Review

NANOSUSPENSION TECHNOLOGY

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ABSTRACT

Solubility is an essential factor for drug effectiveness, independent of the route of administration. Poorly soluble drugs are often a challenging task for formulators in the industry. Large proportions of newly discovered drugs are water insoluble, and therefore poorly bioavailable contributing to deserted development effort. 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 insoluble in water. Nanosuspensions are prepared by using wet mill, high pressure homogenizer, emulsion-solvent evaporation, melt emulsification method and super critical fluid techniques. 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: Nanosuspension, Solubility enhancement, bioavailability

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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 or lipophilic compounds[1].

The formulation of nano-sized particles can be implemented to all drug compounds belonging to biopharmaceutical classification system (BCS) classes II and IV to increase their solubility and hence partition into gastrointestinal barrier[2]. Micronization is used for class II drugs of (BCS), i.e. drugs having a good permeability and poor solubility[3-5]. There are many conventional methods for increasing the solubility of poorly soluble drugs, which include micronization[6], solubilisation using co-solvents[7], salt form[8], surfactant dispersions[9], precipitation technique[10-11], and oily solution. Other techniques are like liposomes[12], emulsions[13-14], microemulsion[15-16], solid dispersion[17-18] and inclusion complexation using cyclodextrins[19-21] show sensible achiever, but they lack in universal applicability to all drugs. These techniques are not applicable for those drugs which are not soluble in aqueous and organic solvents. Nanotechnology can be used to solve the problems associated with these conventional approaches for solubility and bioavailability enhancement.

Nanosuspensions are colloidal dispersions of nanosized drug particles stabilized by surfactants. They can also be defined as a biphasic system consisting of pure drug particles dispersed in an aqueous vehicle in which the diameter of the increases and the maximum plasma level is reached faster. This is one of the unique advantages that it has over other approaches for enhancing solubility.

2. PREPARATION OF NANOSUSPENSION

Mainly there are two methods for preparation of nanosuspensions. The conventional methods of precipitation (Hydrosols[22]) 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 microparticles. 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) [23,24].

2.1 Media Milling (Nanocrystal or Nanosystems)

The method is first developed and reported by Liversidge et.al. (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 impaction of the milling media with the drug resulting into breaking of microparticulate drug to nanosized particles [25, 22].

Advantages:

- Media milling is applicable to the drugs that are poorly soluble in both aqueous and organic media.
- Very dilute as well as highly concentrated nanosuspensions can be prepared by handling 1mg/ml to 400mg/ml drug quantity.
- Nanosize distribution of final nanosize products.

Disadvantages:

- Nanosuspensions contaminated with materials eroded from balls may be problematic when it is used for long therapy.
- The media milling technique is time consuming.

- Some fractions of particles are in the micrometer range.
- Scale up is not easy due to mill size and weight

2.2 High Pressure Homogenation (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 Gap. 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 valve[26].

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 pressure[27].

Advantages

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

Disadvantages

- Preprocessing like micronization of drug is required.
- High cost instruments are required that increases the cost of dosage form[28].

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 $0^{o}C$ or even the freezing point and hence called as deep freeze homogenization[29].

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 step[30].

2.5 Nanojet Technology

This technique, called opposite stream or Nanojet technology, uses a chamber where a stream of suspension is divided into two or more parts, which colloid with each other at high pressure. The high shear force produced during the process results in particle size reduction. Equipment using this principle includes the M110L and M110S microfluidizers (Microfluidics). Dearn 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

2.6. Melt Emulsification Method

In this method drug is dispersed in the aqueous solution of stabilizer and heated above the melting point of the drug and homogenized to give an emulsion. During this process, the sample holder was enwrapped with a heating tape fitted with temperature controller and the temperature of emulsion was maintained above the melting drug solution to an anti-solvent leads to sudden super saturation of the mixed solution, and generation of fine crystalline or amorphous solids. Precipitation of an amorphous material may be favored at high super saturation when the solubility of the amorphous state is exceeded.

2.7 High Pressure Homogenization

In the high pressure homogenization method, the suspension of a drug and surfactant is forced under pressure through a nanosized aperture valve of a high pressure homogenizer. The principle of this method is based on cavitation forces of drug particles in the aqueous phase. These forces are sufficiently high to convert the drug microparticles into nanoparticles. DissoCubes developed by R.H. Muller using a piston-gap-type high pressure homogenizer adopts this technology, which was recently released as a patent US 5,858,410 owned by SkyePharm plc.

Point of the drug. The emulsion was then cooled down either slowly to room temperature or on an ice-bath. The main advantage of melt emulsification technique relative to the solvent diffusion method is total avoidance of organic solvents during the production process.

2.8 Milling Techniques

2.8.1 Media Milling

Media milling is a further technique used to prepare Nanosuspensions. Nanocrystal is a patent protected technology US 5,145,684 developed by Élan Nanosystems. In this technique, 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. In the media milling process, the milling chamber is charged with the milling media, water or suitable buffer, drug and stabilizer. Then the milling media or pearls are rotated at a very high shear rate.

2.8.2 Dry Co-grinding

Recently, Nanosuspensions can be obtained by dry milling techniques. Dry co-grinding can be carried out easily and economically and can be conducted without organic solvents. The co-grinding technique can reduce particles to the submicron level and a stable amorphous solid can be obtained.

2.9 Supercritical Fluid Method

Supercritical fluid technology can be used to produce nanoparticles from drug solutions. The various methods attempted are rapid expansion of supercritical solution process (RESS), supercritical anti-solvent process and 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. The disadvantages of the above methods are 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.
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 microparticle.

3. FORMULATION CONSIDERATIONS

3.1 Stabilizer

The main function of a stabilizer is to wet the drug particles thoroughly, and to prevent ostwald's ripening and agglomeration of nanosusension in order to yield a physically stable formulation by providing steric or ionic barrier. The type and amount of stabilizer has a pronounced effect on the physical stability and in vivo behavior of nanosuspesion. Stabilizers that have been used so far are poloxomers, polysorbate, cellulosics, povidones, and lecithins. Lecithin is the stabilizer of choice if one intends to develop a parentally acceptable and autoclavable Nanosuspensions.

3.2 Co-surfactants

The choice of co-surfactant is critical when using microemulsions to formulate Nanosuspensions. Since co-surfactants can greatly influence phase behaviour, the effect of co-surfactant on uptake of the internal phase for selected microemulsion 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.

3.3 Organic Solvent

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 preferred in the formulation over the conventional hazardous solvents, such as dichloromethane.

3.4 Other Additives

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

4. PROPERTIES OF NANOSUSPENSIONS

4.1 Physical Long-Term Stability.

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 naosusphensions are cellulosics, poloxamer, polysorbates, lecithin, polyoleate and povidones. Lecithin may be preferred in developing parenteral nanosuspensions.

4.2 Internal Structure of Nanosuspensions

The high-energy input during disintegration process causes structural changes inside the drug particles. When the drug particles are exposed to high-pressure homogenisation particles are transformed from crystalline state to amorphous state. The change in state depends upon the hardness of drug, number of homogenisation cycles chemical nature of drug and power density applied by homogeniser

4.3 Adhesiveness

There is a distinct increase in adhesiveness of ultra fine powders compared to coarse powders. This adhesiveness of small drug nanoparticles can be exploited for improved oral delivery of poorly soluble drugs. Improved bioavailability, improved dose proportionality, reduced fed / fasted variability, reduced inter- subject variability and enhanced absorbtion rate (both human and animal data) are some of the important benchmarking effects of a drug formulated as nanoparticles in oral administration. These data have been acquired in vivo in animals but also in humans as reported by the company NanoSystems. A drastically remarkable report is that of the increase in bioavailability for danazole from % (as macrosuspension) to 82% (as nanosuspension).

4.4 Crystalline State and Morphology

A potential change in the crystalline structure of nanosuspensions saying increasing the amorphous fraction in the particle or even creating completely amorphous particles is a characteristic of consideration. The application of high pressures during the production of nanosuspensions was found to promote the amorphous state.

5. EVALUATION OF NANOSUSPENSIONS

Nanosuspensions evaluation is done in similar ways as those used for conventional suspensions such as appearance, color, odor, assay, related impurities, etc. Apart from the aforementioned parameters, the nanosuspensions should be evaluated for their particle size, zeta potential, crystalline status, dissolution studies and *in vivo* studies.

5.1 In-Vitro Evaluations.

- Particle size and size distribution.
- Particle charge (Zeta Potential).
- Dissolution velocity and saturation solubility
- Crystalline state and morphology.

5.1.1 Particle Size and Size Distribution

Particle Size and 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 0.05-80 µm. 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 5 µm, considering that the smallest size of the capillaries is 5-6 µm and hence a higher particle size can lead to capillary blockade and embolism.

5.1.2 Particle Charge (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.

5.1.3 Dissolution Velocity and Saturation Solubility.

Nanosuspensions have an important advantage over 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. An increase in solubility that occurs with relatively low particle size reduction may be mainly due to a change in the surface tension leading to increased saturation solubility. Muller explained that the energy introduced during the particle size reduction process leads to an increase in the surface tension and an associated increase in the dissolution pressure.

6. APPLICATION OF NANOSUSPENSIONS

6.1 Bioavailability Enhancement

The poor oral bioavailability of the drug may be due to poor solubility, poor permeability, or poor stability in the gastrointestinal tract (GIT). Nanosuspensions resolve the problem of poor bioavailability by solving the twin problems of poor solubility and poor permeability across the membrane. Bioavailability of poorly soluble oleanolic acid, a hepatoprotective agent, was improved using a nanosuspension formulation. The therapeutic effect was significantly

enhanced, which indicates higher bioavailability.
This was due to the faster dissolution (90% in 20 min) of the lyophilized nanosuspension powder when compared with the dissolution from a coarse powder (15% in 20 min)

6.2 Ocular Drug Delivery

Nanosuspensions can prove to be a boon for drugs that exhibit poor solubility in lachrymal fluids. The protective barriers of the eye make drug delivery difficult without tissue damage. Poor drug absorption and penetration of drugs to intraocular tissues limit the delivery of drugs. Use of nanoparticles and nanosuspensions for drug delivery to the intraocular tissues is being developed. One example is cross-linked polymer nanosuspensions of dexamethasone, which show enhanced anti-inflammatory activity in a model of rabbit eye irritation.

6.3 Pulmonary Drug Delivery

Aqueous nanosuspensions can be nebulized using mechanical or ultrasonic nebulizers 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 pulmonary diseases.

6.4 Targeted drug delivery

Nanosuspensions are suitable for targeting particular organs because of their surface properties. Along with this, it is easy to alter *in vivo* behavior by changing the stabilizer. The drug will be taken up by the mononuclear phagocytic system which allows region-specific delivery. This can be used for targeting antifungal, antimycobacterial, or antileishmanial drugs to macrophages if the pathogens persist intracellularly.

7. 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 administerd 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.

8. REFERENCES

1. Elaine Merisko-Liversidge, Gary G. Liversidge, Eugene R.Cooper. Nanosizing: a formulation approach for poorly water-soluble compounds. Eur.J.Pharm.Sci.2003; 18:113-120.
2. Dubey R. Impact of nanosuspension technology on drug discovery and development. Drug Deliv Technol 2006; 6:65–7.
3. Amidon GL, Lennerna¨s H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm Res 1995; 12:413–420.
4. Yu LX, Amidon GL, Polli JE, Zhao H, Mehta MU, Conner DP, Shah VP, Lesko LJ, Chen ML, Lee VH, Hussain AS. Biopharmaceutics classification system: the scientific basis for biowaiver Extensions. Pharm Res 2002; 19:921–925.
5. Lennerna¨s H, Abrahamsson B. The use of biopharmaceutic classification of drugs in drug discovery and development: current status and future extension. J Pharm Pharmacol 2005; 57:273–285.
6. Varshosaz J, Talari R, Mostafavi SA, Nokhodchi A. Dissolution enhancement of gliclazide using in situ micronization by solvent change method. Powder Technology 2008; 187:222– 230.
7. Pahala S, Joan MA, Samuel HY. Solubili-

zation of rapamycin. Int J Pharm 2001; 213: 25–29.
8. Abu Serajuddin TM. Salt formation to improve drug solubility. Advanced Drug Delivery Reviews 2007; 59:603–616.
9. Wong SM, Kellaway IW, Murdan S. Enhancement of the dissolution rate and oral absorption of a poorly water soluble drug by formation of surfactant□containing microparticles. Int J Pharm 2006;317 :61-68.
10. Marazban S, Judith B, Xiaoxia C, Steve S, Robert O, Williams III, Keith PJ. Enhanced drug dissolution using evaporative precipitationintoaqueoussolution.IntJPharm2002;243:17-31.
11. True LR, Ian BG, James EH, Kevin LF, Clindy AC, Chritoper JT. Development and characterization of a scalable controlled precipitation process to enhance the dissolution of poorly soluble drugs. Pharm Res 2004;21(11) :2048-57.
12. Riaz M. Stability and uses of liposomes. Pak Pharm Sci 1995;8(2) :69-79.
13. Floyd AG. Top ten considerations in the development of parenteral Emulsions. Pharm Sci Tech 1999;4 :134–143.
14. Nakano M. Places of emulsions in drug delivery. Adv Drug Deliv Rev 2000;45 :1–4.
15. Jadhav KR,Shaikh IM,Ambade KW, Kadam VJ. Applications of microemulsion based drug delivery system. Cur Dr del 2006;3(3) :267-273.
16. Lawrence MJ, Rees GD. Microemulsion-based media as novel drug delivery systems. Adv Drug Deliv Rev 2000;45 :89–121.
17. Leuner C, Dressman J. Improving drug solubility for oral delivery using solid dispersions. Eur J Pharm Biopharm 2000;50(1) :47-60.
18. Hemant NJ, Ravindra WT, Martha D, Vaishali PS, Mohammed J, Mohinder SB, Sailesh AV, Abu Serajuddin TM. Bioavailability enhancement of a poorly water-soluble drug by solid dispersion in polyethylene glycol–polysorbate 80 mixture: Int J Pharm 2004;269 :251-258.
19. Stella VJ, Rajewski RA. Cyclodextrins: their future in drug formulation and delivery. Pharm Res 1997;14:556–567.
20. Loftsson T, Brewster M. Pharmaceutical applications of cyclodextrins. J Pharm Sci 1996;85 :1017–1025.
21. Marcela L, Marı´a M. de Bertorello, Marcela L. Solubilization of naphthoquinones by complexation with hydroxypropyl-b- cyclodextrin. Int J Pharm 1997;159 :13–18
22. RH Müller, C Jacobs and O Kayer. Nanosuspensions for the formulation of poorly soluble drugs. In: F Nielloud, G Marti-Mestres (ed). Pharmaceutical emulsion suspension. New York, Marcel Dekker, 2000: 383-407.
23. Chowdary K.P.R. and Madhavi B.L.R.,Novel drug delivery technologies for insoluble drugs. Ind.Drugs.2005; 42(9): 557-563.
24. Cornelia M. Keck,, Rainer H. Muller. Drug nanocrystals of poorly soluble drugs Produced by high-pressure homogenisation. Eur. J. Pharm.Biopharm.2006; 62: 3–16
25. V.B.Patravale, Abhijit A.Date and R.M.Kulkarni. Nanosuspensions: a promising drug delivery strategy. J.Pharm.Pharcol.2004; 56: 827-840
26. Kayser O. Nanosuspensions for the formulation of aphidicol into improve drug targeting effects against Leishmania infected macrophages. Int. J. Pharm. 196, 2000, 253–56.
27. Krause KP, Kayser O, Mader K, Gust R, Muller RH. Heavy metal intamination of nanosuspensions produced by high pressure homogenizations. Int J. Pharm. 196, 2000, 169–72
28. Moschwitzer J, Achleitner G, Pomper H, Muller RH.Development of an intraveneously injectable chemically stable aqueous omeprazole formulation using nanosuspensions. Eur. J. Pharm. Biopharm. 58, 2004, 615-19.
29. Nanopure RM. Pure drug nanoparticles for the formulation of poorly soluble drug. New Drug. 54, 2001, 62-8.
30. Barret ER. Nanosuspensions in drug delivery. Nat. rev. 3, 2004, 785-96.

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