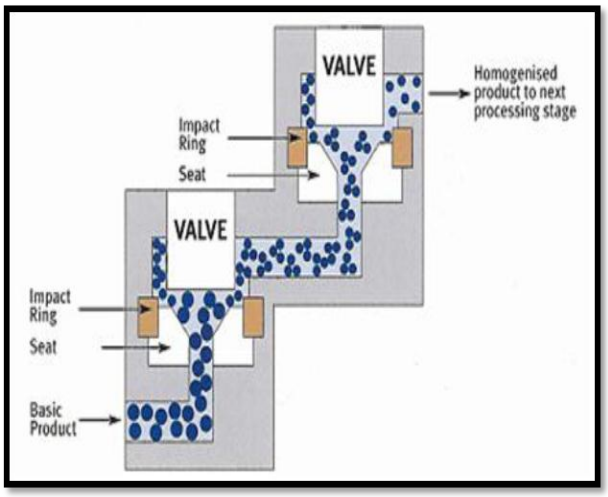

Figure 1: High Pressure Homogenization.

Media milling

In this method, the nanaosuspensions are produced using high-shear media mills or pearl mills. The media mills consists of a milling chamber, a milling shalf and a recirculation chamber. The milling chamber charged with polymeric media is the active component of the mill. The mill can be operated in a batch or recirculation mode. Crude slurry consisting of drug, water & stabilizer is fed into the milling chamber & processed into nano-

crystalline dispersion & the milling media or pearls are then rotated at a very high shear rate. The milling process is performed under controlled temperatures. The typical residence time generated for a nanometer-sized dispersion with a mean diameter of <200nm is 30-60min (Debjit B, Harish G. *et al.,* 2012).

Advantages
Simple technology
Low-cost process regarding the milling itself
Large-scale production possible to some extent

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 the water phase when milling for a long time

Time and costs associated with the separation procedure of the milling material from the drug nanoparticle suspension, especially when producing parenteral sterile products.

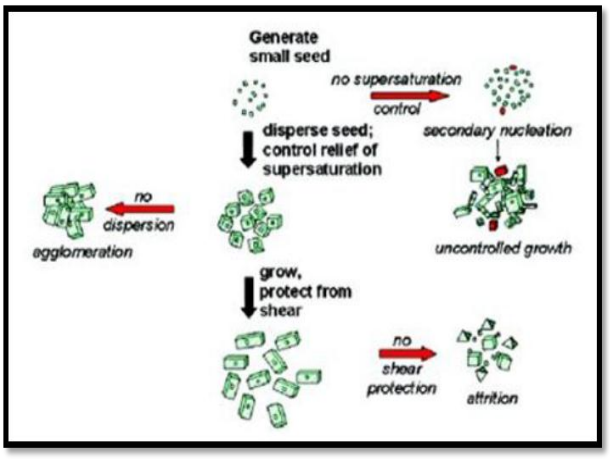

Figure 2: Media Milling Process.

Homogenization in non-aqueous media
Nanopure is suspension homogenized in water free media or water mixtures i.e. the drug suspensions in thenon-aqueous media were homogenized at 0^{o}C or even below the freezing point & hence are called deepfreeze homogenization (Debjit B, Harish G. *et al.,* 2012). The results obtained were comparable to dissocubes and hence can be used effectively for thermolabile substance at milder conditions.

Combined precipitation & homogenization
The drug is dissolved in an organic solvent & this solution is mixed with a miscible anti-solvent for precipitation. In the water-solvent mixture the solubility is low & the drug precipitates. Precipitation has also been coupled with high shear processing. The basic principles of Nanoedge are the same as that of precipitation & homogenization. A combination of these techniques results in smaller particle size & better stability in a shorter time (Yadav. G. *et al.*, 2012).

Nanojet technology
This technique is also called as „opposite stream" uses a chamber where a stream of suspension is divided into two or more parts, which colloid with each other at high pressure upto 4000 bar at high velocity of 1000m/s. The high shear force produces during the process result in particle size reduction (Naha.A, Nampoothiri M. *et al*., 2011).

Emulsification-solvent evapouration techniques
This technique involves preparing a solution of drug followed by its emulsification in another liquid that is anon-solvent for the drug. Evaporation of the solvent leads to precipitation of the drug (Shaha T, Patel D. *et al*., 2007).

Advantages
Use of specialized equipment is not necessary.
Particle size can easily be controlled by controlling the size of the emulsion droplet.
Ease of scale-up if formulation is optimized properly.

Disadvantages
Drugs that are poorly soluble in both aqueous and organic media cannot be formulated by this technique.
Safety concerns because of the use of hazardous solvents in the process.
Need for diultra filtration for purification of the drug Nanosuspension, which may render the process costly.
High amount of surfactant/stabilizer is required as compared to the production techniques described earlier.

Supercritical fluid method
Supercritical fluid technology can be used to produce nanoparticles from drug solutions(Yadav. G. *et al*., 2012). The various methods attempted are rapid expansion of supercritical solution process (RESS), supercritical anti-solvent process & precipitation with compressed anti-solvent process (PCA). The RESS involves expansion of the drug solution in supercritical fluid through a nozzle, which leads to loss of solvent power of the supercritical fluid resulting in precipitation of the drug as fine particles. In the PCA method, the drug solution is atomized into a chamber containing compressed Co2. As the solvent is removed, the solution gets supersaturation & thus precipitates as fine crystals. The supercritical antisolvent process uses a supercritical fluid in which a drug is poorly soluble & a solvent for the drug that is also miscible with the supercritical fluid. The drug solution is injected into the supercritical fluid & the solvent gets extracted by the supercritical fluid & the drug solution gets supersaturated. The drug is then precipitated as fine crystals.

Disadvantages
Use of hazardous solvents and use of high proportions of surfactants and stabilizers as compared with other techniques

Particle nucleation overgrowth due to transient high super saturation, which may also result in the development of an amorphous form or another undesired polymorph

Dry co-grinding
Nanosuspensions prepared by high pressure homogenization & media milling using pearl ball mill are wet –grinding processes (Prabhakar C & Krishna K. *et al.,* 2011). 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 & copolymers after dispersing in a liquid media has been reported. Many soluble polymers & co-polymers such as PVP, PEG, HPMC has been used. Physiochemical properties & dissolution of poorly water soluble drugs were improved by co grinding because of an improvement in the surface polarity & transformation from a crystalline to an amorphous drug. Dry co-grinding can be carried out easily & economically & can be conducted without organic solvents. The co-grinding technique can reduce particles to the submicron level & a stable amorphous solid can be obtained.

Emulsion as template
Apart from the use of emulsion as a drug delivery vehicle, they can also be used as template to produce nanosuspensions (Verma A. 2012). The use of emulsion as templates is applicable for those drugs that are soluble in either volatile organic solvent or partially water-miscible solvents. Such solvents can be used as the dispersed phase of the emulsion. There are two ways of fabricating drugs nanosuspensions by emulsification method. In the first method, an organic solvent or mixture of solvents loaded with drug is dispersed in the aqueous phase containing suitable surfactant to form an emulsion. The organic phase is then evaporated under reduced pressure so that the drug particles precipitates instantaneously to form a nanosuspension stabilized by surfactants. Since one particle is formed in each emulsion droplet, it is possible to control the particle size of the nanosuspension by controlling the size of the emulsion. Optimizing the surfactant composition increases intake of organic phase & ultimately the drug loading in the emulsion. Originally, organic solvents such as methylene chloride & chloroform were used.

Advantages
Use of specialized equipment is not necessary
Particle size can easily be controlled by controlling the size of the emulsion droplet
Ease of scale-up if formulation is optimized properly

Disadvantages
Drugs that are poorly soluble in both aqueous and organic media cannot be formulated by this technique
High amount of surfactant/stabilizer is required as compared to the production techniques described earlier

CHARACTERIZATION OF NANOSUSPENSION

Particle size & particle size distribution
The mean particle size & the width of particle size distribution are important characterization parameters as they govern the saturation solubility, dissolution velocity, physical stability & even biological performance of nanosuspensions .(Watanabe T, Ohno I. *et al.*,2002).

Crystalline state & particle morphology: The assement of the crystalline state & particle morphology together helps in understanding the polymorphic or morphological changes that a drug might undergo when subjected to nanosizing. Additionally, when nanosuspensions are prepared drug particles in an amorphous state are likely to be generated. Hence, it is essential to investigate the extent of amorphous drug nanoparticles generated during the production of nanosuspensions. The changes in the physical state of the drug particles as well as the extent of the amorphous fraction can be determined by X-ray diffraction analysis & can be supplemented by differential scanning calorimetry (Liversidge GG, Cundy KC. 1995). In order to get a actual idea of particle morphology, scanning electron microscopy is preferred.

Zeta potential: The determination of zeta potential of nanosuspension is essential as it gives an idea about the physical stability of the nanosuspension (Verma. A. 2012). The zeta potential of a nanosuspension is governed by both the stabilizer & the drug itself. In order to obtain a nonosuspension exhibiting good stability, for an electrostatically stabilized nanosuspension a minimum zeta potential of 30 mv is required whereas in the case of a combined electrostatic & steric stabilization, a minimum zeta potential of 20mV is desirable.

Ph: The pH of the nanosuspensions can be easily measured by using pH meter.

Osmolarity: Practically, osmolarity of nanosuspension can be measured by using Osmometer (Yadav.G, 2012).

Saturation solubility & Dissolution velocity: Nanosuspensions have an important advantage over other techniques, that it can increase the dissolution velocity as well as the saturation solubility. The saturation solubility of the drug in different physiological buffer as well as at different temperature should be assessed using methods described in the literature. The investigation of the dissolution velocity of nanosuspensions reflects the advantages that can be achieved over convectional formulations, especially when designing the sustained-release dosage forms based

on nanoparticulate drugs. The assessment of saturation solubility & dissolution velocity helps in determining the in *vitro* behaviour of the formulation (Arunkumar N, Deecaraman M. *et al*., 2009).

Surface Hydrophilicy: For intravenous injected nanosuspensions, additional parameters need to be determined which affect the *in vivo* fate of the drug nanoparticles. Surface hydrophilicy is considered as one of the important parameters affecting the *in vivo* organ distribution after i.v. injection. A suitable technique is hydrophobic interaction chromatography (HIC) employed to determine the surface hydrophobicity of nanoparticluate drug carriers (Jiraporn C. 2007).

APPLICATIONS OF NANOSUSPENSIONS

Oral Drug Delivery

Orally administered antibiotics reflect this problem very well. Nanosizing of such drugs can lead to a dramatic increase in their oral absorption and biovailability. The nanosuspension of Amphotericin B showed a significant improvement in its oral absorption in comparison with the convectional commercial formulation (Liversidge GG, Cundy KC. 1995).

Parenteral Drug Delivery

Intravenously administered nanosuspensions of poorly soluble drug tarazepide have been prepared to overcome the limited success achieved using convectional solubilising techniques, such as use of surfactants, cyclodextrins etc. to improve bioavailability .(Nagaraju P, Krishnachaithanya K.*et al.*,2010).

Figure 3: Nanosuspension for Parentral Drug Delivery.

Pulmonary Drug Delivery

The dispersions can be relatively high concentrated. Due to presence of many small particles instead of a few large microparticles, all aerosol droplet are likely to contain drug nanoparticles. Budesonide, a poorly water-soluble corticosteroid, has been successfully prepared as a nanosuspension for pulmonary delivery. (Prabhakar C, Krishna K, *et al.*, 2011).

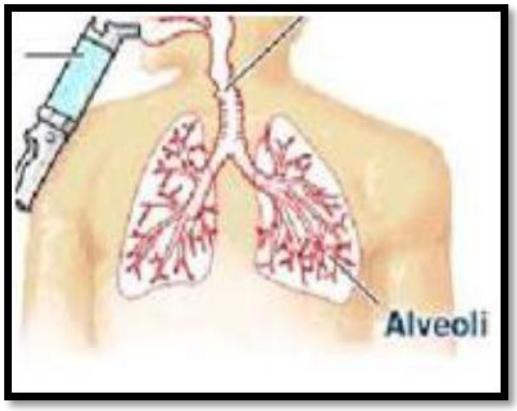

Figure 4: Nanosuspension for Pulmonary Drug Delivery.

Topical Formulations

Drug nanoparticles can be incorporated into creams & water free ointments. The nanocrystalline forms leads to an increased saturation solubility of drug in the topical dosage form, thus enhancing the diffusion of the drug into the skin (Kumar S, Vedha H. *et al*., 2010).

Ocular Drug Delivery

Nanosuspension can be boon for drug that exhibit poor solubility in lachrymal fluids. Nanosuspensions, by their inherent ability to improve the saturation solubility of drug, represented an ideal approach for ocular delivery of hydrophobic drugs & nanoparticulate nature of the drug allows its prolonged residence in the cul-desac, giving sustained release of the drug (Mehnertw, Mader K. 2000).

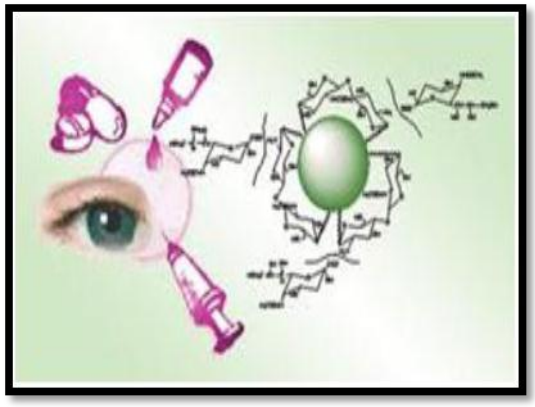

Figure 5: Nanosuspension for Occular Drug Delivery.

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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REFERENCES

1. Nayak S, Panda D, Sahoo J. Nanosuspension: A novel drug delivery system, Journal of pharmacyresearch, 2010; 3(2): 241-246.
2. Prabhakar C, Krishna K. A review on nanosuspensions in drug delivery, International journal of pharma & bio-sciences, 2011; 2(1): 549-558.
3. Shaha T, Patel D, Hirani J, Amin A. Nanosuspensions as a drug delivery systems- a comprehensive review, Drug del tech., 2007; 7: 42-53.
4. Patel M, Shaha A, Patel K. Nanosuspension: A novel approach for drug delivery system, JPSBR, 2011; 1(1): 1-10.
5. Patravale V, Date A, Kulkarni R. Nanosuspension: a promising drug delivery stratergy, J. Pharma. Pharmacol, 2004; 56: 827-840.
6. Jagdale D, Kamble V, Kadam V. Nanosuspension a novel drug delivery system, International Journal of Pharma& Bio-sciences, 2010; 1(4): 352-360.
7. Yadav G, Singh S. Nanosuspension: a promising drug delivery system, 2012; 3(5): 217-243.
8. Naha A, Nampoothiri M, Koteshwar K, Reddy M. Nanosuspension: A novel drug delivery approach, IJRAP, 2011; 2(1): 162-165.
9. Shaha T, Patel D, Hirani J, Amin A. Nanosuspensions as a drug delivery systems- a comprehensive review, Drug del tech, 2007; 7: 42-53.
10. Verma A. Nanosuspensions: advantages & disadvantages, Indian Journal of Novel Drug Delivery, 2012; 4(3): 179-188.
11. Watanabe T, Ohno I, Wakiyama N, Kusai A. Stabilization of amorphous indomethacin by cogrinding in a ternary mixture, Int.J.Pharma, 2002; 2(4): 103-111.
12. Liversidge GG, Cundy KC. Particle size reduction for improvement of oral bioavailability of hydrophobic drugs: Absolute oral bio-availability of nanocrystallinedanazol in beagle dogs, Int. Journal of Pharmacy, 1995; 125(1): 91-95.
13. Arunkumar N, Deecaraman M, Rani C. Nanosuspension technology & its applications in drug delivery, Asian journal of pharmaceutics, 2009; 3(3): 168-173.
14. Jiraporn C. Nanosuspensions technology for drug delivery, Sci& technology, 2007; 4(2): 139-153.
15. Nagaraju P, Krishnachaithanya K, Srinivas V, Padma S. Nanosuspensions: A promising drug delivery system, International Journal of Pharmaceutical Sciences & Nanotechnology, 2010; 2(3): 241-246.
16. Kumar S, Vedha H, Subramanian N, Kumar S. Novel metronidazole nanosuspension as a controlled drug delivery system for antihelmintic activity, Journal of pharmacy research, 2010; 3(10): 110-115.
17. Mehnertw Mader K. Solid lipid nanoparticles: production, characterization & applications, Adv. Drug delivery review, 2000; 47: 165-169.