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Nanosuspension: Way to Enhance the Bioavailibility of Poorly Soluble Drug

Vijay Kumar Singh*, Dinesh Chandra, Preeti Singh, Shaunmdarya kumar, Ambikeshwar Pratap Singh,
Department of Pharmaceutics,
Kamla Nehru Institute of Management and Technology, Faridipur, Sultanpur, India
*E-mail: saundarya.kumar07@gmail.com
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Abstract: Nano suspensions are promising candidates that can be used for enhancing the dissolution of poorly water soluble drugs. Nan suspension is emerging as a preferred approach to address challenges involved in the delivery of BCS class-II compounds (poorly soluble and highly permeable). The development of nanoparticle formulations for BCS class-II drugs such as Itraconazole, Fenofibrate, Candesartan cilexetil would result in enhanced bioavailability, reduced systemic variability and more convenient dosing regimen. Nanosuspensions consist of the pure poorly water-soluble drug without any matrix material suspended in dispersion. The reduction of drug particles into the sub-micron range leads to a significant increase in the dissolution rate and therefore enhances bioavailability. The review article includes the methods of preparation with their advantages and disadvantages, characterization and evaluation parameters and pharmaceutical applications. 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 to enhance dissolution rate.
Key words: Bioavailability & solubility enhancement, nanotechnology

Introduction

In recent years, there has been a considerable interest in the development of novel drug delivery systems using particulate delivery systems like Nanoparticles. Nanoparticles represent a promising drug delivery system of controlled and targeted release. In this context, nanosuspensions will be effective in increasing the solubility, bioavailability of poorly soluble drugs. Nan suspensions are the biphasic colloidal dispersions of man-sized drug particles stabilized by surfactants. Size of the drug particles was less than 1mm. Average particle size ranges from 200-600nm.[1]Nanosuspensions differ from Nanoparticles. Nanoparticles are commonly polymeric colloidal carriers of drugs whereas solid lipid Nanoparticles are lipid 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.[4] Nan suspension formulation approach is most suitable for the compounds with high log P value, high melting point and high dose.[2] Solubility is one of the important parameter to achieve desired conc. of drug in systemic circulation for pharmacological response to be shown. Drug efficacy can be severely limited by poor aqueous solubility and some drugs also show side effects due to their poor solubility. A number of methodologies can be adapted to improve solubilization of poor water soluble drug and further to improve its bioavailability. [3]micron = 10^{-6}m= 10^{-4}cm = 10^{-3}mm. Nanotechnology can be used to resolve the problems associated with these conventional approaches for solubility and bioavailability enhancement. Nanotechnology is defined as the science and engineering carried out in the nanoscale that is 10^{-9} meters[15]. The drug micro particles/micronized drug powder is transferred to drug Nanoparticles by techniques like Bottom Up Technology (precipitation) and Top Down Technology[15] or disintegration methods. Nano is a Greek word, which means 'dwarf'. Here Niño means it is the factor of 10^{-9} or one billionth. Some comparisons of nanoscale are given below,

0.1 nm = Diameter of one Hydrogen atom
2.5 nm = Width of a DNA molecule[17].
1micron = 1000nm.
1nm = 10^{-9}m= 10^{-7}cm = 10^{-6}mm.

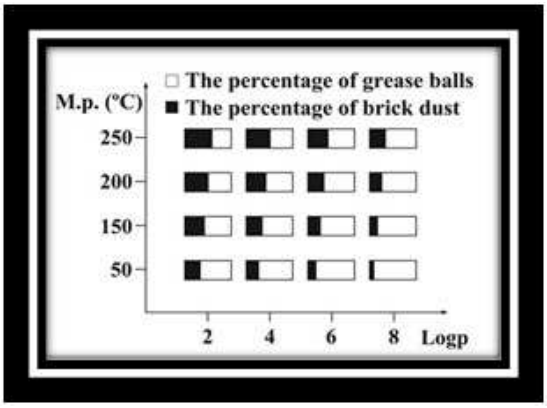

Fig. (1). The relationship between drug classification and the log P/melting point (modified after Wassail, et. al.

For example,78% of compounds with a C log of 6 and low melting point are grease ball, whereas 52% of compounds with melting point of 250 and a C log P of 2 belong to brick dust[6] (Fig. **1**) Grease ball molecules have easily passed through the drug development process pipeline to reach the market by adopting appropriate formulation strategies, By contrast brick dust molecules are poorly soluble not only in water but also in oils, the above formulation strategies do not work effectively due to low encapsulation efficiency and low loading.[7] For these reasons, Muller *et al*.[8,9] firstly developed nano suspensions,a sub-micro colloidal dispersion system, to overcome the above limitations in 1995. As for this system, pure drug particles ranging in size from 10-1000 nm[10], were stabilized by surfactants, polymeric materials. Nan suspensions can successfully formulate the brick dust molecules for improved dissolution and good absorption.[11] secondly, the high drug loading can be achieved as a drug exists in the form of pure solids, and can significantly reduce the administration volume of high dose.[11]Drug particle size reduction leads to an increase in surface area and consequently in the rate of dissolution as described by the Nernst–Brunner and Levich modification of the Noyes–Whitney equation[2].In addition, an increase in saturation solubility is postulated by particle size reduction due to an increased dissolution pressure explained by the Ostwald–Freundlich equation[2].The stability of the particles obtained in the nanosuspension is attributed to their uniform particle size which is created by various manufacturing processes. The absence of particles with large differences in their size in nano suspension prevents existence of different saturation solubility's and concentration gradients, consequently preventing the Oswald ripening effect. Molecules diffuse from the higher concentration area around small particles which have higher saturation solubility to an area around larger particle possessing low drug concentration.[17]

2. Requirement of Nano suspension Technology:

Most of drug coming from high screening are poorly water soluble drug. Formulation of poorly soluble drug is always being a challenge.[4] One of the major problem is associated with them is low bioavailability due to less absorption.[3] These problem can be overcome by using nano suspension. Nan suspension formulation approach is most suitable for the compounds with high log P value, high melting point and high dose.[15] High drug loading can be achieved as a drug exists in the form of pure solids, and can significantly reduce the administration volume of high dose[11]; Nano suspensions can increase the physical and chemical stability of drugs as they are actually in the solid state[12,13]; finally, nano suspensions can provide the passive targeting

3. Advantages of Nano suspensions

Nan suspension technology increases the dissolution velocity and saturation solubility of the drug: According to the **Nernst–Brunner and Levich modification of the Noyes Whitney dissolution model equation** (Dressman et al 1998; Horter & Dressman 2001), the dissolution velocity of the nanosuspension increases due to a dramatic increase in the surface area of the drug particles from microns to particles of nanometer size:

dX/dt¼((D_A)/h) (Cs_X/V)

Where dX/dt is the dissolution velocity, D is the diffusion coefficient, A is the surface area of the particle, h is the diffusional distance, Cs is the saturation solubility of the drug, X is the concentration in the surrounding liquid and,V is the volume of the dissolution medium. In addition, as described by the Prandtl equation, the decrease in the diffusional distance with increasing curvature of ultrafine nano-sized particles contributes to the increase in the dissolution velocity.The Prandtl equation (Mosharraf & Nystro¨m 1995) describes the hydrodynamic boundary layer thickness or diffusional distance (hH) for flow passing a flat surface:

hH¼k (L1/2/V1/2)

Where L is the length of the surface in the direction of flow, k denotes a constant, V is the relative velocity of the flowing liquid against a flat surface and hH is the hydrodynamic boundary layer thickness. [17]

3.1 Nano suspension Provide passive targeting

Most of drug have fail to achieve favorable outcomes because they do not have the ability to reach the target site of action. A significant amount of the administrated drug is distributed over the normal tissues or organs that are not involved in the pathological process, often leading to severe side effects. An effective approach to overcome this critical issue to development of targeted drug delivery systems.

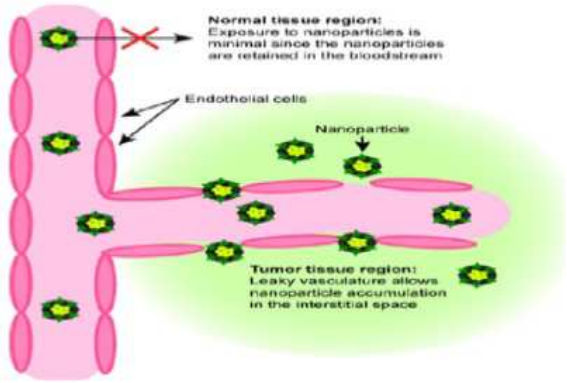

Fig: 2 Nanosuspension provide passive targeting which enhance permeability and availability"

3.2. 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 homogenizer.[14]

3.4. Ease of manufacture and scale-up

Unlike nanoparticulate carriers such as polymeric nanoparticles, which were investigated earlier, nanosuspensions are easy to manufacture. The production processes described earlier are easily scaled up for commercial production.[17]

3.5. Nanosuspension provide Versatility

The flexibility offered in the modification of surface properties and particle size, and ease of post-production processing of nanosuspensions enables them to be incorporated in various dosage forms, such as tablets, pellets, suppositories and hydrogels, for various routes of administration, thus proving their versatility.[17]

3.6. Nanosuspension enhance Bioavailability[15]

Drug with poor solubility, poor permeability or poor solubility in gastrointestinal tract will leads to poor oral bioavailability. Nanosuspension resolves the problem of poor bioavailability by solving the problem of poor solubility, and poor permeability across the membranes.

3.7. Nanosuspension provide Long-term physical stability:

Dispersed systems show physical instability due to Ostwald ripening which is responsible for crystal growth to form microparticles. Ostwald ripening is caused due to the difference in dissolution velocity/ saturation solubility of small and large particles. In nanosuspensions all particles are of uniform size hence there is little difference between saturation solubility of drug particles because of that Ostwald ripening is totally absent in nanosuspension which is also responsible for long-term physical stability of nanosuspensions[14]

4. Formulation Consideration:

4.1. Stabilizer: The type and amount of stabilizer has a pronounced effect on the physical stability and in-vivo behaviour of nanosuspensions[13] 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 (Rawlins 1982; Mu¨ ller & Bo¨hm 1998) and agglomeration of nanosuspensions in order to yield a physically stable formulation by providing steric or ionic barriers.[17]The drug-to-stabilizer ratio in the formulation may vary from 1:20 to 20:1 and should be investigated for a specific case[18].example lecithine, PVPK30,PVA, SLS.

4.2. Organic solvents :-The pharmaceutical acceptance & less suitable hazardous water miscible solvents, such as ethanol & isopropanol and partially water miscible solvents, such as ethyl acetate, ethlyl formate,butyl lactate, triacetin, propylene carbonate & benzyl alcohol are preferred in the formulation of nanosuspensions[9].

4.3. Cosurfactantns :- 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[17]. 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. [9].

4.4. 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[17].Buffers (acetate, phosphate), cryprotectants (sucrose as sugar), osmogent (mannitol, sorbitol)[9]

5. Method of Formulation of Nanosuspension:

5.1.1. Bottom Up Technology The conventional methods of precipitation (Hydrosols) are called Bottom Up technology. Using a precipitation technique, the drug is dissolved in an organic solvent and this solution is mixed with a miscible antisolvent. In the water-solvent mixture the solubility is low and the drug precipitates[14].

The limitation of this precipitation technique is that the drug needs to be soluble in atleast one solvent and this solvent needs to be miscible with nonsolvent.[20]

5.1.2. Top Down Technology '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 (Disso cubes), High Pressure Homogenization in nonaqueous media (Nanopure) and combination of Precipitation and High-Pressure Homogenization (Nanoedege) . Few other techniques used for preparing nanosuspensions are emulsion as templates, microemulsion as templates etc. Figure 2 showing the methods of preparation of nanosuspensions by various methods[14.]

5.1.3. Media milling (Nano Crystals)

This patent-protected technology was developed by Liversidge et al (1992). Formerly,the technology was owned by the company NanoSystems but recently it has been acquired by Elan Drug Delivery. In this method the nanosuspensions are produced using high-shear media mills or pearl mills[20]. The media mill consists of a milling chamber, a milling shaft and a recirculationchamber (Figure 1). 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[14.]

5.1.4. Principle

The high energy and shear forces generated asa result of the impaction of the milling media with the drug provide the energy input to break the microparticulate drug into nano-sized particles. The milling medium is composed of glass, zirconium oxide or highly cross-linked polystyrene resin. The process can be performed in either batch or recirculation mode. In batch mode, the time required to obtain dispersions with unimodal distribution profiles and mean diameters<200nm is 30–60 min.[17].

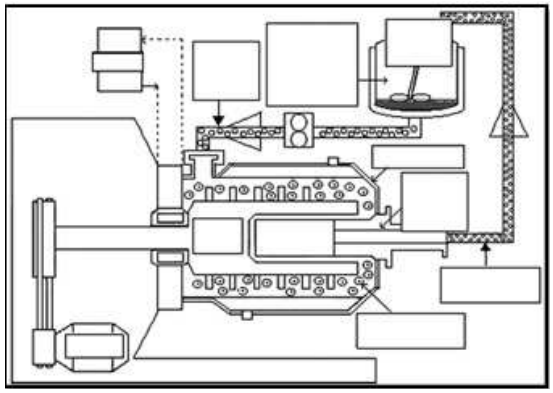

Figure: 3 Schematic representation of the media milling process.

5.1.5. Advantages

- Drugs that are poorly soluble in both aqueous and organic media can be easily formulated into nanosuspensions[14].
- Ease of scale-up and little batch-to-batch variation.
- Narrow size distribution of the final nano-sized product.

5.1.6. Disadvantages

- The major concern is the generation of residues of milling media, which may be introduced in the final

- product as a result of erosion (Buchmann et al 1996;
- Mu¨ ller & Bo¨hm 1998)[17].
- General applicability to most drugs[20]
- Useful for formation of very dilute as well as highly concen-trate nanosuspension[20]
- Simple technique
- Aseptic production possible
- Low risk of product contamination.

5.2. High pressure homogenization:

R.H.Muller developed Dissocubes technology in 1999. The instrument can be operated at pressure varying from 100 –1500 bars (2800–21300psi) and up to 2000 bars with volume capacity of 40ml (for laboratory scale)[20].High pressure homogenization has been used to prepare nano suspension of many poorly water soluble drugs. 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[17].

Different methods developed based on this principle for preparation of nano suspensions are Dissocubes, Nanopure, Nanoedge, Nanojet technology[18].

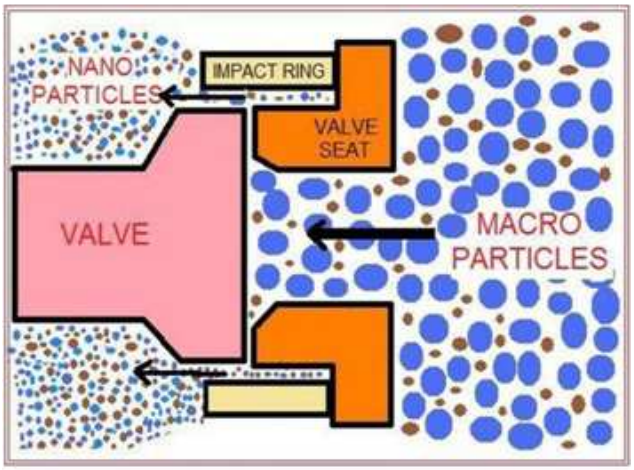

Figure: 4 Schematic representation of the high-pressure homogenization process[18].

5.2.1. Principle

Based on cavitation in the aqueous phase. The particles cavitations forces are sufficiently high to convert the drug micro particles into nano particles. The concern with this method is the need for small sample particles before loading and the fact that many cycles of homogenization are required[14]. Figure: 4 Schematic representation of the high-pressure homogenization process[18].

5.2.2. Advantages

- Useful for formation of very dilute as well as highly concen-trate nanosuspension [20]
- Aseptic production possible
- Low risk of product contamination
- Drugs that are poorly soluble in both aqueous and organic media can be easily formulated into nanosuspensions[17].
- Ease of scale-up and little batch-to-batch variation (Grau et al 2000).
- Narrow size distribution of the nanoparticulate drug present in the final product (Mu¨ ller & Bo¨hm 1998).
- Allows aseptic production of nanosuspensions for parenteral Administration$_{15}$.
- Flexibility in handling the drug quantity, ranging from 1 to 400mgmL_1, thus enabling formulation of very

5.2.3. Disadvantages

- Prerequisite of micronized drug particles.
- Prerequisite of suspension formation using high-speed mixers before subjecting it to homogenization.

5. 3. Homogenization in Nonaqueous Media (Nanopure)

Nanopure is suspensions homogenized in water-free media or water mixtures[18]. The drugs that are chemically labile can be processed in such nonaqueous media or water miscible liquids like polyethyleneglycol-400, PEG 1000 etc. The homogenization can be done at room temperature, 0o C and below freezing point (-20oC). Various steroidal drugs like 17 Destradiol Hemihydrates, Hydrocortisone and Diclofenac sodium were formulated with this Method[61].

5. 4. Combined Precipitation and Homogenization (Nanoedege)

The precipitated drug nanoparticles have a tendency to continue crystal growth to the size of microcrystals. They need to be processed with high-energy forces (Homogenization). So the precipitated particle suspension is subsequently homogenized which preserve the particle size obtained after the precipitation step[14].The Nanoedge technology by the company Baxter covers a combination of precipitation and subsequent application of high energy shear forces,highpressure homogenization with piston homogenizers NANOEDGE® process is particularly suitable for drugs that are soluble in non aqueous media possessing low toxicity, such as Nmethyl- 2-pyrrolidinone.[19]

5. 5. Homogenization in Water (Dissocubes)

Muller developed Dissocubes technology in 1999. The instrument can be operated at pressure varying from 100 – 1500 bars and up to 2000 bars with volume capacity of 40ml . For preparation of nano-suspension, we have to start with the micronized drug particle size less than 25µm to prevent blocking of homogenization gap[20].

Depending on the homogenization temperature and the dispersion media, there is a difference between the Dissocubes® technology and the Nanopure® technology.Dispersion medium of the suspensions was water.[24].

Due to the reduction in diameter from the large bore cylinder (e.g. 3 cm) to the homogenization gap, the dynamic pressure (streaming velocity) increases and simultaneously decreases the static pressure on the liquid. The liquid starts boiling, and gas bubbles occur which subsequently implode, when the suspension leaves the gap and is again under normal pressure (cavitation). Gas bubble formation, implosion lead to shock waves which cause particle diminution.[25]Pistongap homogenizer which can be used for the production of nanosuspensions are e.g. from the companies APV Gaulin, Avestin or Niro Soavi.[27-29].The disadvantages of this method is hydrolysis of water sensitive drugs can occur, as well as problems during drying steps.For these reasons, the Disso cubes technology is particularly suitable if the resulting nanosuspension is directly used without modifications, such as drying steps.[21]

5.6.Nanojet technology

In this technique the precipitated suspension is further homogenized to get smaller particle size and to avoid crystal growth is performed in water using water miscible solvent,as methanol, ethanol, and isopropanol. It is desired to remove the solvent completely by including evaporation step to provide a solvent free modified starting material followed by high pressurehomogenization.[19]

5.6.1. Emulsions as templates Apart from the use of emulsions as a drug delivery vehicle,they can also be used as templates to produce nanosuspensions .The use of emulsions as templates is applicable for those drugs that are soluble in either volatile organic solvent or partially water-miscible solvent[17].

5.6.2. Principle

An organic solvent or mixture of solvents loaded with the drug is dispersed in the aqueous phase containing suitable surfactants to form an emulsion[18].The organic phase is then evaporated under reduced pressure so that the drug particles precipitate 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.[20.]

5.6.3. 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.

5.6.4. 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 diultrafiltration 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.
- The production of drug nanosuspensions from emulsion templates has been successfully applied to the poorly

5.7. Microemulsions as templates

Microemulsions are thermodynamically stable and isotropically clear dispersions of two immiscible liquids, such as oil and water, stabilized by an interfacial film of surfactant and co-surfactant (Eccleston 1992).[17].

5.7.1. Principle

The drug can be either loaded in the internal phase or pre-formed microemulsions can be saturated with the drug by intimate mixing.The suitable dilution of the microemulsion yields the drug nanosuspension by the mechanism described earlier. [17]. If all the ingredients that are used for the production of the nanosuspension are present in a concentration acceptable for the desired route of administration, then simple centrifugation or ultracentrifugation is sufficient to separate the nanosuspension[18].

5.7.2. Advantages

- High drug solubilization, long shelf-life and ease of manufacture, make them an ideal drug delivery vehicle.

- The advantages and disadvantages are the same as for emulsion templates. The only added advantage is the need for less energy input for the production of nanosuspensions by virtue of microemulsions.

5.7.3. Supercritical fluid method

The organic solvents used in the preparation of conventional methods as solvent extraction evaporation, solvent diffusion and organic phase separation methods are hazardous to environment and physiological systems. To rectify the problem occurred through the conventional method supercritical fluid technology has been investigated for the preparation of biodegradable micro and nanoparticles, because supercritical fluids are environmentally safe. The most common techniques using supercritical fluids are supercritical anti-solvent (SAS), precipitation with compressed anti-solvent process (PCS) and rapid expansion of supercritical solution (RESS). The process of SAS employs a liquid solvent, e.g. methanol, which is completely miscible with the
supercritical fluid (SC CO2), to dissolve the solute to be micronized; at the process condition, because the solute is insoluble in the supercritical fluid, the extract of the liquid solvent by supercritical fluid leads to the instantaneous precipitation of the solute, resulting in the formation of nanoparticles. Dexamethasone49 phosphate drug nanoparticles (for microencapsulation) and griseofulvin[50] nanoparticles were prepared by using SAS method. RESS differs from the SAS process in that its solute is dissolved in a supercritical fluid and then the solution is rapidly expanded through a small nozzle into a region lower pressure, thus the solvent power of supercritical fluid dramatically decreases and solute eventually precipitates.

5.8. Dry Co-Grinding

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 and copolymers after dispersing in a liquid media has been reported.[14] Physicochemical properties and dissolution of poorly water soluble drugs were improved by co-grinding because of an improvement in the surface polarity and transformation from a crystalline to an amorphous drug .[15]. Many soluble polymers and co-polymers such as PVP, polyethylene glycol (PEG), hydroxypropyl methylcellulose (HPMC) and cyclodextrin derivatives have been used. Physicochemical properties and dissolution of poorly water soluble drugs were improved by co-grinding because of an improvement in the surface polarity and transformation from a crystalline to an amorphous drug[14]

6. Characterization of Nanosuspensions

The essential characterization parameters for nanosuspensions are as follows.

6.1. Mean particle size and particle size distribution.

The mean particle size and the width of particle size distribution are important characterization parameters as they govern the saturation solubility, dissolution velocity, physical stability and even biological performance of nanosuspensions. It has been indicated by Mu¨ ller & Peters (1998) that saturation solubility and dissolution velocity show considerable variation with the changing particle size of the drug. [15]

6.2. Photon correlation spectroscopy: (PCS) (Mu¨ ller & Mu¨ ller 1984) can be used for rapid and accurate determination of the mean particle diameter of nanosuspensions. Moreover, PCS can even be used for determining the width of the particle size distribution (polydispersity index, PI). The PI is an important parameter that governs the physical stability of nanosuspensions and should be as low as possible for the long-term stability of nanosuspensions. A PI value of 0.1–0.25 indicates a fairly narrow size distribution whereas a PI value greater than 0.5 indicates a very broad distribution. No logarithmic normal distribution can definitely be attributed to such a high PI value. Although PCS is a versatile technique, because of its low measuring range (3nm to 3 _m) it becomes difficult to determine the possibility of contamination of the nanosuspension by micro particulate drugs (having particle size greater than 3 _m). [16]

6.3. Laser diffractometry (LD): Hence, in addition to PCS analysis, analysis of nanosuspensions should be carried out in order to detect as well as quantify the drug micro particles that might have been generated during the production process. Laser diffractometry yields a volume size distribution and can be used to measure particles ranging from 0.05–80 _m and in certain instruments particle sizes up to 2000 _m can be measured. The typical LD characterization includes determination of diameter 50% LD (50) and diameter 99% LD (99) values, which indicate that either 50 or 99% of the particles are below the indicated size. The LD analysis becomes critical for nanosuspensions that are meant for parenteral and pulmonary delivery. Even if the nanosuspension contains a small number of particles greater than 5–6 _m, there could be a possibility of capillary blockade or emboli formation, as the size of the smallest blood capillary is 5–6 _m. It should be noted that the particle size data of a nanosuspension obtained by LD and PCS analysis are not identical as LD data are volume based and the PCS mean diameter is the light intensity weighted size. The PCS mean diameter and the 50 or 99% diameter from the LD analysis are likely to differ, with LD data generally exhibiting higher values. The nanosuspensions can be suitably diluted with deionized water before carrying out PCS or LD analysis. For nanosuspensions that are intended for intravenous administration, particle size analysis by the Coulter counter technique is essential in addition to PCS and LDanalysis. Since the Coulter counter gives the absolute number of particles per volume unit for the different size classes, it is a more

efficient and appropriate technique than LD analysis for quantifying the contamination of nanosuspensions by microparticulate drugs. [16-18]

6.4. Crystalline state and particle morphology.

The assessment of the crystalline state and particle morphology together helps in understanding the polymorphic or morphological changes that a drug might undergo when subjected to nan osizing. Additionally, when nano suspensions are prepared drug particles in an amorphous state are likely to be generated. Hence, it is essential to investigate the extent of amorphous drug nano particles generated during the production of nano suspensions. 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 (Mu¨ ller & Bo¨hm 1998; Mu¨ ller & Grau 1998) and can be supplemented by differential scanning calorimetry (Shanthakumar et al 2004). In order to get an actual idea of particle morphology, scanning electron microscopy is preferred (Mu¨ ller & Bo¨hm 1998). [20]

6.5. Particle charge (zeta potential).

The determination of the zeta potential of a nano suspension is essential as it gives an idea about the physical stability of the nano suspension. The zeta potential of a nano suspension is governed by both the stabilizer and the drug itself. In order to obtain a nano suspension exhibiting good stability, for an electrostatically stabilized nano suspension a minimum zeta potential of _30mV is required whereas in the case of a combined electrostatic and steric stabilization, a minimum zeta potential of _20mV is desirable (Mu¨ ller & Jacobs 2002b). [20-21]

6.6. Saturation solubility and dissolution velocity.

The determination of the saturation solubility and dissolution velocity is very important as these two parameters together help to anticipate any change in the in-vivo performance (blood profiles, plasma peaks and bioavailability) of the drug. As nanosuspensions are known to improve the saturation solubility of the drug, the determination of the saturation solubility rather than an increase in saturation solubility remains an important investigational parameter. The saturation solubility of the drug in different physiological buffers as well as at different temperatures 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 conventional formulations, especially when designing the sustained-release dosage forms based on nanoparticulate drugs. The dissolution velocity of drug nanosuspensions in various physiological buffers should be determined according to methods reported in the pharmacopoeia. [22,24]

6.7. 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

7. Application of Nanosuspension in Drug Delivery

7. 1. Parenteral drug delivery

To fulfill the distinctly higher regulatory hurdles, the drug nanocrystals need to be produced in an aseptic process. Alternatively, nanosuspensions can be sterilized by autoclaving or alternatively by gamma irradiation as well as sterile filtration [33-34]. IV administration of omeprazole nanosuspension is suitable in order to protect it from chemical degradation of orally administered omeprazole[45]. The bioavailability of poorly soluble drugtarazepide is increased in the nanosuspension form than the conventional solubilization techniques such as surfactants,cyclodextrins etc[46]. Potential benefit:Tissue targeting, Rapid dissolution, Longer duration of retention in systemic circulation.[18]

7. 2. Pulmonary Drug Delivery

The drug nanosuspension can benebulized using commercially available nebulizers. Disposition in the lungs can be controlled via the size distribution of the generated aerosol droplets. drug nanocrystals show an increased mucoadhesiveness, leading to a prolonged residence time at the mucosal surface of the lung [35]. Hernandez-Trejo and cowotkers formulate physically stable nanosuspensions were formulated to deliver bupravaquone at the site of lung infection using nebulisation [37].

7. 3. Ophthalmic Drug Delivery:

Nanosuspension attains saturation solubility in the lachrymal fluid, representing an ideal approach for the ocular delivery of the hydrophobic drugs. The nanosized drug particles had shown a prolonged residual time in cul-de-sac, giving sustained release of drug.[38]. Higher bioavailability,Less irritation,More consistent dosing[18]

7. 4. oral drug delivery:potential benefit : Rapid dissolution and High bioavailability, Reduced fed/fasted ratio.[18]

7.5. Subcutaneous and intramuscular: Higher bioavailability, Rapid onset,Reduced tissue irritation.[18]

7. 5. Target Drug 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[39].Nanosuspensions afford a means of administrating poorly soluble drugs to brain with decreased side effects. Example is successful targeting of the peptide Dalargin to the brain by employing surface modified polyisobutyl cyanoacrylate nanoparticles[43].

7. 6. Topical Formulations:

Drug nanoparticles can also be incorporated into water free ointments and creams, which have an increased saturation solubility and enhanced diffusion of drug into the skin[40]. 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[44].

Conclusion

Poor aqueous solubility is rapidly becoming the leading hurdle for formulation scientists working on oral delivery of drug compounds and leads to employment of novel formulation technologies. The use of drug nanocrystals is a universal formulation approach to increase the therapeutic performance of these drugs in any route of administration. Almost any drug can be reduced in size to the nanometer range. Currently, attention is turned to improving the diminution performance to produce drug nanocrystals well below 100 nm, also in cases of very hard drugs..New technologies are in development to produce final dosage forms with higher drug loadings, better redispersability at their site of action, and an improved drug targeting. Dissolution of drug is the rate determining step for oral absorption of the poorly water soluble drugs. The various techniques can be used to enhance the solubility of the drug. Because of solubility problem of many drugs the bioavailability of them gets affected and hence solubility enhancement becomes necessary.

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