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NANOSUSPENSION: A NOVEL TECHNOLOGY FOR THE DRUG DELIVERY SYSTEM

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ABSTRACT

Poor solubility of the drug decreases the bioavailability of the drug. This problem is more worsen because of more than the 40% of the newly discovered drug product are poorly water soluble. Formulation of these mainly the BCS class II and BCS class IV drug into the conventional dosage form is a challenging problem faced by the pharmaceutical scientist. Nanosuspension can be used to solve the problems of poor bioavailability. Nanosuspension is the colloidal dispersion of the drug particle in an aqueous vehicle, which is stabilized by the surfactant or polymer or both. Nanosuspension increases the saturation solubility and dissolution rate. Nanosuspension can be prepared by the bottom up and top down approaches such as nanoprecipitation, media milling, high pressure homogenization, solvent evaporation etc. Nanosuspension delivered through the various route like oral, parenteral, ocular and topical. The following review article focuses onto the advantages, disadvantages, methods of preparation, characterization and applications of nanosuspension.

KEYWORDS: Nanosuspension, colloid, saturation solubility, dissolution rate, bioavailability

INTRODUCTION

Formulation of the poorly water soluble drug into the suitable dosage form has always been a challenging problem faced by the formulation scientist. More than the 40% or more of the new chemical entities being generated through the drug discovery programme are poorly water soluble or lipophilic compound. Therefore the pharmaceutical industries are constantly

seeking new approach in order to obtain an adequate oral bioavailability of this type of new chemical entities. Formulation of poorly water soluble or practically insoluble (i.e. BCS class II and BCS class IV drug) drug has always been a challenging problem confronted by the pharmaceutical scientist. The formulation of drug nanosized particle can be implemented to all the compounds belonging to the BCS class II and BCS class IV to increase their solubility, dissolution and hence their absorption into the gastrointestinal tract. The low saturation solubilility and dissolution velocity leads to the poor bioavailability. The problem which are more severe to the drug such as Itracanazole and carbamazepine (BCS class II) as they are poorly soluble in the both the aqueous and organic phase.[1-4]

There are number of formulation approach have been used to solve the problems associated with the low solubility and bioavailability of the drug such as micronization, use of co-solvent, use of permeation enhancer, surfactant dispersion, salt formation and precipitation technique, microsphere, emulsion, microemulsion, Liposomes, supercritical processing, Solid Dispersion and Inclusion complex formation with β–CD, but they lack the universal applicability to all drugs. These methods have some limitations such as addition of large amount of additives and toxicity problems. In case of the drug that are insoluble in both organic as well as aqueous media instead of using lipidic system, nanosuspension are used as a formulation approach. Nanosuspension have revealed their potential to undertake the problems associated with the delivery of poorly water soluble and lipid soluble drugs and are unique because of their simplicity and the advantages they confer over the other strategies.[2-6]

Nanosuspension

Nanosuspension is the colloidal dispersion of the fine drug particle in the aqueous vehicle which is stabilized by surfactant, polymer, or the mixture of both. They can also be defined as the biphasic system consisting of pure drug particle dispersed in an aqueous vehicle in which the diameter of the suspended particle is less than 1 micrometer in size. The particle size distribution of the solid drug particle in the nanosuspension is less than 1µ with the average particle size in the range of 200 and 600nm. Reduction of the drug particle to the nanometer range which leads to increase in dissolution rate not only because of the increase in surface area but also due to increase in saturation solubility. Nanosuspension which is suitable for the compound with high melting point, High log P value, and high dose.[2- 12]

Nanosuspension was derived from the two words, ‘Nano’ is a greek word, which means dwarf, or which means very small nanorange and ‘suspension’ is a biphasic liquid system or

the biphasic dosage form i.e. combination of two phases. Nano means it is the factor of 10^{-9} or one billionth. Some comparision of nanoscale are given below,[2,4]

0.1nm = Diameter of 1 H atom

2.5nm = Width of DNA molecule

1µ = 1000nm

1nm = 10^{-9} m = 10^{-7} cm = 10^{-6} mm

µ = 10^{-6} m = 10^{-4} cm = 10^{-3} mm

Nanosuspension differ from the nanoparticle. Nanoparticle is commonly the polymeric colloidal carrier. In the nanosuspension the drug molecule can be maintained in the crystalline state which leads to increase dissolution rate and improve the bioavailability. Drug particle size reduction leads to an increase in the surface area and consequently the rate of dissolution as described by the Nernst Brunner and Levich modification of the Noyes – Whitney equation.

$$dx/dt = DA/h\ (Cs- x/V)$$

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

In addition an increase in saturation solubility is postulated by particle size reduction due to increase in dissolution pressure explained by the Ostwald – Freundlich equation.

$S= S_{\infty} \exp. (2\gamma M/r\rho RT)$

Where s is the saturation solubility, S saturation solubility of the infinitely large crystal, is the interfacial tension, is the density, r particle radius, M is the molecular weight, R is the gas constant and T is the temperature.

Depending upon the production technique changes into the crystalline structure occur. An increasing amount of the amorphous fraction induce the higher saturation solubility.[6,10,13-15]

Advantages of nanosuspension

- ✓ It can be applied for the poorly water soluble drugs.
- ✓ Long term physical stability due to the presence of stabilizers.
- ✓ Nanosuspension can be incorporated in tablets, pellets, hydrogels and suppositories.
- ✓ Rapid dissolution and tissue targeting can be achieved by IV route of administration.

- ✓ Improved in biological performance due to high dissolution rate & saturation solubility of the drug.
- ✓ Reduced tissue irritation in case of subcutaneous/intramuscular administration.
- ✓ The absorption from absorption window of the drugs can be increased, due to reduction in the particle size.
- ✓ Drugs with high log P value can be formulated as nanosuspensions to increase the bioavailability of such drugs.
- ✓ Dose reduction is possible.
- ✓ Increase the physical and chemical stability as they are in the solid state.
- ✓ Nanosuspension provide the passive targeting of the drug.

Disadvantages of nanosuspension

- ✓ Physical stability, sedimentation & compaction can cause problems.
- ✓ It is bulky sufficient care must be taken during handling & transport.
- ✓ Uniform & accurate dose cannot be achieved.

Criteria for the selection of drug candidate for the preparation of nanosuspension

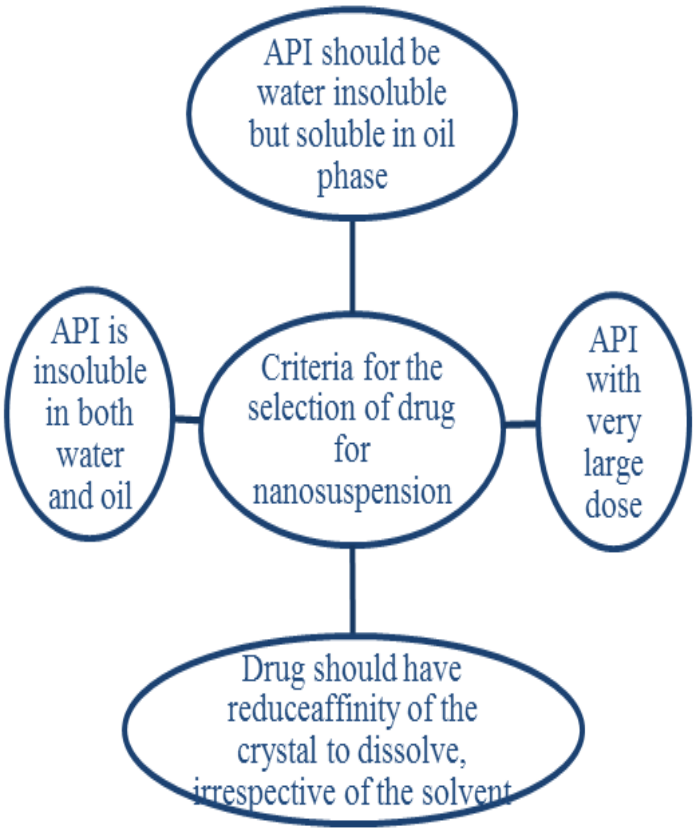


Fig. 1: Criteria of drug selection.

Post production processing

Due to the stability problem the nanosuspension can be converted to the solid dosage form by lyophilisation and spray drying. Nanosuspension converted to the powder, tablet, capsule and pellets. Matrix former should be added into it to prevent destabilization of the particle due to the creating additional thermal stresses such as heating during spray drying and freezing during lyophilisation.[14, 16-18]

Method of preparation of nanosuspension

Mainly there are two methods of the nanosuspension preparation. The conventional method of precipitation is called 'Bottom up Technology'. The 'Top Down Technologies' are the disintegration method and which are preferred over the precipitation method. The top down technologies which include media milling (Nanocrystals), High Pressure homogenization in Water (Dissocubes), High Pressure Homogenization in Non-aqueous Media (Nanopure), and the combination of precipitation and High Pressure Homogenization (Nanoedge).[4,19]

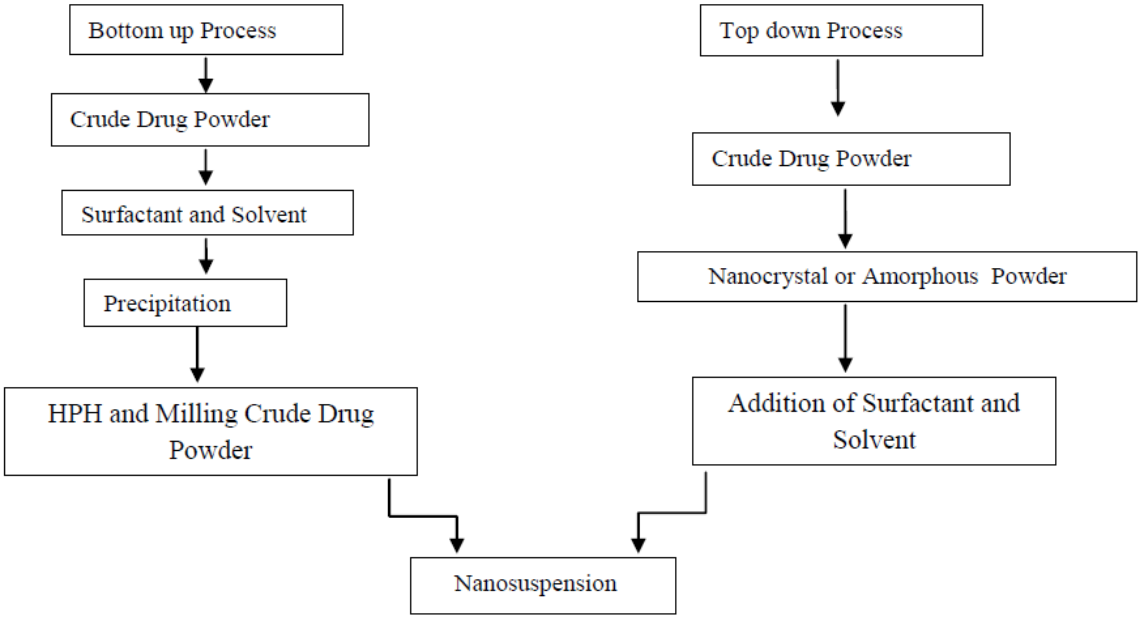


Fig. 2: Approaches for the preparation of Nanosupension.[20]

A) Bottom up technology

As the name suggest this approach starts from molecular level, and goes via the molecular association to the formation of solid particles. The conventional method of precipitation are called Bottom up Technology.[21]

Advantages

1. Use of simple and low cost equipment.
2. Higher saturation solubility is the advantage for precipitation compared to other methods of Nanosuspension preparation.

Disadvantages

1. The drug needs to be soluble in at least one solvent (thus excluding all new drugs that are simultaneously poorly soluble in aqueous and in organic media).
2. The solvent needs to be miscible with at least one nonsolvent.
3. Solvent residues need to be removed, thus increasing production costs.
4. It is a little bit tricky to preserve the particle character (i.e. size, especially the amorphous fraction). In general, it is recommended that a second consecutive process has to be performed for particle preservation that is spray drying or lyophilisation.[4]

1. Nanoprecipitation method/Antisolvent precipitation

It is an effective way to prepare micro or nano sized drug particle. Using the precipitation technique the drug which is dissolved in the organic solvent and this solution is mixed with miscible antisolvent in the presence of suitable surfactant. Rapid addition of the drug solution into the antisolvent leads to the supersaturation of drug. In the precipitation involves two phases nuclei formation and crystal growth. When preparing the stable nanosuspension with a minimum particle size, a high nucleation rate and but low growth rate is necessary. Both the rate is depend on temperature. Nanoprecipitation method also known as solvent displacement method as well as antisolvent precipitation method.[20,15]

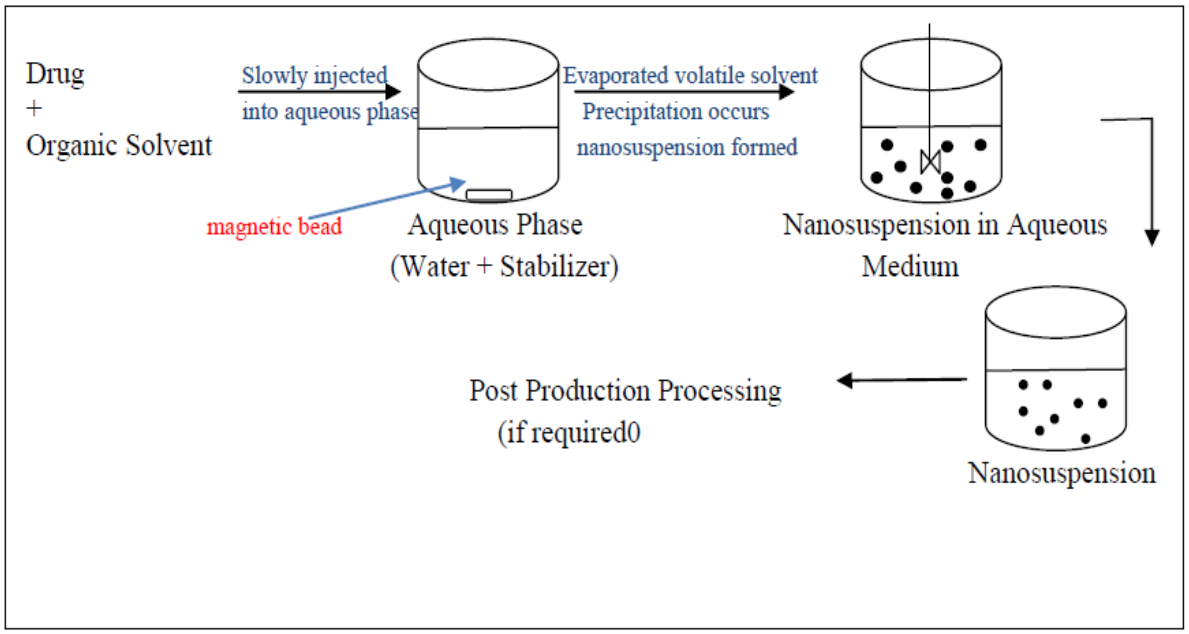


Fig. 3: Nanoprecipitation method for the preparation of nanosuspension.

Advantages

1. Simple process
2. Ease of scale up
3. Low cost equipment

Disadvantages

1. Drug is soluble in at least one solvent and this solvent needs to be miscible of non-solvent.
2. Growing of drug crystal needs to be limited by surfactant addition.[9]

A) Top down technology

It is the disintegration method. This method is preferred over the precipitation method. This method involves Media milling and HPH.[9,22]

1. Media milling technique

Used for the preparation of nanosuspension. The nanosuspension is prepared by using high shear media mills or pearl mills.

The mills consist of

Milling Chamber

Milling Shaft

Recirculation Chamber

In the media milling process, the milling chamber is charged with a milling media, water, drug and stabilizer. After that the milling media or pearls are rotated at a very high shear rate.

Principle: The high shear rate which leads to the impaction of the milling media with drug leads to the breaking of the micronized drug particle to nanosized particle. The milling media which is composed of glass, zirconium oxide, or highly cross linked polystyrene resin. The unimodel distribution profile and the mean diameter of <200 requires a time of 30-60min. It is suitable for batch operation and continuous operation.[4,9, 22]

Advantage

1. Both dilute as well as concentrated nanosuspension can be prepared.
2. Nanosized distribution of final nanosized particle.
3. Large-scale production possible to some extent (batch process).

Disadvantage

1. Ball residues will be present as contamination in the final product.
2. More time consuming.
3. Duration of the process not being very production friendly.
4. Potential growth of germs in the water phase when milling for a long time.
5. Time and costs associated with the separation procedure of the milling material from the drug nanoparticle suspension, especially when producing parenteral sterile products.[4,9]

2. High pressure homogenization

The process was developed by the R. H. Muller in 1999 (Dissocube Method) & the first patent was taken by the DDS Gmbh. Later the patent was transferred to Skype pharmaceuticals. This technique used for the poorly water soluble drug. In which the instrument is operated at a pressure of 100-1500 bars & it can be extended to upto 2000bars, with the mainly volume capacity of about 40ml. This pressure is sufficient to convert the micronized particle to the nanosize range.[21-22]

Principle

During the homogenization, the fracture of the drug particle is brought about by the cavitation, high shear forces, & the collision of the particle against each other. The particle cavitation forces are sufficiently high to convert the drug macroparticles into nanoparticle.[3]

Advantage

1. Useful for formation of very dilute as well as highly concentrate nanosuspension aseptic production scale.
2. Low risk of product contamination.
3. Drugs that are poorly soluble in both aqueous and organic media can be easily formulated into nanosuspension.

Disadvantage

1. Prerequisite of micronized drug particle.
2. Prerequisite of suspension formation using high speed mixture before subjecting it to homogenization.[9]

3. Dissocubes (Homogenization in water)

Muller developed this technique in 1999. In the dissocube technique dispersion medium of the suspension is water. This technique can be operated at a varying pressure from 100 – 1500 bars and upto 2000 bars with the volume capacity of 40ml. Homogenization involves the forcing of the suspension under pressure through a valve having a narrow aperture. In this case, the suspension of the drug is made to pass through a small orifice that result in a reduction of the static pressure below the boiling pressure of water, which leads to boiling of water and formation of gas bubbles. When the suspension leaves the gap and normal air pressure is reached again, the bubbles implode and the surrounding part containing the drug particles rushes to the center and in the process colloids, causing a reduction in the particle size. Most of the cases require multiple passes or cycles through the homogenizer, which depends on the hardness of drug, the desired mean particle size and the required homogeneity. Before subjecting the drug to the homogenization process, it is essential to form a pre-suspension of the micronized drug in a surfactant solution using high-speed stirrers. The major advantage of high- pressure homogenization over media milling is that it can be used for both diluted as well as concentrated suspensions and also allows aseptic production.[2, 4,6,22]

4. Nanopure (Homogenization in non-aqueous media)

Nanopure it is a technique in which the dispersion medium is water free media or water mixture. In nanopure technology, the drug suspensions in the non- aqueous media were homogenized at 00 C or even below the freezing point and hence are called "deep-freeze" homogenization. The results obtained were comparable to DissoCubes and hence can be used

effectively for thermolabile substances at milder conditions. The nanocrystals of the drug dispersed in liquid polyethylene glycol (PEG) or various oils can be directly filled as drug suspensions into HPMC capsules or gelatin.[4, 12, 22]

5. Nanoedge (Combined precipitation and homogenization)

The basic principle of nanoedge technology is same as that of precipitation and homogenization. The drug is dissolved in an organic solvent and this solution is mixed with a miscible anti-solvent for precipitation. In the water-solvent mixture, the solubility is low and the drug precipitates. Precipitation has also been coupled with high shear processing. A combination of these techniques results in smaller particle size and better stability in a shorter time. The major drawback of the precipitation technique, such as crystal growth and long-term stability, can be resolved using the Nanoedge technology.[4,12, 22]

6. Nanojet

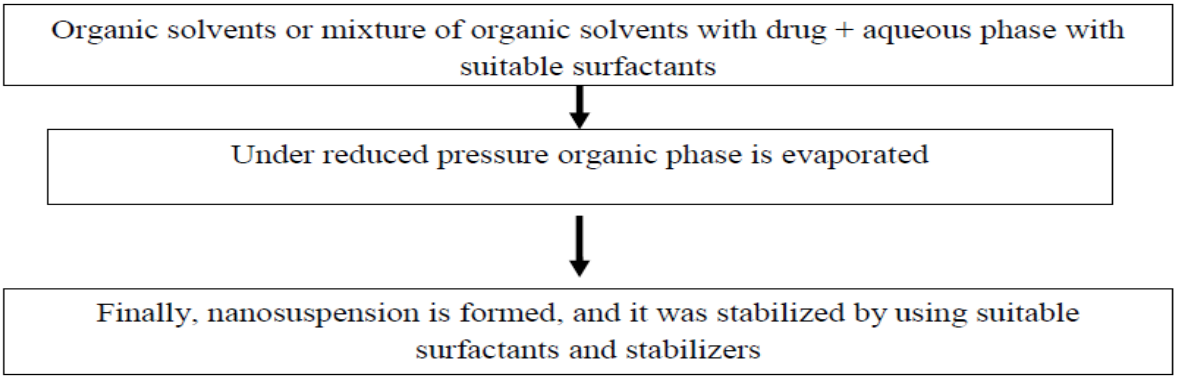
This technique, called 'opposite stream or Nanojet technology', uses a chamber where a stream of suspension is divided into two or more parts, which colloid with each other at high pressure upto 4000 bar at the high velocity of 1000m/s. The high shear force produced during the process results in particle size reduction.[12]

7. Emulsion as a template[4, 19, 22]

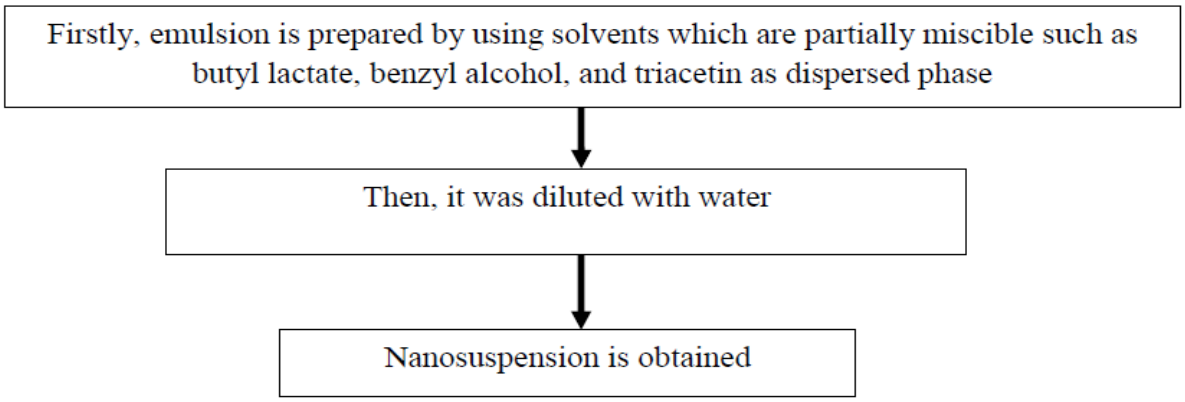
Apart from the use of emulsion as drug delivering vehicle they can also be used as templates to produce nanosuspension. The use of emulsions as templates is applicable for those drugs that are soluble in either volatile organic solvent or partially water-miscible solvent. Such solvents can be used as the dispersed phase of the emulsion.

This method is done by two types

Type 1:



Type 2:



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

8. Microemulsion as a template

This technique follows an organic solvent or mixture solvent loaded with the drug dispersed in an aqueous phase containing suitable surfactants to form an emulsion. The organic phase is then evaporated under reduced pressure to make drug particles precipitate instantaneously to form the nanosuspension which is stabilized by surfactants. 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.[4, 10, 22]

The advantages and disadvantages are similar to emulsion as templates.

9. Supercritical fluid method

Supercritical fluid technology can be used to produce nanoparticles from drug solutions. 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 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. s. 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. The drug solution is injected into the supercritical fluid and the solvent gets extracted by the supercritical fluid and the drug solution gets supersaturated. The drug is then precipitated as fine crystals.

Disadvantages

- ✓ Use of hazardous solvents and use of high proportions of surfactants and stabilizers as compared with other techniques,
- ✓ Particle nucleation overgrowth due to transient high super saturation, which may also result in the development of an amorphous form or another undesired polymorph.[7,22]

10. Melt emulsification method

In this technique the drug is dispersed in the aqueous solution of stabilizer and this mixture was heated above the melting point of the drug and homogenized to form emulsion. During the heating process the sample holder was enwrapped with a heating tape fitted with temperature controller and to maintain the temperature of emulsion above the melting point of drug. The emulsion was cooled down either at room temperature or in the ice bath.

Advantage

Melt emulsification technique relative to the solvent diffusion method is total avoidance of organic solvents during the production process.[2,7,10,21]

11. Dry -co-grinding

Recently, nanosuspensions can be obtained by dry milling techniques. This technique can prepare the stable nanosuspension by dry milling of the poorly water soluble drug with a soluble polymer after dispersing into the liquid media. Dry grinding helps to improve the

surface polarity of the drug. Various water soluble polymer and co-polymer can be used like PVP, polyethylene glycol (PEG), hydroxypropyl methylcellulose (HPMC) and cyclodextrin derivatives etc.[4, 21, 22]

Formulation consideration of nanosuspension[2,4,21,22]

1. Stabilizer

The main function of stabilizer to wet the drug particle & prevent Ostwald ripening. It can provide physically stable formulation by steric and ionic barrier and prevent agglomeration of nanosuspension. The type and amount of stabilizer have pronounced effect on physical stability and in vivo behaviour of the nanosuspension.

Example – Poloxamer, Polysorbates, Cellulosics, Povidones, Lecithin's.

Lecithin is the choice of stabilizer for the parenteral and autoclavable nanosuspension. The drug to stabilizer ratio in the formulation is 1:20 to 20:1. In some cases mixture of stabilizer is required to obtain a stable nanosuspension.

2. Organic solvents

Pharmaceutically less hazardous water miscible solvents are used for the preparation of nanosuspension.

Table 1: Types of organic solvent used in the preparation of nanosuspension.

Sr. no.	Solvent	Example	Remark
I	Water Miscible Solvents	Methanol, Ethanol, Chloroform and Isopropanol	Pharmaceutically acceptable and less hazardous
II	Partially Water Miscible Solvents	Ethyl acetate, Ethyl formate, Triacetin, Propylene carbonate, Benzyl Alcohol	Prefferd over the conventional hazardous solvents

3. **Surfactant:** Surfactant is used to improve the dispersion by reducing the interfacial tension. They act as a wetting or foaming agent.
   Example – Tween 80 or span

4. **Co- surfactant:** The choice of surfactant is critical when using micro- emulsion to formulate nanosuspension.
   Example – Ethanol, Glycofurol, Bile Salts, Transcutol

5. **Other additives:** Depending on the route of administration or the properties of the drug moiety, nanosuspension may contain additives such as buffers, salts, polyols, osmogent, cryoprotectants.

Applications of nanosuspension[4,12,21,22,23,24]

1. **Oral drug delivery system**

In the conventional dosage form there are number of problem such as poor bioavailability and inadequate dissolution. Therefore the oral nanosuspension solve these problem due to the increase surface area, adhesiveness leads to improve the dissolution rate and absorption. Nanosuspension can lead to increased mucoadhesion which can increase gastrointestinal transit time and lead to increased bioavailability. The enhancement in oral bioavailability can be attributed to increased surface area, saturation solubility and the adhesiveness of the drug Nanosuspension. Taste masking of particulate system is also easily possible.

2. **Parenteral drug delivery**

In this day, number of methods is available to increase solubility such as solublization, vesicular system, salt formation, cyclodextrin complexation, but these methods have some problem like cost of manufacturing process, acceptability of parenteral and solublization capacity, therefore nanosuspension technology is used to solve above problem. Nanosuspensions can be used to transform poorly soluble non-injectable drugs into a formulation suitable for intravenous administration.

3. **Ocular drug delivery**

Nanosuspension is also used for ocular drug delivery to sustain the release of drug. Nanosuspension attains saturation solubility in the lachrymal fluid, representing an ideal approach for the ocular delivery of the hydrophobic drug. The size of the nanosuspension is suitable for topical ocular drug delivery.

4. **Pulmonary drug delivery**

Nanosuspension can be advantageous for delivering drugs that exhibit poor solubility in pulmonary secretion. Currently available approaches for pulmonary delivery such as aerosols or dry powder inhalers possess certain disadvantages such as limited diffusion at required site, less residence time etc, which can be overcome by Nanosuspension.

5. Transdermal drug delivery

Drug nanoparticles can also be incorporated into water free ointment and cream, which have an increased saturation solubility and enhanced diffusion of the drug into the skin. 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 drug into the skin.

6. Targeted drug delivery

Nanosuspension can play a crucial role in the targeting the particular organ which is affected by any disease or disorder. The phagocytotic uptake of nanocrystals can be avoided by preparing stealth nanocrystals or by preparing smart crystals i.e. drug particles below particle size of 100nm, which can be used as a targeted drug delivery system. Due to method simplicity, development of nanosuspension is a commercially viable option for targeted delivery. The surface properties of particles such as surface hydrophobicity, charge, presence and concentration of certain functional groups determine its organ distribution. Thus, Tween 80 coated nanocrystals can be used for brain targeting.

7. Bioavailability enhancement

Poor solubility, poor permeability or poor stability of a drug in the gastrointestinal tract (GIT) renders the poor oral bioavailability of the drug. Nanosuspensions enhance the bioavailability by increasing the solubility and permeability of the drug across the membrane.

Characterization of nanosuspension

1. Color, odor and taste

This parameter is important for the orally administered nanosspension formulation. Changes into the color, odor and taste indicated the chemical instability of the nanosuspension formulation.[4]

2. Mean particle size and particle size distribution

There are various techniques for determining the particle size distribution such as photon correlation spectroscopy (PCS). PCS determining the width of the particle size distribution (PI, Polydispersity index). PI value in the range of 0.1 to 0.25 indicates the narrow size distribution & PI value in the range of o.5 indicates very broad distribution. Laser Diffraction (LD) & Coulter counter multisizer. PCS can be used to measure the particle size distribution in the range of 3nm to 3µm and LD used to measure the particle size in the range of 0.05 to

80µm The particle size distribution having the direct impact on the solubility, dissolution rate and the stability of the nanosuspension. Motic microscope can also be used for determining the particle size.[3,6,9,19,25]

3. Zeta potential

Zeta potential is an important parameter for the stability of the nanosuspension. A minimum zeta potential of ±30mV is required for electrostatically stabilized nanosuspension and ±20mV is required for both the steric and electrostatically stabilized nanosuspension. The particle surface charge is ideally quantified in terms of zeta potential.[26-27]

4. Dissolution velocity and saturation solubility

Nanosuspension increases the dissolution velocity as well as saturation solubility. This parameter can be determined in various physiological medium at different temperature. Ostwald freundlich equation and Kelvin equation explain the increase in saturation solubility. It can help in determining the in vivo behavior of the formulation.[19,25,27-28]

5. Stability

Stability of the nanosuspension depends on the particle size. As the particle size of the nanosuspension decreases to the nanorange it can increases the surface energy and they tend to agglomerate. To reduce the agglomeration of the particle stabilizers can be used. Stabilizers provide the steric or ionic barrier to the particle surface. Nanosuspension can be stored at different stress conditions like it can be stored at different temperature condition, thermal cycling and mechanical shaking and changes into the mean particle size observed followed for 3 month.[12,18]

6. Drug content

Drug content of the nanosuspension can be determined by extracting the nanosuspension in suitable solvent. After that centrifuged it and supernatant can be assessed by using UV at absorbance maxima. The drug cont0ment can be determined by using calibration curve.[6,12]

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