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Review Article

A Review on: Nanosuspensions - An Innovative Acceptable Approach in Novel Delivery System

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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. Conventional approaches for enhancement of solubility have limited applicability, especially when the drugs are poorly soluble simultaneously in aqueous and in non-aqueous media. Nanosuspension technology can be used to improve the stability as well as the bioavailability of poorly soluble drugs. Nano suspensions are biphasic systems consisting of pure drug particles dispersed in an aqueous vehicle, stabilized by surfactants. These are simple to prepare and are more advantageous than other approaches. Techniques such as wet milling, high-pressure homogenization, emulsification-solvent evaporation and super critical fluid have been used in the preparation of nano suspensions. It has the advantage of delivery by various routes, including oral, parenteral, pulmonary and ocular routes.

INTRODUCTION

Nanotechnology:

Nanotechnology is the study of manipulating matter on an atomic and molecular scale. Generally, nanotechnology deals with developing materials, devices, or other structures possessing at least one dimension sized from 1 to 100 nanometer.

History:

The history of nanotechnology traces the development of the concepts and experimental work falling under the broad category of nanotechnology. Although nanotechnology is a relatively recent development in scientific research, the development of its central concepts happened over a longer period of time. The emergence of nanotechnology in the 1980s was caused by the convergence of experimental advances such as the invention of the scanning tunneling microscope in 1981 and the discovery of fullerenes in 1985, with the elucidation and popularization of a conceptual framework for the goals of nanotechnology beginning with the 1986 publication of the book Engines of Creation.

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The field was subject to growing public awareness and controversy in the early 2000s, with prominent debates about both its potential implications as well as the feasibility of the applications envisioned by advocates of molecular nanotechnology, and with governments moving to promote and fund research into nanotechnology. The early 2000s also saw the beginnings of commercial applications of nanotechnology, although these were limited to bulk applications of nonmaterial's rather than the transformative applications envisioned by the field.

Nanosuspensions:

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 suspended particle is less than 1 µm in size. Nanosuspensions can be used to enhance the solubility of drugs that are poorly soluble in aqueous as well as lipid media. As a result, the rate of flooding of the active compound 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. It is useful for molecules with poor solubility, poor permeability or both,

which poses a significant challenge for the formulators. Nanosuspensions differ from Nanoparticles, which are polymeric colloidal carriers of drugs (Nanospheres and nanocapsules), and from solid-lipid nonoparticles (SLN), which are lipidic carriers of drug.A pharmaceutical nanosuspension is biphasic systems consisting of nano sized drug particles stabilized by surfactants for either oral or topical use or parenteral and pulmonary administration.The particle size distribution of the solid particles in nanosuspensions are usually less than one micron with an average particle size ranging between 200 and 600 nm [1-2].

PROPERTIES OF NANO SUSPENSIONS [3-5]:

A. 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 μm, especially below 1 μm. It does not occur for powders of size normally processed in pharmacy.

B. 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.

C. Adhesiveness

As the particle size decreases the adhesive properties of the particles will be improved and thus improved oral delivery of poorly soluble drugs. Improved bioavailability, improved dose proportionality, reduced fed/fasted variability, reduced inter-subject variability and enhanced absorption rate (both human and animal data) are some of the main effects observed on oral administration. These data have been acquired in vivo in animals but also in humans as reported by the company Nano Systems. A drastically remarkable report is that of the increase in bioavailability for danazole from 5 % (as macro suspension) to 82% (as nanosuspension).

D. 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 dissolution velocity increase due to increase in the surface area from micron size to particles of nanometer size.

$$\frac{Dx}{dt} = \frac{(D \times A)}{h} \times \frac{(C_s - X)}{V}$$

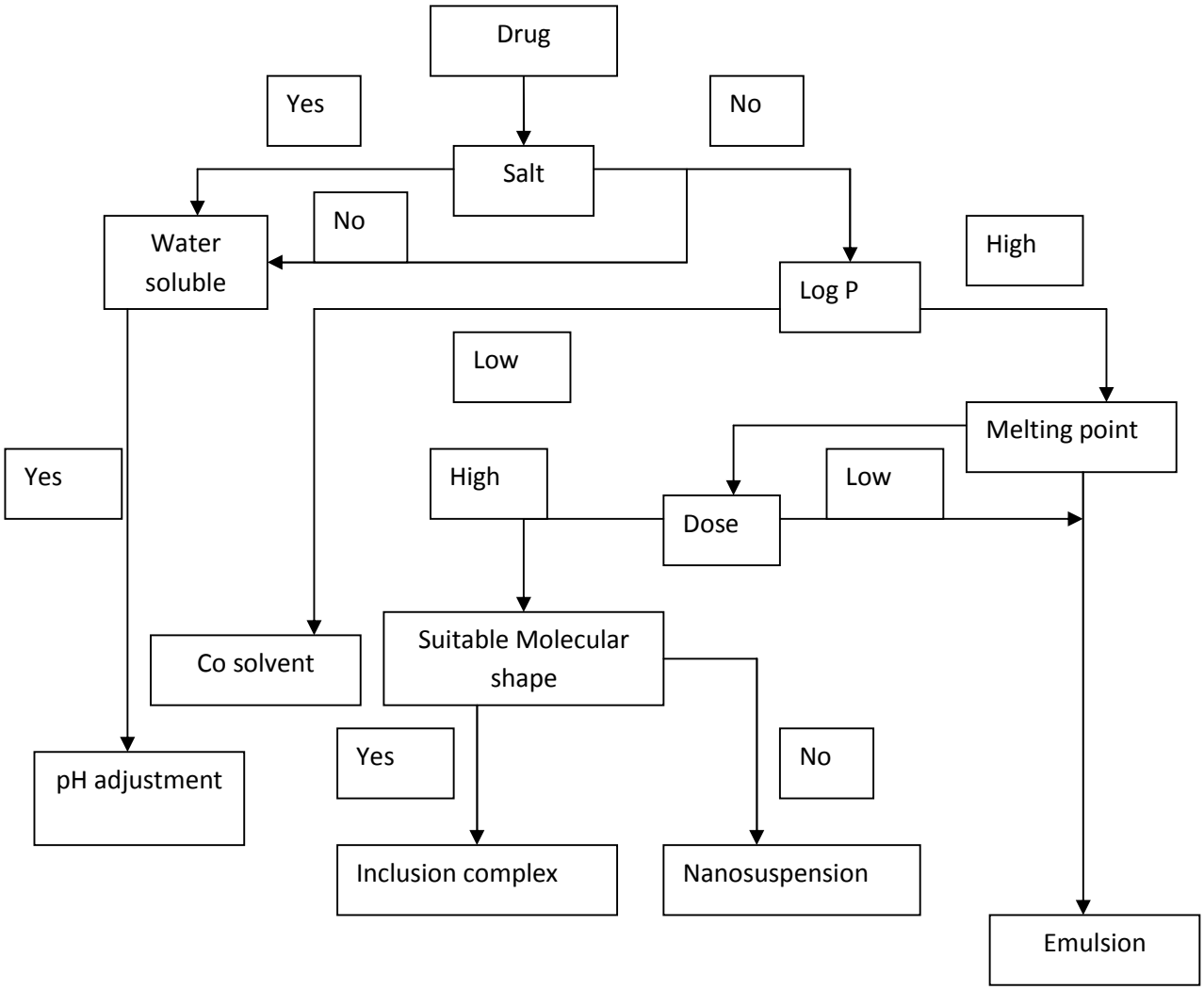
Where D is diffusion coefficient, A is surface area of particle, dx/dt is the dissolution velocity, V is volume of dissolution medium and X is the concentration in surrounding liquid.

WHEN TO GO FOR NANOSUSPENSIONS APPROACH [6]:

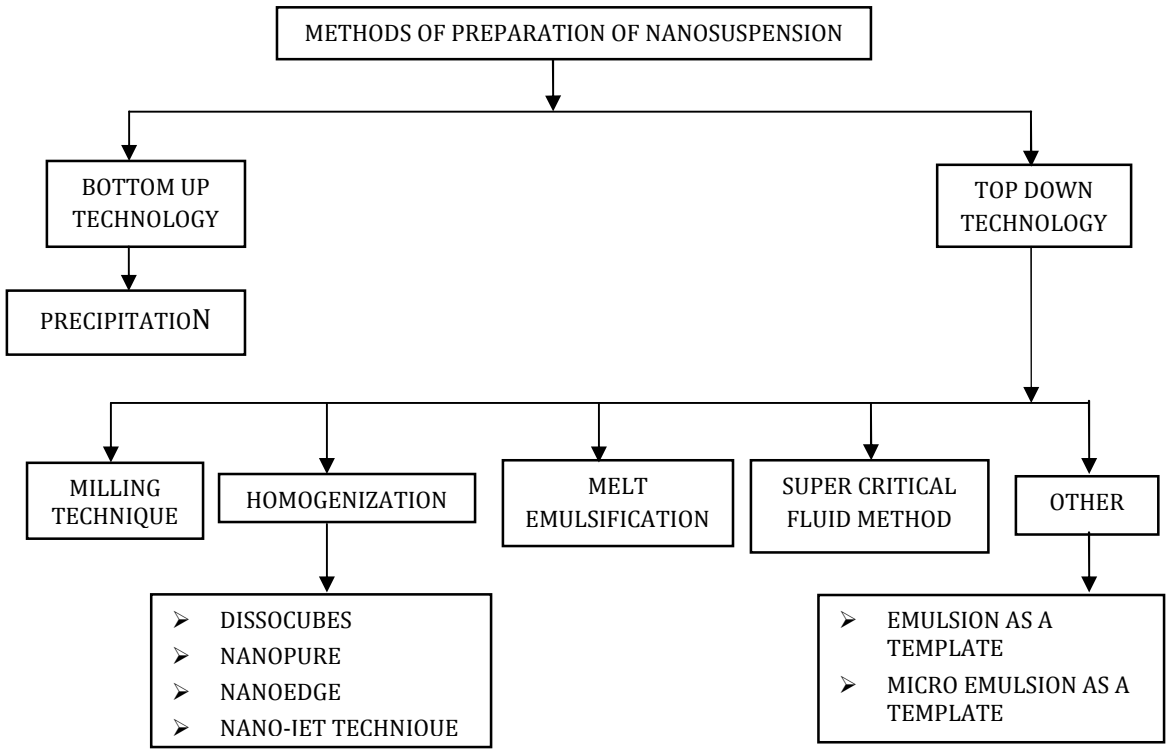
Preparing nanosuspensions is preferred for the compounds that are insoluble in water (but are soluble in oil) with high log P value. Conventionally the drugs that are insoluble in water but soluble in oil phase system are formulated in liposome, emulsion systems but these lipidic formulation approaches are not applicable to all drugs. In these cases nanosuspensions are preferred. In case of drugs that are insoluble in both water and in organic media instead of using lipidic systems nanosuspensions 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. Figure1 shows selection criteria for formulation approach to enhance solubility of poorly soluble drugs.

Table 1: Potential benefits of nanosuspension technology

Route of administration	Potential benefits
Oral	• Rapid onset • Reduced fed/fasted ratio • Improved bioavailability
Intravenous	• Rapid dissolution, • Tissue targeting • Longer duration of retention in systemic circulation
Ocular	• Higher bioavailability, • More consistent dosing • less irritation
Inhalation	• Higher bioavailability, • More consistent dosing
Subcutaneous/ Intramuscular	• Higher bioavailability • Rapid onset • Reduced tissue irritation



The criteria for selection of various technologies to enhance solubility of poorly soluble drugs



Methods of preparation of nanosuspension

FORMULATION CONSIDERATIONS[7]

A. Stabilizer

Stabilizer plays an important role in the formulation of nanosuspensions. In the absence of an appropriate stabilizer, the high surface energy of nano-sized particles can induce agglomeration or aggregation of the drug crystals. The main functions of a stabilizer are to wet the drug particles thoroughly, and to prevent Ostwald's ripening and agglomeration of nanosuspensions in order to yield a physically stable formulation by providing steric or ionic barriers. The type and amount of stabilizer has a pronounced effect on the physical stability and in-vivo behaviour of nanosuspensions. In some cases, a mixture of stabilizers is required to obtain a stable nanosuspension.The drug-to-stabilizer ratio in the formulation may vary from 1:20 to 20:1 and should be investigated for a specific case. Stabilizers that have been explored so far include cellulosics, poloxamers, polysorbates, lecithins and povidones. Lecithin is the stabilizer of choice if one intends to develop a parenterally acceptable and autoclavable nanosuspension.

B. Organic Solvent

Organic solvents are used in the formulation of nanosuspension if emulsions or microemulsions are used as a template. The pharmaceutically acceptable less hazardous water miscible solvent, such as methanol, ethanol, chloroform, ispropanol, and partially water miscible solvents ethyl acetate, ethyl formate, butyl lactate, triacetin, propylene carbonate, benzyl alcohol, are preferent in the formulation over the conventional hazardous solvents, such as dichloromethane.

C. Co-surfactants

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

D. Other Additives

Nano suspensions 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.

METHODS OF PREPARATION

Bottom up Technology

Bottom-up technologies build-up nanoscale particles from molecular solutions.

a. Precipitation Method

Precipitation method is a general method used to prepare submicron particles of poorly soluble drugs. The most common method of precipitation used is anti solvent addition method in this method, drug is dissolved in solvent and then solution is mixed with solvent to which drug is insoluble in the presence of surfactant. Rapid addition of solution to such solvent (generally water) leads to rapid supersaturation of drug in the solution, and formation of ultrafine amorphous or crystalline drug. This method involves nuclei formation and crystal growth which are mainly dependent on temperature. High nucleation rate and low crystal growth rate are primary requirements for preparing a stable suspension with minimum particle size.

Advantages

- Simple process
- Low cost equipment
- Ease of scale up

Disadvantages

- Drug has to soluble at least in one solvent and that this solvent needs to be miscible with a non solvent
- Growing of drug ctystals needs to be limit by surfactant addition

Top down Technology

a. Milling Technique

I. Media Milling

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.The media millconsists of a milling chamber, a milling shaft and a recirculation chamber.The milling chamber is charged with the milling media, water, drug and stabilizer,as depicted in Figure,and the milling media or pearls are then rotated at a very high shear rate. The milling process is performed under controlled temperatures.

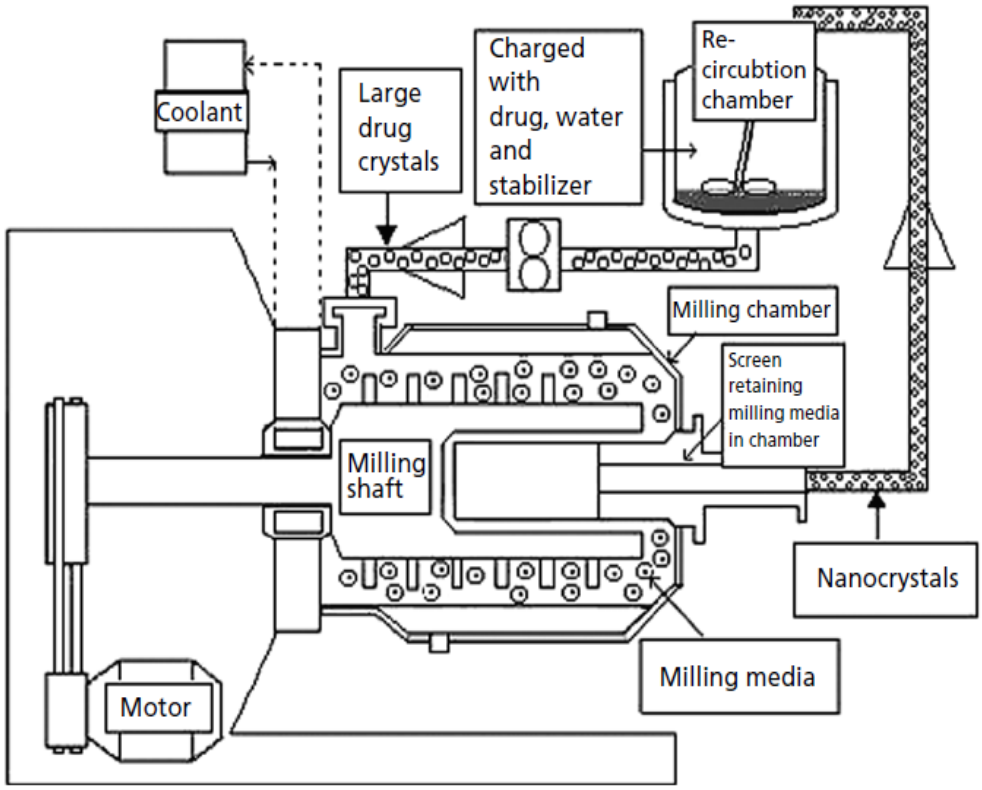


Figure 1: Schematic representation of the media milling process

Principle

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. 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. The media milling process can successfully process micronized and non-micronized drug crystals. Once the formulation and the process are optimized, very little batch-to-batch variation is observed in the quality of the dispersion.

Advantages

- Drugs that are poorly soluble in both aqueous and organic media can be easily formulated into nanosuspensions.
- 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 from1 to 400mgmL_1, enabling formulation of very dilute as well as highly concentrated nanosuspensions.

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.This could be problematic when nanosuspensions are 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.
- technique is time consuming and scale up is not easy due to mill size and weight.

II. Dry Co grinding

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.

Many soluble polymers and co-polymers such as PVP, polyethylene glycol (PEG), hydroxypropyl methylcellulose (HPMC) and cyclodextrin derivatives have been used 43. 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.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.

Advantages

- easy process
- no organic solvent required
- short grinding time

Disadvantages

- generation residue of milling media

b. High Pressure Homogenization

It is the most widely used method for the preparation of the nanosuspensions of many poorly water soluble drugs.Different methods developed based on this principle for preparation of nanosuspensions are Dissocubes, Nanopure, Nanoedge, Nanojet technology. 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. This technique involve the following three steps: First, drug powders are dispersed in a stabilizer solution to form Npresuspension; after that, presuspension is homogenized by high pressure homogenizer at a low pressure sometimes for premilling; and finally homogenized at a high pressure for10 to 25 cycles until the nanosuspensions are formed with desired size.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 pistongap homogenizers from Avestin(Avestin Inc., Ottawa, Canada) and Stansted (Stansted Fluid PowerLtd, 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. 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).

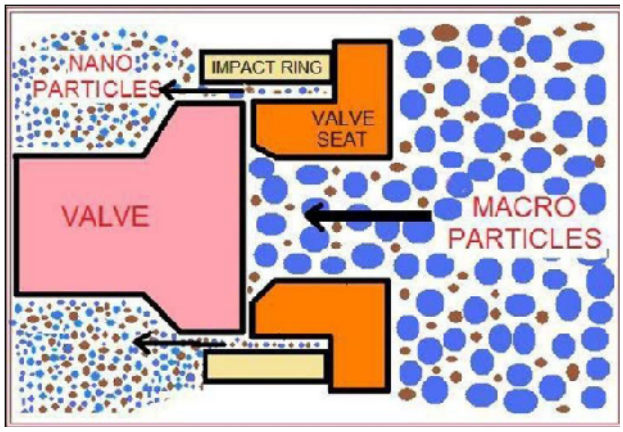


Figure 2: Schematic cartoon of the high-pressure homogenization process

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 25 μm, 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. To improve the efficiency of nano-sizing, the addition of viscosity enhancers is advantageous in certain cases as increasing the viscosity increases the powder density within the dispersion zone (homogenization gap).

Effect of homogenization pressure:

The homogenizer can handle varying pressures, ranging from 100 to 1500 bars. It is expected that the higher the homogenization pressure, the lower the particle size obtained.

Number of homogenization cycles

For many drugs it is not possible to obtain the desired particle size in a single homogenization cycle. Typically, multiple cycles are required. Hence, depending on the hardness of the drug, the desired mean particle size and the required

homogeneity of the product, homogenization can be carried out in three, five or 10 cycles. It is anticipated that the higher the number of homogenization cycles,the smaller the particle size obtained.

I. High Pressure Homogenisation In Water (Dissocubes)

Dissocubes technology was developed by Muller in 1999.The instrument can be operated at pressure varying from 100 to 1 500 bars (2 800 – 21 300 psi) and up to 2 000 bars with volume capacity of 40 ml (for laboratory scale). For preparation of nanosuspension, it is essential to prepare a presuspension of the micronized drug in a surfactant solution using high-speed stirrer. According to Bernoulli's Law, the flow volume of liquid in a closed system per crosssection isconstant. 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 cavitation) and normal air pressure is 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. Preprocessing like micronization of drug and high-cost instruments increases the overall cost of dosage form. Various drugs like Amphotericin B, Ordinon, Thiomerasol,Fenofibrate, Melarsoprol, Buparvaquone, Prednisolone, Carbamazepine And Dexamethasone were prepared as nanosuspensions using this method.

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.
- It allows aseptic production of nanosuspensions for parentral administration20.

Disadvantages

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

II. Homogenization In Nonaqueous Media (NANOPURE)

Nanopure is suspension homogenized in water-free medium. It is "deep-freeze" homogenization where the drug suspensions in no aqueous medium are homogenized at 0oC or sometimes below the freezing point. Because of very high boiling point and low vapor pressure of water, oils, and fatty acids, the drop of static pressure is not enough to begin cavitations in nanopure technology.

III. Microprecipitation – High-pressure homogenization (NANOEDGE):

The principle involved in Nanoedge 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.

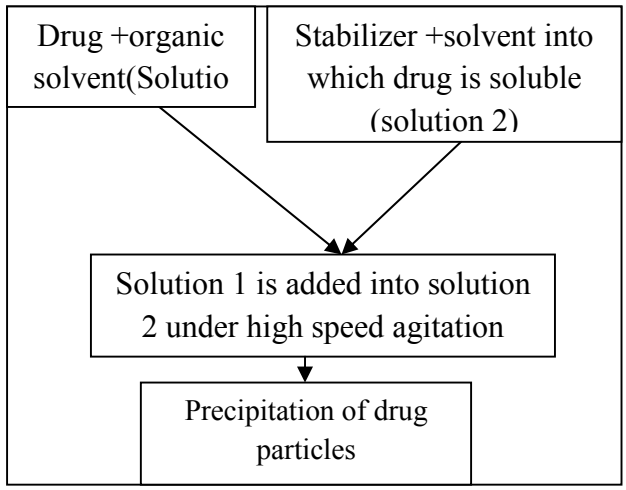


Figure 3: Method for preparation of nanoedge

IV. Nanojet Technology

This technique is also called opposite stream technology, uses a chamber where a stream of suspension is divided into two or more parts. Both streams are colloid with each other at high pressure. The high shear force produced during the process results in particle size reduction. Dearns had prepared nanosuspensions of atovaquone using the microfluidization process.

Disadvantage

- 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.

c. 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 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. Nanosuspension of ibuprofen was prepared by this method.

d. Supercritical Fluid Method

The organic solvents used in the preparation of conventional methods such 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 application of supercritical fluids for the production of nanoparticles has found widespread use due to a number of advantageous properties. Supercritical fluids exist at temperatures beyond their critical temperature (*Tc*) and pressures above their critical pressure (*Pc*), as shown in Figure. Supercritical fluids have diffusivities higher than those of traditional liquid solvents, viscosities similar to gases, and densities that can be tuned by small changes in pressure, all of which make them unique reaction media. Supercritical carbon dioxide (CO_2) is the most commonly used supercritical fluid for pharmaceutical particle production because it is nonflammable, nontoxic, inexpensive, and has mild critical parameters (Tc = 31.3 °C, Pc = 73.7 bar). Supercritical CO_2 has been used as both a solvent, in the rapid expansion of supercritical solution (RESS), and as an antisolvent, in the supercritical antisolvent (SAS), particle production technologies.

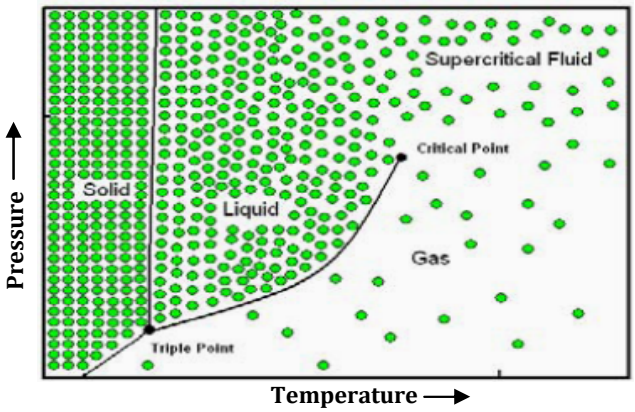


Figure 4: Generic pressure versus temperature phase diagram highlighting the supercritical fluid region

I. Rapid Expansion of Supercritical Solution (RESS)

In the RESS method, the pressure-dependent solubilizing power of supercritical CO_2 is exploited. A bulk drug is dissolved in supercritical CO_2 in a high pressure vessel. The solution is then depressurized through a nozzle into a collection vessel at ambient conditions. When depressurization occurs, the supercritical CO_2 becomes gaseous CO_2, in which the drug is not soluble, and the drug precipitates. The faster the rate of depressurization, the smaller the particles will precipitate. A schematic of the RESS process is given in Figure.

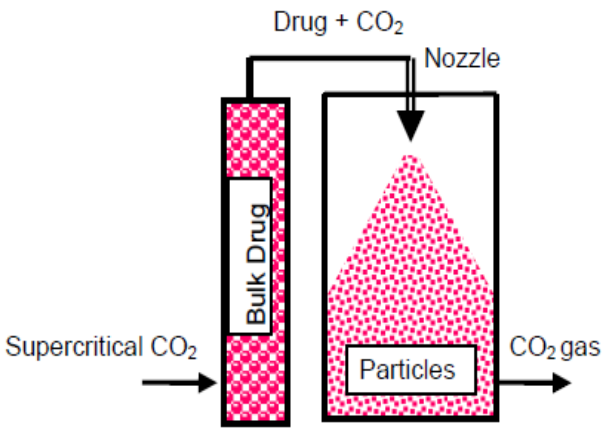


Figure 5: Schematic of RESS process

As with all particle production technologies, the conditions under which the process is carried out, such as solubilization temperature, expansion temperature, pressure drop across nozzle, and nozzle geometry, as well as the molecular structure of the drug, greatly affect particle morphology.

Disadvantage

- A disadvantage of the RESS process is the limited solubility of many pharmaceutical compounds in supercritical CO_2.

II. Supercritical Antisolvent (SAS)

In this method, the drug is dissolved in a liquid organic solvent and this solution is sprayed through a fine nozzle into a high pressure vessel filled with supercritical CO_2. As the CO_2 dissolves into the liquid solvent, the solubilizing power of the organic solvent is reduced, inducing supersaturation and causing particle precipitation. Excess CO_2 is flushed through the vessel to remove residual solvent and the vessel is depressurized to collect the particles. A schematic of the SAS process is shown in Figure.

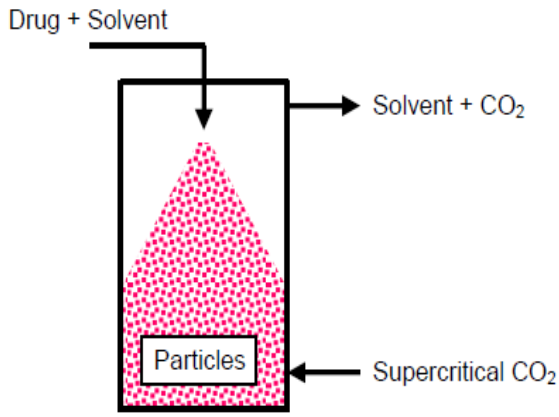


Figure 6: Schematic of SAS process

III. Precipitation with Compressed Antisolvent Process (Pcs)

In the PCA method, the drug solution is atomized into the CO_2 compressed chamber.As the removal of solvent occurs, the solution gets supersaturated and finally precipitation occurs.

Disadvantages of supercritical fluid method

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.

C. Other Methods

I. Emulsion as a template

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. Such solvents can be used as the dispersed phase of the emulsion. There are two ways of fabricating drug nanosuspensions by the emulsification method.

In the first method, an organic solvent or mixture of solvents loaded with the drug is dispersed in the aqueous phase containing suitable surfactants to form an emulsion. 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. Optimizing the surfactant composition increases the intake of organic phase and ultimately the drug loading in the emulsion. Originally, organic solvents such as methylene chloride and chloroform were used. However, environmental hazards and human safety concerns about residual solvents have limited their use in routine manufacturing processes. Relatively safer solvents such as ethyl acetate can still be considered for use. Another method makes use of partially water-miscible solvents such as butyl lactate, benzyl alcohol and triacetin as the dispersed phase instead of hazardous solvents. The emulsion is formed by the conventional method and the drug nanosuspension is obtained by just diluting the emulsion. Dilution of the emulsion with water causes complete diffusion of the internal phase into the external phase, leading to instantaneous formation of a nanosuspension. The nanosuspension thus formed has to be made free of the internal phase and surfactants by means of diultrafiltration in order to make it suitable for administration. However, 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.The production of drug nanosuspensions from emulsion templates has been successfully 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.

Advantages

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

Disadvantages

- Drugs that are poorly soluble in both aqueous and organic media cannot be formulated by this technique.
- Safety concerns because of the use of hazardous solvents in the process.
- Need for 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.

II. 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 .Their advantages such as high drug solubilization, long shelf-life and ease of manufacture, make them an ideal drug delivery vehicle.Taking advantage of the microemulsion structure, one can use microemulsions even for the production of nanosuspensions. Oil-in-water microemulsions are preferred for this purpose. The internal phase of these microemulsions could be either a partially miscible liquid or a suitable organic solvent, as described earlier. 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. 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 nanosuspension thus formed has to be made free of the internal phase and surfactants by means of diultrafiltration in order to make it suitable for administration. However, 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. 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.

Advantages of Nanosuspensions:

A. Increase in the dissolution velocity and saturation solubility of the drug

This is an important advantage that makes nanosuspensions amenable to numerous applications. The reason behind the increase in the dissolution velocity and saturation solubility of the nanosuspensions can be given as follows. According to the Nernst–Brunner and Levich modification of the Noyes Whitney dissolution model equation,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:

$$\frac{dX}{dt} = \frac{(D \times A)}{h} \times \frac{(C_s - X)}{V}$$

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.

The increase in the saturation solubility of the drug with a decrease in particle size can be explained by Ostwald–Freundlich's equation:

$$\mathbf{Log\ (Cs/\ C\alpha) = 2\sigma V/2.303RT\rho r}$$

where Cs is the saturation solubility, Cα is the solubility of the solid consisting of large particles, σ is the interfacial tension of substance, V is the molar volume of the particle material, R is the gas constant, T is the absolute temperature, ρ is the density of the solid and r is the radius.

B. Improved biological performance

An increase in the dissolution velocity and saturation solubility of a drug leads to an improvement in the in vivo performance of the drug irrespective of the route used.

C. Ease of manufacture and scale-up

Unlike nanoparticulate carriers such as polymeric nanoparticles, which were investigated earlier, nanosuspensions are easy to manufacture.

D. Long-term physical stability

Another special feature of nanosuspensions is the absence of Ostwald ripening, which is suggestive of their long-term physical stability. Ostwald ripening has been described for ultrafine dispersed systems and is responsible for crystal growth and subsequently formation of Microparticles.

E. 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.

Evaluation of Nanosuspensions:

The characterization of the nanosuspensions is also similar to that of the suspensions such as colour, odour, presence of impurities and other important characteristics as mentioned below.

A. In-Vitro Evaluations

B. In-vivo evaluation

a. Particle size and size distribution

It is the most important parameter in the evaluation of the suspensions as it is having the direct effect on the solubility and dissolution rate and the physical stability of the formulation. The mean particle size and the width of particle size can be determined by Photon Correlation Spectroscopy (PCS) laser diffraction and coulter current multisizer. Particle size and polydispersity index (PI) governs the saturation solubility, dissolution velocity and biological performance. PCS measures the particle size in the range of 3nm-3 µm only. PI governs the physical stability of nanosuspension and should be as low as possible for long-term stability (Should be close to zero). LD measures volume size distribution and measures particles ranging from 0.05- 80µm upto 2000µm. Atomic Force Microscopy is used for visualization of particle shape. 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.

b. Particle charge (Zeta Potential)

The particle charge is of importance in the study of the stability of the suspensions. Usually the zeta potential of more than ±40mV will be considered to be required for the stabilisation of the dispersions. For electrostatically stabilized nanosuspension a minimum zeta potential of ±30mV is required and in case of combined steric and electrostatic stabilization it should be a minimum of ±20mV of zeta potential is required.

c. Crystalline Sate and Particle Morphology

It is of importance as there are chances of the polymorphism during the storage of the nanosuspensions. Hence it is necessary to study the crystal morphology of the drug in suspension. Differential Scanning Calorimetry (DSC) is most commonly used for such studies. When nanosuspensions are prepared drug particles may get converted to amorphous form hence it is essential to measure the extent of amorphous drug generated during the production of nanosuspensions. The X-Ray Diffraction (XRD) is commonly used for determining change in crystallinity and the extent of the amorphous form of drug.

d. Saturation solubility and Dissolution Velocity

The main advantage associated with the nanosuspensions is improved saturation solubility as well as dissolution velocity. These are studied in different physiological solutions at different pH. Kelvin equation and the Ostwald-Freundlich equations can explain increase in saturation solubility. Determination of these parameters is useful to assess in vivo performance of the formulation.

e. Stability of Nanosuspensions

Stability of the suspensions is dependent on the particle size. As the particle size reduces to the nanosize the surface energy of the particles will be increased and they tend to agglomerate. So stabilizers are used which will decrease the chances of Ostwald ripening and improving the stability of the suspension by providing a steric or ionic barrier. Typical examples of stabilizers used in nanosuspensions are cellulosics, poloxamer, polysorbates, lecithin, polyoleate and povidones. Lecithin may be preferred in developing parenteral nanosuspensions.

B. In vivo evaluation

The in vivo evaluation of the nanosuspensions is specific to drug and route of administration. Most commonly the formulation was given by required route of administration and the plasma drug levels were estimated using HPLC-UV visible Spectrophotometry.

- Surface hydrophilicity/hydrophobicity (determines interaction with cells prior to phagocytosis)
- Adhesion properties
- interaction with body proteins

Applications:

A. Parenteral administration

Nanosuspensions can be administered via different parenteral administration routes ranging from intraarticular via intraperitonal to intravenous injection. For administration by the parenteral route, the drug either has to be solubilized or has particle/globule size below 5 ìm to avoid capillary blockage. Paclitaxel nanosuspensions revealed their superiority over taxol in reducing the median tumour burden.Similarly, aphidicolin, a poorly water soluble new anti-parasitic lead molecule, when administered as a nanosuspension resulted in an improvement in EC50 in comparison to DMSO-dissolved drug.

B. Oral drug delivery

The oral route is the preferred route for drug delivery because of its numerous well-known advantages. The efficacy or performance of the orally administered drug generally depends on its solubility and absorption through the gastrointestinal tract. Hence, a drug candidate that exhibits poor aqueous solubility and/or dissolution-rate limited absorption is believed to possess low and/or highly variable oral bioavailability. Owing to low oral bioavailability, such a drug candidate would have to be administered in a larger excess than actually required if it were completely bioavailable in order to achieve a therapeutically active concentration, thus making the therapy costly. Orally administered antibiotics such as atovaquone and bupravaquone reflect this problemvery well.Nanosizing of such drugs can lead to a dramatic increase in their oral absorption and subsequently bioavailability. The amelioration in oral bioavailability can be attributed to the adhesiveness of the drug nanosuspension, increased surface area (due to reduction in particle size by 10–50-fold), increased saturation solubility, leading to an increased concentration gradient between the gastrointestinal tract lumen and blood, and increased dissolution velocity. This enhancement in bioavailability will lead to a subsequent reduction in drug dose, rendering the therapy cost-effective and obliterating any undue drug dumping in the body.

C. Ophthalmic drug delivery

Nanosuspensions could prove to be vital for drugs that exhibit poor solubility in lachrymal fluids. Suspensions offer advantages such as prolonged residence time in a cul-de-sac, which is desirable for most ocular diseases for effective treatment and avoidance of high tonicity created by water soluble drugs. One example of a nanosuspension intended for ophthalmic controlled delivery was developed as a polymeric nanosuspension of ibuprofen. This nanosuspension is successfully prepared using Eudragit RS100 by a quasi-emulsion and solvent diffusion method.

D. Pulmonary drug delivery

Aqueous nanosuspensions can be nebulized using mechanical or ultrasonic nebulizers for lung delivery. Budesonide, a poorly water-soluble corticosteroid, has been successfully prepared as a nanosuspension for pulmonary delivery.

E. Target drug delivery

Nanosuspensions can also be used for targeted delivery as their surface properties and *in vivo* behavior can easily be altered by changing either the stabilizer or the milieu. Their versatility, ease of scale up and commercial product enable thedevelopment of commercial viable nanosuspensions for targeted delivery. Targeting of *Cryptosporidium parvum*, the organism responsible for cryptosporidiosis, was achieved by using surface modified mucoadhesive nanosuspensions of bupravaquone.

F. Topical formulations

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

CONCLUSION:

Nanosuspensions appear to be a unique and yet commercially viable approach to combating problems such as poor bioavailability that are associated with the delivery of hydrophobic drugs, including those that are poorly soluble in aqueous as well as organic media. Production techniques such as media milling and high-pressure homogenization have been successfully

employed for large-scale production of nanosuspensions. The advances in production methodologies using emulsions or micro emulsions as templates have provided still simpler approaches for production but with limitations. Further investigation in this regard is still essential. Attractive features, such as increased dissolution velocity, increased saturation solubility, improved bioadhesivity, versatility in surface modification and ease of post production processing, have widened the applications of nanosuspensions for various routes. The applications of nanosuspensions in parenteral and oral routes have been very well investigated and applications in pulmonary and ocular delivery have been realized. However, their applications in buccal, nasal and topical delivery are still awaiting exploration. The development of stealth nanosuspensions laced with functionalized surface coatings capable of eliciting passive or active targeting as per the requirement can be regarded as the future step in the nanosuspension research.

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