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REVIEW ARTICLE

NANOSUSPENSION TECHNOLOGY: A INNOVATIVE SLANT FOR DRUG DELIVERY SYSTEM AND PERMEABILITY ENHANCER FOR POORLY WATER SOLUBLE DRUGS

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ABSTRACT:

Nanosuspension contains submicron colloidal dispersion of pharmaceutical active ingredient particles in a liquid phase stabilized by surfactants. The poor water solubility of drugs is major problem for drug formulation. The reduction of drug particles into the sub-micron range leads to a significant increase in the dissolution rate, bioavailability as well as improve stability. Nanosuspension consists of the pure poorly water-soluble drug without any matrix material suspended in dispersion. Nanosuspension many attempts have been made to deliver poorly water soluble drugs as a nanosuspension prepared by adopting various methods. Techniques such as media milling and high pressure homogenization have been used commercially for producing nanosuspension. Recently, engineering of nanosuspension employs emulsions and microemulsion as templates. The unique features of nanosuspension have enabled their use in various dosage forms, including specialized delivery systems such as mucoadhesive hydrogels, parenteral, peroral, ocular and pulmonary routes.

Keywords: Nanosuspension, Solubility enhancement, Saturation solubility, Homogenization.

INTRODUCTION

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 nanosuspension is between 200 and 600 nm [1]. Nanosuspension differs 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 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. In addition, the diffusional distance on the surface of drug nanoparticles is decreased, thus leading to an increased concentration gradient. The increases in surface area and concentration gradient lead to a much more pronounced increase in the dissolution velocity as compared to a micronized product. Another possible explanation for the increased saturation solubility is the creation of high energy surfaces when disrupting the more or less ideal drug microcrystals to nanoparticles. The absence of particles with large differences in their size in nanosuspension prevents the existence of different saturation solubility and concentration gradients, consequently preventing the Oswald ripening effect [2,3]. Ostwald ripening is responsible for crystal growth and subsequently formation of microparticles. It is caused by a difference in dissolution pressure/saturation solubility between small and large particles. Molecules diffuse from the higher concentration area around small particles which have higher saturation solubility to an area around larger particles possessing a lower drug concentration. This leads to the formation of a supersaturated solution around the large particles and consequently to drug crystallization and growth of the large particles. Preparation of nanosuspension is simple and applicable to all drugs which are aqueous insoluble.

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Various formulation parameters that play a crucial role in the successful formulation of drugs are aqueous solubility, stability at ambient temperature and humidity, photo stability, compatibility with solvent and excipient. More than 40% of the new chemical entities being generated through drug discovery programmers are poorly water-soluble or lipophilic compounds. The formulation of nano-sized particles can be implemented to all drug compounds belonging to biopharmaceutical classification system (BCS) classes II, III and IV to increase their solubility and hence partition into gastrointestinal barrier. Nanosuspension is favored for compounds that are insoluble in water (but are soluble in oil) with high log P value, high melting point and high doses. Nanosuspension technology can also be used for drugs which are insoluble in both water and organic solvents.[4] Nanosuspensions contain a pure poorly water soluble drug of nano size range (1-1000nm) in dispersion. Nanosuspension is submicron colloidal dispersion of pure particles of drug stabilized by surfactants. Nanosuspension consists of pure poorly water soluble drug without any matrix material suspended in dispersion.[5]

The major advantages of nanosuspension technology are: [6]

- ✓ Oral administration of nanosuspensions provide rapid onset, reduced fed/fasted ratio and improved bioavailability.
- ✓ Rapid dissolution and tissue targeting can be achieved by IV route of administration.
- ✓ Reduced tissue irritation in case of subcutaneous/intramuscular administration.
- ✓ Higher bioavailability and more consistent dosing in case of ocular administration and inhalation delivery.
- ✓ Drugs with high log P value can be formulated as nanosuspensions to increase the bioavailability of such drugs.
- ✓ Improvement in biological performance due to high dissolution rate and saturation solubility of the drug.
- ✓ Long term physical stability.
- ✓ Nanosuspensions can be incorporated in tablets, pellets, hydrogels and suppositories are suitable for various routes of administration.

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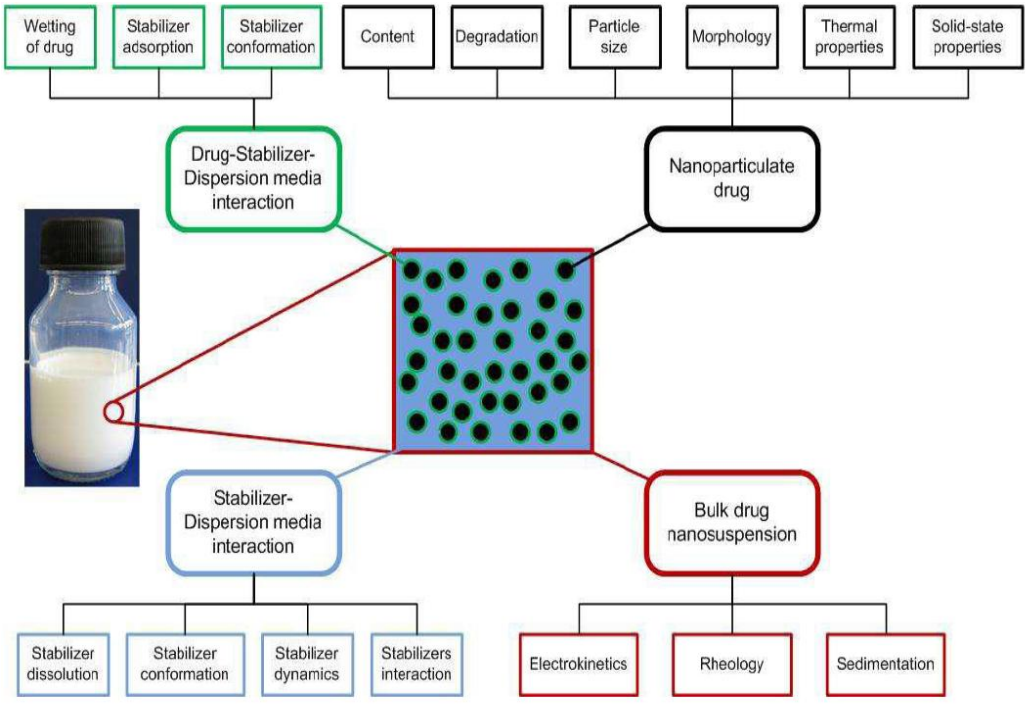

Interesting special features of nanosuspensions are: [7]

- ✓ Increase in saturation solubility and consequently an increase in the dissolution rate of the drug.
- ✓ Increase in adhesive nature, thus resulting in enhanced bioavailability.
- ✓ Increasing the amorphous fraction in the particles, leading to a potential change in the crystalline structure and higher solubility.
- ✓ Absence of Ostwald ripening, producing physical long term stability as an aqueous suspension.
- ✓ Possibility of surface-modification of nanosuspension for site specific delivery.

WHEN TO GO FOR NANO SUSPENSIONS APPROACH

Preparing nano suspensions is preferred for the compounds that are insoluble in water (but are soluble in oil) with high log P value. Conventionally the drugs that are insoluble in water but soluble in oil phase system are formulated in liposome, emulsion systems but these lipidic formulation approaches are not applicable to all drugs. In these cases nano suspensions are preferred. In case of drugs that are insoluble in both water and in organic media instead of using lipidic systems nano suspensions are used as a formulation

approach. Nanosuspension formulation approach is most suitable for the compounds with high log P value, high melting point and high dose. [8]

PROPERTIES OF NANO SUSPENSIONS [8,9]

1. *Physical Long-Term Stability*:

Nanosuspension is a highly dispersed system; therefore, physical instability due to Ostwald ripening would be expected. According to the Ostwald Freundlich equation, the saturation solubility increases with decreasing particle size. However, this effect is only pronounced for particles below approximately 2 ìm, especially below 1 ìm. It does not occur for powders of size normally processed in pharmacy.

2. *Saturation Solubility of Nanosuspension*:

Dissolution of drug is increased due to increase in the surface area of the drug particles from micrometers to the nanometer size. According to Noyes-Whitney equation (equation no.1) dissolution velocity increase due to increase in the surface area from micron size ton particles of nanometer size,

Dx/dt = [(D x A/ h)] [Cs-X/V] ---------- (1)

Where D is diffusion coefficient, A is surface area of particle, dx/dt is the dissolution velocity, V is volume of dissolution medium and X is the concentration in surrounding liquid.

According to the Prandtl equation, for small particles the diffusional distance h decreases with decreasing particle size. The decrease in h increases Cs (saturation solubility) and leads to an increase in gradient (Cs-Cx)/h and thus to an increase in the dissolution velocity. According to Ostwald-Freundlich equation decrease in particle size below 1ìm increases the intrinsic solubility or saturation solubility. [10]

3. *Internal structure of Nanosuspension*:

The high-energy input during disintegration process causes structural changes inside the drug particles. When the drug particles are exposed to high-pressure homogenization particles are transformed from crystalline state to amorphous state. The change in state depends upon the hardness of drug, number of homogenization cycles chemical nature of drug and power density applied by homogenizer. [11,12]

Increasing dissolution rate through nanosuspension — theoretical aspects [6,7,8]

The increased saturation solubility and the accelerated dissolution velocity are the most important differentiating features of drug nanocrystals. In general, the saturation solubility (Cs) is defined as a drug-specific constant depending only on the solvent and the temperature. This definition is only valid for drug particles with a minimum particle size in the micrometer range. A particle size reduction down to the nanometer range can increase the drug solubility. The solid API dissolution rate is proportional to the surface area available for dissolution as described by the Nernst–Brunner/Noyes–Whitney equation:

$$\frac{dX}{dt} = \frac{A \cdot D}{h}\left(C_s - \frac{Xd}{V}\right)$$

Where, dX/dt=dissolution rate, Xd=amount dissolved, A=particle surface area, D=diffusion coefficient, V=volume of fluid available for dissolution, Cs=saturation solubility, h=effective m=boundary layer thickness.

Based on this principle, API micronization has been extensively used in the pharmaceutical industry to improve oral bioavailability of drug compounds. It is evident that a further decrease of the particle size down to the sub-micron range will further increase dissolution rate due to the increase of the effective particle surface area [9]. For example in the case of aprepitant, the nanocrystals dispersion of 120-nm particle size exhibits a 41.5-fold increase in surface area over the standard 5 µm suspension [10]. Furthermore, as described by the Prandtl equation, the diffusion layer thickness (h) will also be decreased thus resulting in an even faster dissolution rate [11]. In addition to the dissolution rate enhancement described above, an increase in the saturation solubility of the nanosized API is also expected [12], as described by the Freundlich– Ostwald equation:

$$S = S_\infty \exp\left(\frac{2\gamma M}{r\rho RT}\right)$$

where S=saturation solubility of the nanosized API, S8=saturation solubility of an infinitely large API crystal, ϒ is the crystal-medium interfacial tension, M is the compound molecular weight, r is the particle radius, ρ is the density, R is a gas constant and T is the temperature.

Assuming a molecular weight of 500=1 g/ml and a. value of 15–20 mn m-1 for the crystal-intestinal fluid interfacial tension, the above equation would predict an approximately 10–15% increase in solubility at a particle size of 100 nm. However a more significant increase in solubility appears to occur in reality e.g. Muller and Peters reported an increase of 50% in the solubility of an insoluble antimicrobial compound when the particle size was reduced from 2.4 µm to 800 or 300 nm [12]. This increase in solubility leads to a further increase in dissolution rate and, as a result, nanosuspension often achieve significantly higher exposure levels compared to suspensions of micronized API, even when the same surfactants are used. Finally, the increase in surface wetting by the surfactants in the nanosuspension formulations most likely results in a further enhancement of the dissolution rates compared to micronized suspensions.

EFFECT OF FORMULATION COMPONENTS ON PHYSICO-CHEMICAL CHARACTERERISTICS

1) Stabilizer [13,14,15]

Nanosuspension often employs stabilizers in order to prevent the phenomena of Ostwald ripening as discussed previously. In the absence of a suitable

stabilizer, the high surface energy of the particles in the nano-range can aggregate to form larger particles, thereby rendering the formulation unstable. The main function of the stabilizer is to wet the drug particle completely in order to inhibit agglomeration with another particle. It provides stearic or ionic barriers by way of which inter-particulate interactions in the nanosuspension are prevented. However, the concentration of the stabilizer in the nanosuspension must be optimum. Ideally, the drug-to-stabilizer ratio might vary 1:20 to 20:1. Various stabilizers have been investigated for their use in nanosuspension including cellulosic, poloxamers, polysorbates, lecithin and povidones. PVA of varying grades has been found to be a very effective stabilizer for nanosuspension produced by various methods.

Effect on Physicochemical Characteristics [13]

PVA or Polyvinyl Alcohol has both hydrophobic and hydrophilic parts like acetate and hydroxyl groups respectively. These help in getting absorbed and oriented at the interface. In fact, the effectiveness of PVA in reducing the interfacial tension is such that it even promotes to maintaining low particle size of the nanoparticles in the nanosuspension. Even surfactants like Poloxamer and Tween 80 have been utilized for reducing the interfacial tension at the surface of the nanoparticles in the nanosuspension.

2) Organic solvents: [13,14,15]

Organic solvents are often employed in the formulation of nanosuspension by a variety of techniques.

Effect on Physicochemical Characteristics

One of the most important things to be kept in mind while utilizing organic solvents is their miscibility with water. The more the solvent is miscible and readily diffusible with water, the more effective will be the formation of nanoparticles.

3) Co-surfactants [13,14,15]

Employing co-surfactants becomes important when nanosuspension is formulated from micro emulsion. Co-surfactants influence phase behavior significantly and various solubilizers such as Transcutol, Glycofurol, Ethanol, and Isopropanol can be used as co-surfactants in the formulation of microemulsion.

4) Other additives [13,14,15]

It might be so that a number of other additives are employed in the nanosuspension like osmogent, cryoprotectant or buffers depending upon the route of administration or to enhance the inherent properties of the drug.

5) Temperature [13,14,15]

Maintaining optimum temperature conditions while carrying out the formulation of nanosuspension is important. Optimally it is very important to carry out the formulation at low temperature conditions while carrying out homogenization. For nanosuspension manufactured using the emulsion technique, it is significant that when the drug loaded organic solvent is added to the aqueous surfactant solution, homogenization is carried out in an ice bath or other provisions are made for lowering the temperature. The reason behind this is that since organic solvents are involved in the formulation, keeping a higher temperature will lead to rapid removal of the solvent from the system leading to formation of irregular particles. On the other hand in low temperature conditions, the solvent diffuses slowly out of the system leading to the formation of spherical and complete nanoparticles.

6) Stirring Speed[14,15]

Stirring speed is also an important formulation variable. The homogenization of nanosuspension leads to maintenance of low particle size and this is achieved either through High Pressure Homogenization (HPH) or High Shear Homogenization (HSH). It has been observed that on an average, increasing the speed of stirring during HSH or increasing the number of cycles during HPH leads to a reduction in the particle size towards the nano-sized range. However, it has been noted that operating the instruments at high speed conditions are not always optimum and an average speed has to be maintained. Optimally, for HSH 20000 RPM and for HSH around 5 to 6 cycles have been recommended. This is because higher agitation speeds often lead to formation of a huge amount of foam in the suspension which often leads to early separation of the solid nanoparticles from the aqueous medium. As a result, this can lead to ineffective size reduction and insufficient formation of the nanoparticles.

Post-production processing [16,17,18,19]

Post-production processing of nanosuspension becomes essential when the drug candidate is highly susceptible to hydrolytic cleavage or chemical degradation. Processing may also be required when the best possible stabilizer is not able to stabilize the nanosuspension for a longer period of time or there are acceptability restrictions with respect to the desired route. Considering these aspects, techniques such as lyophillization or spray drying may be employed to produce a dry powder of nano-sized drug particles. Rational selection has to be made in these unit operations considering the drug properties and economic aspects. Generally, spray drying is more economical and convenient than lyophillization. The effect of post-production processing on the particle size of the nanosuspension and moisture content of dried Nanosized drug should be given due consideration.

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Table 1: Various formulation excipients along with their functions: [7]

Excipient	Function	Example
Stabilizers	Wet the drug particles thoroughly, prevent - Ostwald's ripening and agglomeration of nanosuspension, providing steric or ionic barrier.	Lecithin, Poloxamer, Polysorbate, Cellulosic, Povidones
Co-surfactants	Influence phase behavior when micro -emulsions are used to formulate nanosuspension.	Bile salts, Dipotassium Glycerrhizinate, Transcutol, Glycofurol, Ethanol, Isopropanol.
Organic solvent	Pharmaceutically acceptable less hazardous -solvent for preparation of formulation.	Methanol, Ethanol, Chloroform, Isopropanol, Ethyl acetate, Ethyl format, Butyl lactate, Triacetin, Propylene carbonate.
Other additives	According to the requirement of the route of - administration or the properties of the drug moiety.	Buffers, Salts, Polyols,osmogens, Cryoprotectant..

Table 2: Advantages of nanosuspension over conventional formulations: [20,21,22]

Route of administration	Disadvantages of conventional formulations	Benefits of nanosuspension
Oral	Slow onset of action/ poor absorption	Rapid onset of action/ improved solubility so improved bioavailability
Ocular	Lacrimal wash off/ low bioavailability	Higher bioavailability/ dose consistency
Intravenous	Poor dissolution/ non-specific action	Rapid dissolution/ tissue targeting
Intramuscular	Low patient compliance due to pain	Reduced tissue irritation
Inhalations	Low bioavailability due to low solubility	Rapid dissolution/ high bioavailability/ dose regulation

PREPARATION OF NANOSUSPENSION

There are two methods for preparation of nanosuspension namely 'Bottom up technology' and 'Top down technology'. In Bottom up technology the drug is dissolved in a solvent, which is then added to non-solvent that causes precipitation of the fine drug particles. All-Trans retinoic acid nanosuspension was prepared with a precipitation method. Use of simple and low cost equipment and also benefit for higher saturation solubility is the advantage for precipitation technique compared to other methods of nanosuspension preparation. Precipitation technique is not applicable to drugs which are poorly soluble in aqueous and non aqueous media. In this technique, the drug needs to be soluble in at least one solvent which is miscible with nonsolvent. The major challenge is to avoid crystal growth due to Ostwald ripening being caused by different saturation solubility's in the vicinity of differently sized particles. The top down technologies include (a) media milling (b) high pressure homogenization (c) emulsion diffusion method (d) supercritical fluid method and these are preferred over the precipitation methods. [23]

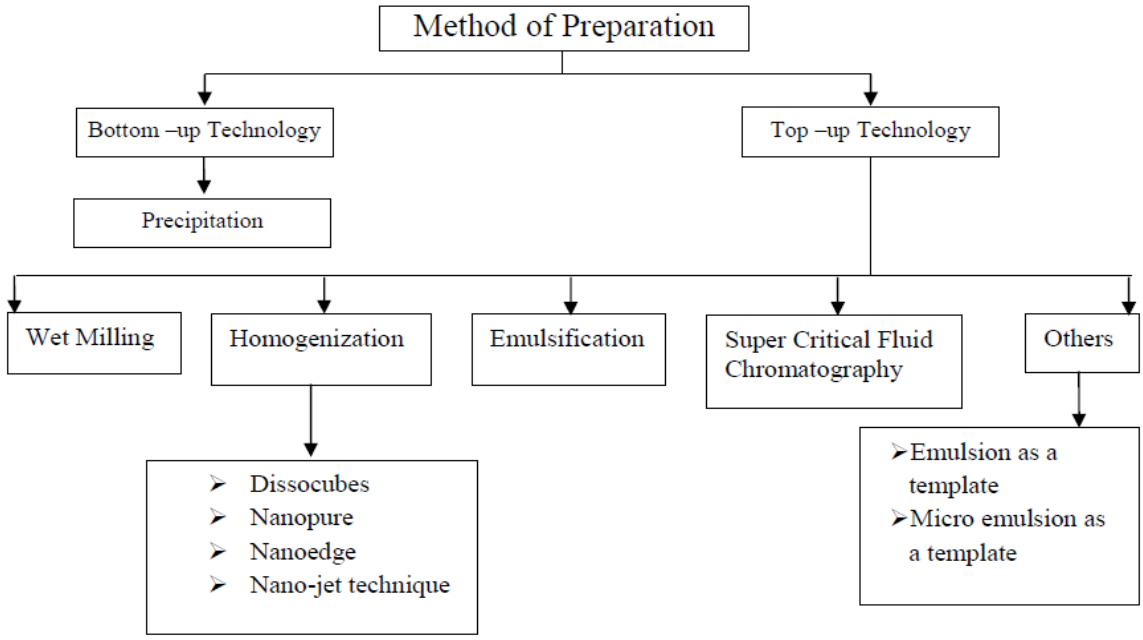

Figure 1: Flow Chart Showing Various Preparations Method[23]

A) Milling techniques: [24,25,26,27,28]

Media milling (Nanocrystals)

This method was developed by Liversidge. In this method the nanosuspension is produced using high-shear media mills or pearl mills. It consists of a milling chamber, a milling shaft and a recirculation chamber. Milling medium is framed of glass, zirconium oxide or highly cross-linked polystyrene resin. The milling chamber is charged with the milling media, water, drug and stabilizer, and the milling media or pearls are then rotated at a very high shear rate. All process is performed under controlled temperatures. The high energy and shear forces generated as a result of the impaction of the milling media with the drug provide the energy input to break the microparticulate drug into nano-sized particles. A nanosuspension of Naproxen with a mean particle size of 300-600 nm was prepared using pearl milling technique. [24,25,26,27,28]

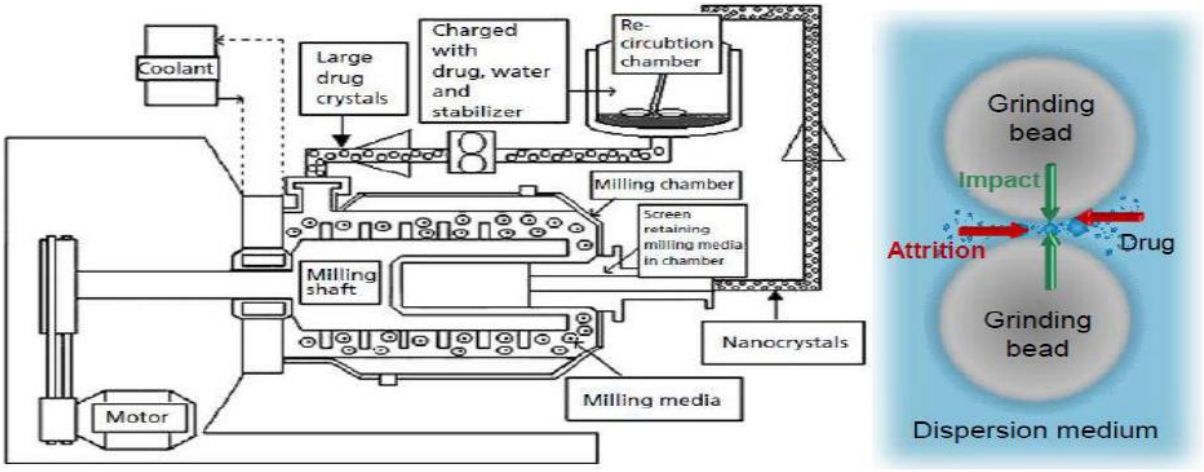

Figure 2: Schematic representation of Media milling process [25]

Advantages: [24,25,26,27,28]

- ✓ Drugs that are poorly soluble in both aqueous and organic media can be easily formulated into nanosuspension.
- ✓ Ease of scale-up and little batch-to-batch variation.
- ✓ Narrow size distribution of the final nano-sized product.
- ✓ Flexibility in handling the drug quantity, ranging from 1 to 400mgmL-1, enabling formulation of very dilute as well as highly concentrated nanosuspension.

Disadvantages: [24,25,26,27,28]

The major concern is the generation of residues of milling media, which may be introduced in the final product as a result of erosion .This could be problematic when nanosuspension is intended to be administered for a chronic therapy. The severity of this problem has been reduced to a great extent with the advent of polystyrene resin-based milling medium.

Dry Co-grinding [24,25,26,27,28]

Preparing stable nanosuspension using poorly soluble drugs with soluble polymers and copolymers after dispersing in a liquid media has been reported. The colloidal particles formation of many poorly water soluble drugs; griseofulvin, glibenclamide and nifedipine obtained by grinding with polyvinylpyrrolidone (PVP) and sodium dodecylsulfate (SDS). Many soluble polymers and co-polymers such as PVP, polyethylene glycol (PEG), hydroxypropyl methylcellulose (HPMC) and cyclodextrin derivatives have been used. Physicochemical properties improved because of an improvement in the surface polarity and transformation from a crystalline to an amorphous drug. It 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. [24,25,26,27,28]

High pressure homogenization (dissocubes/nanopure):

Homogenization involves the forcing of the suspension under pressure through a valve having a narrow aperture. The most commonly used homogenizer in the preparation of nanosuspension is the APV micron LAB 40(APV Deutschland GmbH, Lubeck, Germany). However, other piston-gap homogenizers from Avestin (Avestin Inc., Ottawa, Canada) and Stansted (Stansted Fluid Power Ltd, Stansted, UK) can also be used. The instrument can be operated at pressures varying from 100 to 1500 bars. In some instruments, a maximum pressure of 2000 bars can be reached. [24,25,26,27,28]

Principle:

During homogenization, the fracture of drug particles is brought about by cavitation, high-shear forces and the collision of the particles against each other. The drug suspension, contained in a cylinder of diameter about 3 mm, passes suddenly through a very narrow

homogenization gap of 25µm, which leads to a high streaming velocity. In the homogenization gap, according to Bernoulli's equation, the dynamic pressure of the fluid increases with the simultaneous decrease in static pressure below the boiling point of water at room temperature. In consequence, water starts boiling at room temperature, leading to the formation of gas bubbles, which implode when the suspension leaves the gap (called cavitation) and normal air pressure is reached again. The implosion forces are sufficiently high to break down the drug microparticles into nanoparticles. Additionally, the collision of the particles at high speed helps to achieve the nano-sizing of the drug. [24,25,26,27,28] A high pressure homogenizer consists of a high pressure plunger pump with a subsequent relief valve with fixed valve seat and an adjustable valve. These parts form and adjustable radial precision gap. It is advisable to start with micronized drug particles (<25µm)for production of nanosuspension in order to prevent blocking of homogenization gap. Before subjecting the drug to the homogenization process, it is essential to form a presuspension of the micronized drug in a surfactant solution using high-speed stirrers. Hence generally a jet milled drug is employed as the starting material for producing dissocubes. Homogenization can be performed in water(dissocubes)or alternatively in nonaqueous media(nanopure). Most of the cases require multiple passes or cycles through the homogenizer, which depends on the hardness of the drug, the desired mean particle size, and required homogeneity. High-pressure homogenizers are available with different capacities ranging from 40ml (for laboratory purposes) to a few thousand litres (for large-scale production). [24,25,26,27,28]

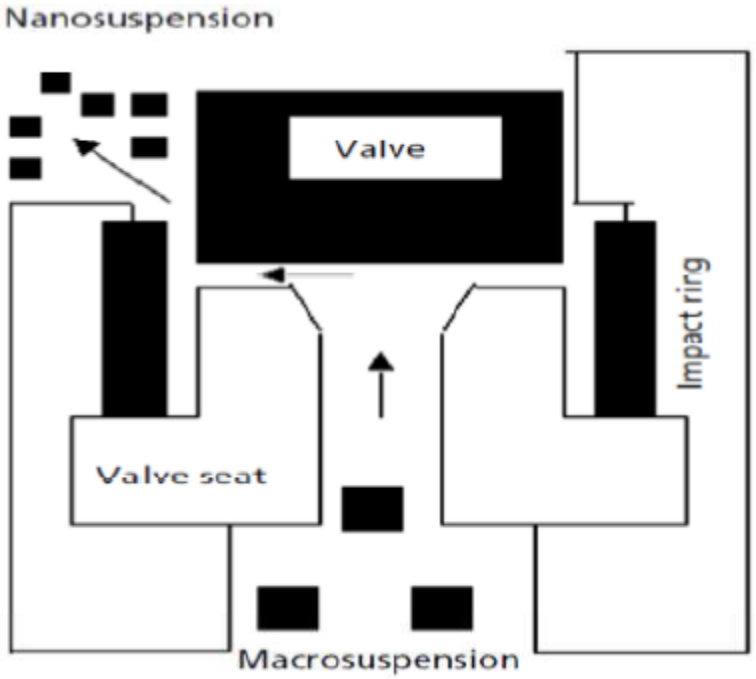

Figure 3:Schematic representation of high pressure homogenization process[24,25,26,27,28]

Advantages: [24,25,26,27,28]

- Drugs that are poorly soluble in both aqueous and organic media can be easily formulated into nanosuspensions.
- Narrow size distribution of the nanoparticulate drug present in the final product.
- Allows aseptic production of nanosuspensions for parenteral administration.

Disadvantages: [24,25,26,27,28]

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

B) Combined precipitation and homogenization (Nanoedege): [24,25,26,27,28]

Principle involved is same that of the precipitation and homogenization techniques. This technique has an advantage of getting smaller particle size and greater stability in short period of time. In this technique the precipitated suspension is further homogenized to get smaller particle size and to avoid crystal growth. Precipitation is performed in water using water miscible solvent, such 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 pressure homogenization. [24,25,26,27,28]

Nanojet technology [24,25,26,27,28]

It 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. 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. [24,25,26,27,28]

C) Emulsion solvent diffusion method:

Apart from the use of emulsion as drug delivering vehicle they can also be used as templates to produce nanosuspension. The use of emulsions as templates is applicable for those drugs that are soluble in either volatile organic solvent or partially water-miscible solvent. Such solvents can be used as the dispersed phase of the emulsion. An organic solvent or mixture of solvents loaded with the drug is dispersed in the aqueous phase containing suitable surfactants with stirring to form an emulsion. The obtained emulsion was further homogenized by high pressure homogenization. After homogenization cycles the emulsion was diluted with water, homogenized by homogenizer to diffuse the organic solvent and convert the droplets into solid particles. Control the particle size of the nanosuspension by controlling the size of the emulsion. Optimizing the surfactant composition increases the intake of organic phase and ultimately the drug loading in the emulsion. Originally methanol, ethanol, ethyl acetate, chloroform are used as organic solvents. [24,25,26,27,28]

Advantages: [24,25,26,27,28]

- ✓ 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: [24,25,26,27,28]

- ✓ 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.
- ✓ It applied to the poorly water-soluble and poorly bioavailable anti-cancer drug mitotane, where a significant improvement in the dissolution rate of the drug (five-fold increase) as compared to the commercial product was observed.

Microemulsions as templates [24,25,26,27,28]

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.Their advantages, such as high drug solubilization, long shelf-life and ease of manufacture, make them an ideal drug delivery vehicle. Recently, the use of microemulsions as templates for the production of solid lipid nanoparticles and polymeric nanoparticles has been described. The internal phase of these microemulsions could be either a partially miscible liquid or a suitable organic solvent. The drug can be either loaded in the internal phase or pre-formed microemulsions can be saturated with the drug by intimate mixing. The influence of the amount and ratio of surfactant to co-surfactant on the uptake of internal phase and on the globule size of the microemulsion should be investigated and optimized in order to achieve the desired drug loading .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. The production of drug nanosuspensions using microemulsions as templates has been successfully applied to the poorly water-soluble and poorly bioavailable antifungal drug griseofulvin, where a significant improvement in the dissolution rate of the drug (three-fold increase) as compared to the commercial product was observed.

Melt emulsification method [24,25,26,27,28]

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 point of the drug. The emulsion was then cooled down either slowly to room temperature or on an ice-bath. The main advantage is total avoidance of organic solvents during the production process. Nanosuspension of ibuprofen was prepared by this method. This method show greater dissolution rate than formulating by solvent diffusion method.

Supercritical fluid method: [24,25,26,27,28]

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. In the PCA method, the drug solution is atomized into a chamber containing compressed CO2. As the solvent is removed, the solution gets supersaturated and thus precipitates as fine crystals. The supercritical anti-solvent process uses a supercritical fluid in which a drug is poorly soluble and a solvent for the drug that is also miscible with the supercritical fluid.

Disadvantages: [24,25,26,27,28]

- ✓ 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.

CHARACTERIZATION OF NANOSUSPENSION [24,25,26,27,28]

According to Muller's review, the necessity characterization parameters for nanosuspensions are size and size distribution, particle charge (zeta potential), crystalline status, as well as dissolution velocity and saturation solubility.

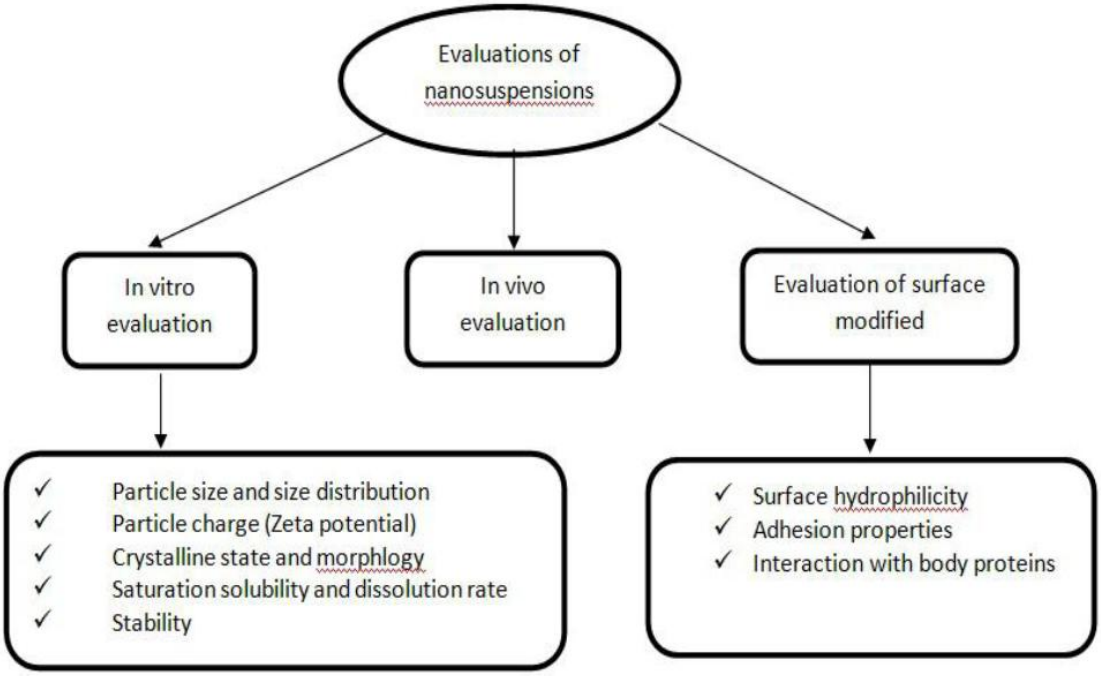

Figure 4: Flowchart showing various methods for characterization of nanosuspensions[24,25,26,27,28]

Particle size distribution: [24,25,26,27,28]

The most important characterization parameter, also called P**olydispersity Index** which governs the physicochemical properties like saturation solubility, dissolution velocity, physical stability and even biological performance. Different methods for determining particle size distribution are photon correlation spectroscopy (PCS), laser diffraction (LD), and coulter counter multisizer.

- ✓ PCS can even be used for determining the width of the particle size distribution. PCS determines the particle size in the range of (3nm to 3 µm).
- ✓ 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) A PI value of 0.1–0.25 indicates a fairly narrow size distribution

b) PI value greater than 0.5 indicates a very broad distribution.

c) Laser diffractometry (LD) analysis detect and quantify the drug microparticles that might have been generated during the production process. LD determines the particle size in the range of 0.05-80µm upto 2000µm. 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.

For parental use the particle size should be less than 5µm, considering that the smaller size of the capillaries is 5-6µm and hence a higher particle size can lead to capillary blockade and embolism.

Particle charge (zeta potential): [24,25,26,27,28]

The physical stability of a nanosuspension is governed by the particle charge (zeta potential) is effected by the stabilizer and the drug itself.

- ✓ For electrostatically stabilized nanosuspension a minimum zeta potential of ±30mv is required.
- ✓ For combined steric and electrostatic stabilized nanosuspensions a minimum of ±20mv is required.

Crystalline state and particle morphology: [24,25,26,27,28]

It is important to know the crystal morphology of the drug in the nanosuspension. Polymorphic or morphological changes in drug that occur during nanosizing can be determined by the knowledge of crystalline state and particle morphology. Amorphous state of the drug formed during preparation of

nanosuspension is determined by X-ray diffraction analysis. It gives information about the changes in the physical state of the drug particles as well as the extent of the amorphous fraction. Differential scanning calorimetry can be used additionally. Scanning electron microscopy is also used to get exact information about particle morphology. Effect of high pressure homogenization on the crystalline structure of the drug is estimated by X-ray diffraction analysis in combination with differential scanning calorimetry. Techniques like scanning electron microscopy (SEM), atomic force microscopy (AFM) or transmission electron microscopy (TEM) are preferred for determining the exact size and morphology of nanoparticles in suspension.

Saturation solubility and dissolution velocity: [24,25,26,27,28]

Nanosuspensions can increase the dissolution velocity as well as the saturation solubility. The saturation solubility of the drug in different physiological buffers as well as at different temperatures. The assessment of saturation solubility and dissolution velocity helps in determining the in vitro behaviour of the formulation.

In-Vivo Pharmacokinetic correlation: [24,25,26,27,28]

For intravenously injected nanosuspensions, the organ distribution in part depends on the nanoparticle size and surface property. Surface hydrophilicity/hydrophobicity and interactions with plasma proteins are considered as important factors affecting the *in-vivo* organ distribution behaviour after i.v. injection of nanosuspensions. 2-D PAGE can be employed for the quantitative measurement of protein adsorption to nanoparticle surface after i.v. injection of drug nanosuspensions to animals. [24,25,26,27,28]

PREFERRED DOSAGE FORMS OF NANOSUSPENSIONS [24,25,26,27,28]

Aqueous or non-aqueous drug nanosuspensions exhibiting a physical long-term stability should be sufficient to place them on the market as liquid products. In the case of drug nanosuspensions in pure water or in water containing mixtures, they can be used as granulation fluid in the granulation process for the production of tablets or alternatively as wetting agents for the extrusion mass to produce pellets. Spray-drying of the nanosuspension is also possible. The produced powders can then be used again for tablet or pellet production or alternatively be filled in hard gelatin or HPMC capsules. The drug nanocrystals produced in non-aqueous media such as oils or liquid/solid PEG can be used directly for filling in capsules. Production of drug nanosuspensions in melted PEG which is solid at room temperature opens further perspectives. Direct filling of capsules with the hot nanosuspension is possible.[35] Alternatively after solidification of the PEG, the drug nanocrystal containing mass can be ground and filled as a powder into the capsules. To summarize, there are different ways to transfer the drug nanocrystals to a final dry oral dosage form for the patient.

APPLICATION OF NANOSUSPENSIONS [24,25,26,27,28]

1 Parenteral administration

Advantages

Liposomes are much more tolerable and versatile in terms of parenteral delivery. However, they often suffer from problems such as physical instability, high manufacturing cost and difficulties in scale-up. Nanosuspensions would be able to solve the problems mentioned above. In addition, nanosuspensions have been found to increase the efficacy of parenterally administered drugs. For administration by the parenteral route, the drug either has to be solubilized or has particle/globule size below 5 µm 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.

2 Peroral administrations

Advantages

Nanosizing of drugs can lead to a dramatic increase in their oral absorption and subsequent bioavailability. Improved bioavailability can be explained by the adhesiveness of drug nanoparticles to the mucosa, the increased saturation solubility leading to an increased concentration gradient between gastrointestinal tract lumen and blood and the increased dissolution velocity of the drug. Aqueous nanosuspensions can be used directly in a liquid dosage form and a dry dosage form such as tablet or hard gelatin capsule with pellets.

3 Pulmonary drug delivery

Advantages

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.

4 Target drug delivery

Advantages

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.

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Table 1: Current marketed formulations using nanosuspension technology:

38	Aphidicolin	To improve drug targeting effect against Leshmania infected macrophages	Kayser .O [60]
39	Cloricromene	To improve stability of the drug and its availability at the ocular level.	Rosario P *et al* [61]
40	Buparvaquone	To enhance effectiveness if the drug in the treatment of Pneumocystis pneumonia. (pulmonary)	Norma H-K *et al* [62]
41	Retinoic acid	To attain controlled release and high saturation solubility of the drug	Zhang.X *et al* [63]
42	1,3-dicyclohexyl urea	To maintain DCU free plasma levels above the soluble epoxide hydrolase inhibitor. (oral I.V bolus & I.V infusion dosing)	Jan L.W *et al* [64]
43	Risperidone	To treat Psychotic disorders. (parenteral)	Muthu M.S *et al* [65]
44	Acyclovir	For prolonged release of drug & to increase bioavailability. (ocular)	Panchaxari D *et al* [66]
45	Atorvastatin	To enhance solubility of the drug	Arunkumar N *et al* [67]
46	Hesperetin	To enhance the effect of drug through dermal delivery	Prabhat R.M *et al* [68]
47	Meloxicam	To enhance the dissolution of the drug. (oral)	Ambrus.R *et al* [69]
48	Itraconazole	To increase aqueous solubility & dissolution & hence to increase oral bioavailability. (aerosols)	Shivanandh P *et al* [70]
49	Forskolin	To enhance antiglaucoma efficacy. (ocular)	Saurabh G *et al* [71]
50	Silyben	Increase in bioavailability and sustained drug release drug profile is observed. (oral & I.V)	Yancci W *et al* [72]
51	Miconazole	To increase bioavailability	Ana M.C *et al* [73]
52	Diclofenac	To enhance solubility of the drug. (intramuscular)	Amit R P *et al* [74]
53	Simvastatin	To enhance dissolution of the drug compared to suspension	Vikram.M.P *et al* [75]
54	Famotidine	To improve dissolution rate of the drug. (mucoadhesive)	Dhaval J.P *et al* [76]

7. CONCLUSION

The nanosuspensions technology can be successfully utilized for overcoming problems associated with poorly soluble drugs or lipophilic drugs insoluble in both organic and aqueous media. Large scale production methods of production of nanosuspensions like media milling or high pressure homogenization have been employed for manufacture. There exist a number of patented technologies which have a huge commercial application and can be utilized for further advancements in the area of formulation of poorly soluble drugs. The recent advancements in the work being done related to nanosuspensions show that many formulations are being developed on a laboratory scale which have a potentially important clinical significance and can be used for the mitigation of diseases.

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