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Review

Formulation Aspects Of Nanosuspension In Drug Delivery: A Review

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Abstract Low bioavailability is one of the critical problems associated with poorly solubl Published on: 04 Oct 2024 drugs. The problem becomes more complicated for drugs belonging to BCS Class I category. Hence, a promising and an attractive alternative to the above problem is formulating the BCS Class II drugs as nanosuspension. Nanosuspensions are biphasic Published by: systems and submicron colloidal dispersions of nanosized pure drug particles in a liquid **DrSriram Publications** phase stabilized by polymers and surfactants. The method of preparation of nanosuspension is very simple and applicable to a wide variety of water insoluble drugs A nanosuspension also alters the pharmacokinetic properties of a drug and henc 2024 All rights reserved. enhances the safety and efficacy in addition to overcoming the problems of poo solubility and bioavailability. A few techniques that are commercially employed for the manufacturing of nanosuspension are high-pressure homogenization, media milling, etc The unique characteristics of Nanosuspension has enabled its use by various routes sucl **Creative Commons** as an oral, pulmonary, ocular, topical, and mucoadhesive. Improved drug dispersibility Attribution 4.0 International and drug solubilization, enhanced therapeutic efficacy and reduced toxicity are the few License. among the numerous advantages possessed by the nanosuspension. Therefore, the presen review focusses on the achievements of nanosuspensions in the drug delivery system is order to improve the solubility, stability, and bioavailability of the drugs. Preparation methods and applications of the nanosuspensions are described in this review article. **Keywords:** Nanosuspension, Drug Delivery System, Pharmacokinetic Properties, Bioavailability.

INTRODUCTION

Drug delivery system is a system that enables the introduction of therapeutic agents in the body and enhances its safety and efficacy by controlling the time, rate and place of release in the body [1]. It is typically concerned with the duration and quantity of presence of drug [2]. A wide range of parameters like stability and

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solubility at room temperature, compatibility with solvent, excipient, and photostability play a crucial role in the successful formulation of drugs. Studies also highlight that about 40% of the new chemical entities or compounds being generated by drug discovery programs or by the pharmaceutical industry are lipophilic or poorly water soluble or "insoluble" in water. The drugs belonging to the BCS class II category have low solubility and high permeability.

Hence the major problem to the dosage form formulation is solubilizing the drug in the absorption medium, which can be achieved by using dissolution enhancement techniques [3,4]. Various strategies suggested to improve the dissolution of drugs with low solubility include micronization, surfactant dispersion method, use of fatty solutions, penetration enhancer or cosolvents, salt formation, precipitation, etc.. The above techniques alone are not sufficient and has limited utility in enhancing the solubility of the poorly soluble drugs. Other approaches for increasing solubility include vesicular system like liposomes, emulsion, dispersion of solids and microemulsion methods, and also inclusion complexes with cyclodextrins. These approaches show beneficial effect as drug delivery system but the major problem associated with these techniques are lack of universal applicability to all drugs. Nanoparticle engineering has been developed and reported for pharmaceutical applications over the last decades. Therefore, this problem is a challenge that motivates the researchers to develop a nano-size pharmaceutical preparations ($< 1 \mu m$) which could increase the dissolution rates as well as their bioavailabilities.

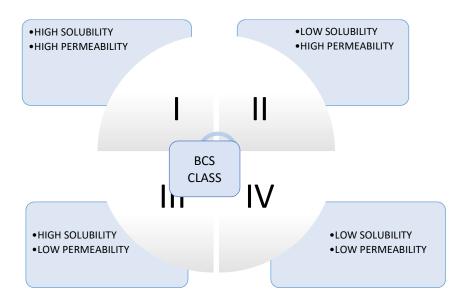
Nanosuspensions are biphasic systems and submicron colloidal dispersions of nanosized pure drug particles in a liquid phase stabilized by polymers and surfactants. [5,6] Nanosuspensions consist of the poorly water-soluble drug without any matrix material suspended in dispersion. These can be utilized to improve the solubility of drugs that are poorly soluble in water as well as lipid media. Increase in solubility inturn, increases the rate of flooding of active compound and hence the maximum plasma level can be attained faster. This approach is advantageous for molecules with poor permeability, poor solubility, or both, which poses a significant challenge for the formulators. Nanosuspensions are also known as "nanocrystals" [7]. Because of the vapor pressure effect, A nanosized particle increases the dissolution velocity and the saturation solubility [8]. Nanosuspensions can be administered by any route [9]. Rapid onset and improved bioavailability can be achieved by oral administration of nanosuspension. [10]. Nanosuspension is most suitable for compounds possessing high log P value, high dose and high melting point.

According to Noyes–Whitney and Ostwald–Freundlich principles, the particle size in the nanometer range can contribute to increased dissolution velocity and saturation solubility for a nanosuspension, which is usually accompanied by an increase in bioavailability [11,12,13].

For combating the problem 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, formulation of nanosuspension appear to be a unique and also commercially viable approach. [14,15]

Homogenization, Combined Precipitation Homogenization in Non Aqueous Media, Nanoprecipitation, and Nanojet Technology etc. are the various techniques used in the preparation of nanosuspension [16].

BCS CLASSIFICATION

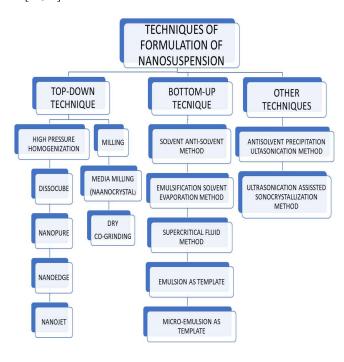


Formulation of nanosuspension

S.No.	INGREDIENT	ROLE	EXAMPLE
1	Stabilizers	Used for wetting the drug particles, preventing agglomeration and ostwald's ripening and providing barriers such as ionic and steric barriers. The drug-to-stabilizer ratio in the components may also fluctuate from 1:20 to 20:1 and need to be investigated for a unique case.	Lecithins, Poloxamers, Polysorbate, Cellulosics, Povidones [17].
2	Cosurfactants	When nanosuspensions are prepared using microemulsion, cosurfactants influence the phase behaviour.	Bile salts, DipotassiumGlycerrhizinate, Transcutol, Glycofurol, Ethanol [18], Isopropanol.
3	Surfactants	These are incorporated for enhancing the dispersion by reducing the interfacial tension. These also behave as deflocculating and wetting agent.	Tweens and Spans [17]
4	Organic solvent	Pharmaceutically acceptable less hazardous solvent for preparation of formulation.	Methanol, Ethanol [18], Chloroform, Isopropanol, Ethyl acetate, Ethyl formate, Butyl lactate, Triacetin, Propylene carbonate, Benzyl alcohol. [19].
5	Other additives	The choice of additive differs according to the route of administration or the properties of the drug moiety	Buffers, Salts, Polyols, Osmogens, Cryoprotectant.

Techniques of preparation of nanosuspension

- Mainly there are two methods for preparation of Nanosuspensions.
- The traditional methods of precipitation (Hydrosols) are refered as "Bottom up technology".
- The other method is referred as "Top Down Technologies" (disintegration method), are preferred over the precipitation methods [20,21]



Top-down techniques

The strategy applied is Disintegration method. Here, the size of large particles is reduced and hence a nano size range of particle is obtained [22]. It includes media milling and high pressure homogenisation.

High pressure homogenization

It involves 3 steps

- Step 1: Drug powder is dispersed in stabilizer to form a pre-suspension.
- Step 2: For pre-milling, the presuspension formed is homogenised in high pressure homogeniser at low pressure.
- Step -3: Finally, the nanosuspension of desired size are formed by homogenising at a high strain for 10 to 25 cycles. The factors influencing the physical characteristics (such as particle size) of the resulting nanosuspensions are:
 - Homogenization pressure,
 - Number of homogenization cycles,
 - Hardness of drugs, and
 - Temperature (when thermosensitive drugs are processed).

The various techniques [23] of High-Pressure Homogenization are as follows:

Homogenization in aqueous media (Disso cubes)

Medicament + Surfactant

In appropriate dispersion medium

Micro-sized suspension

The above suspension is driven through homogeniser's small valve hole using high pressure

Homogenization in Non-aqueous Media (Nanopure)

Suspensions that are homogenized in anhydrous media or water combinations are known as Nanopure. This method is also indicated as "Deep freeze method" [25], since the drug suspensions in the anhydrous media are homogenized at 0 °C or even below the freezing point.

Combined Precipitation and Homogenization (Nanoedge)

In this method, the drug is dissolved in an organic solvent, and the resulting solution is stirred with a miscible anti-solvent for precipitation. Here, Precipitation has additionally been integrated with high shear processing. This is done by a combining rapid precipitation with high-pressure homogenization. When the drug solution is rapidly added to an anti-solvent, supersaturation of the stirred solution takes place. This also generates fine crystalline or amorphous solids. At an high supersaturation, where the solubility of the amorphous state is exceeded [24], Precipitation of an amorphous material may additionally be recognized.

Nanojet

This is also referred as "opposite stream technology". In this method, the particle size is reduced by generating high shear forces[26], which makes the divided parts of stream of suspension to colloid with each other at high pressure in a chamber.

Advantages

- 1. In this technique, the metal contamination because of erosion is less noticeable than in media milling.
- 2. This technique is regarded as safe technique for the production of nanosuspension.
- 3. Under processing condition of 20 cycles and pressure of 1500 bar, less than 1 ppm metal contaminations were detected

Disadvantages

- 1. This method requires pretreatment before starting the homogenization to acquire microparticles.
- 2. This method requires more cycles of homogenization.

Milling

In this technique, the mechanical energy is utilized to breakdown and convert coarse particles into fine particles. [27]

Media milling (nanocrystal)

In this method, either high-shear media mills or pearl mills are used to produce nanosuspension. The media mill comprises of a milling chamber, a milling shaft, and a recirculation chamber. The active part of the mill is the milling

chamber charged with polymeric media. The operation of mill can be carried out in 2 ways, i.e, batch or recirculation mode. First, a nano crystalline dispersion is obtained by feeding and processing the crude slurry into the milling chamber. The crude slurry comprises of drug, water and stabiliser. Then, at a very high shear rate, the milling media (pearls) are rotated. This milling technique is carried out above the controlled temperatures.

Advantages

- 1. Scale up is easy
- 2. Batch-to-batch variations are less.

Disadvantages

- 1. Contamination of the final product
- 2. Due to erosion of pearls, problems may arise upon administration.

Dry Co-grinding:

Co-grinding method helps to improve the physicochemical properties and dissolution of poorly water-soluble drugs by improving the surface polarity and transforming a crystalline drug to an amorphous drug. The polymers and co polymers used in this method are as follows:

- 1. PVP
- 2. PEG
- 3. HPMC
- 4. Cyclodextrin derivatives

Advantages

- 1. It is simple process
- 2. It can be carried out without organic solvents [28]
- 3. It require short grinding time
- 4. It is a economic process

Disadvantages

1. Residues of milling media may be generated.

Bottom-up techniques

In this method, as the name indicates, particle size is grown from molecular range to nano range (initiation and progression from molecular level) to achieve nano size [29]. The traditional methods of precipitation (Hydrosols) are referred as "Bottom-up technology". The main focus is to prepare an API supersaturated solution and then precipitate it to a nano size. Here, the drug is first dissolved in an organic solvent and then the resulting solution is mixed with a miscible anti-solvent. The solubility is low in the water solvent blend and hence the drug will precipitate. Crystal development should be controlled by adding a suitable surfactant to avoid microparticle formation. It includes the supercritical fluid process, solvent anti-solvent method and emulsification-solvent evaporation technique.

Solvent-antisolvent method

In this method, the precipitation of solute is achieved by the addition of an anti-solvent. First, drug is dissolved in suitable solvent (usually water). Then an antisolvent is added to the drug solution in presence of surfactant. Supersaturation is achieved by rapid mixing of drug solution and antisolvent. This results in the generation of amorphous or crystalline API.

The 2 major phases of this method are

- Nuclei formation and
- Crystal growth.

In general, high nuclei growth and low crystal growth are desired for formulation of nanosuspension. Both the above phases are temperature dependent and hence optimization of temperature plays a crucial part.

Advantages

- 1. Easy
- 2. Scalable
- 3. Economic
- 4. Simple

Disadvantages

1. The drug must be soluble in at least one solvent

2. Crystal growth must be keenly observed outside the nano-range by using an appropriate solvent

Emulsification-solvent evaporation technique

First, a solution of drug is prepared via emulsification in every other non-solvent liquid for the drug [30]. Evaporation of the solvent can contribute to the precipitation of the drug. By using high-pressure stirrer, excessive shear pressure can be generated which can be used to control the particle aggregation and crystal growth.

Advantages

- 1. Equipment used is simple and economic
- 2. Higher saturation solubility

Disadvantages

- 1. The drug must be soluble in at least one solvent
- 2. The solvent must be miscible with at least one nonsolvent.
- 3. Solvent residues must be removed, which in turn increases the production costs.
- 4. It is a little bit tricky to preserve the particle character (i.e. size, especially the amorphous fraction).

Supercritical fluid process

In this method, the particle size reduction is achieved by supercritical fluid technique using solubilization and nanosizing technique. By this method, drug particles can be micronized to sub-micron levels.

Disadvantages

- In comparison with other techniques, hazardous solvents and high proportion of surfactants and stabilizers are used.
- 2. Due to transient high super saturation, Particle nucleation overgrowth may occur, which inturn may also result in the development of an amorphous form or another undesired polymorph

Emulsion as templates [31]

The use of emulsions as templates is applicable for those drugs that are soluble in both volatile organic solvent or a partly water-miscible solvent. An organic solvent or combination 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 immediately to form a nanosuspension stabilized via surfactants. Since one particle is formed in each emulsion droplet, it is feasible to manage the particle size of the nanosuspension via controlling the size of the emulsion

Advantages

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

Disadvantages

- 1. Drugs that are poorly soluble in both aqueous and organic media cannot be formulated by this technique [32,33].
- 2. Safety concerns because of the use of hazardous solvents in the process.
- 3. Need for ultrafiltration for purification of the drug Nanosuspension, which may render the process costly.
- 4. High amount of surfactant/stabilizer is required as compared to the production techniques described earlier.

Microemulsion as templates [34]:

The drug can be either loaded in the internal phase or pre-formed microemulsions can be saturated with the drug with the aid of intimate mixing. The drug nanosuspension can be obtained by appropriate dilution.

Advantages

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

Disadvantages

- 1. Drugs that are poorly soluble in both aqueous and organic media cannot be formulated by this technique.
- 2. Need for ultra-filtration for purification of the drug Nanosuspension, which may render the process costly.
- 3. High amount of surfactant/stabilizer is required as compared to the production techniques described earlier

Other methods

Antisolvent pecipitation-ultra sonication method

Drug was dissolved completely in solvent to prepare the organic phase and the solution was then filtered through a 0.45-µm filtered to remove the precipitated impurities. The antisolvent phase was prepared separately by dispersing stabilizer polyvinyl alcohol in distilled water. At a fixed temperature, 2 ml of organic solution was injected drop wise by syringe into 20ml of anti-solvent using mechanical stirrer at 3600 rpm for 1 h. The resultant nanosuspension samples were ultrasonicated with a probe sonicator 20–25 kHz for the specified period. During the ultrasonication, the temperature was controlled at 4–8°C using an ice—water bath

Ultrasound assissted sonocrystallization technique

It is a novel technique for preparing nanosuspension. 20 to 100 kHz frequency range is generally employed for the nanosuspension and the particle size is reduced in this range. Further, this method also retards the crystal growth and nucleation [35].

Applications of nanosuspension Oral

Nanosuspensions can contribute to enhanced mucoadhesion which can enhance the gastrointestinal transit time and thus lead to enhanced bioavailability [36]. The enhancement in the oral bioavailability can be as a result of saturation solubility, increased surface area and the adhesiveness of the drug Nanosuspension. Taste masking can be achieved effortlessly.

Parentral

Nanosuspensions can be employed to convert the poorly soluble non-injectable drugs into a formulation suitable for intravenous administration. The methods used for preparation of Nanosuspension are sufficient to produce uniform particles with better control over maximum particle size.

Ocular delivery

Nanosuspensions has become a boon for drugs that are poorly soluble in lachrymal fluids. This approach proves to be an ideal approach for the ocular delivery of the hydrophobic drugs since it posses the inherent ability to enhance the saturation solubility of various drugs[37].

Pulmonary

Nanosuspension paves way for drugs that are poorly soluble in pulmonary secretions[38]. The aerosol or the dry powder inhalers available in the market possess certain limitations that can be overcome by the nanosuspensions.

The drugs that have been formulated for pulmonary delivery are fluticasone and budesonide.

Dermal

The enhanced diffusion of drug into the skin can be achieved by the enhanced saturation solubility possessed by the nanocrystalline form. Bioadhesiveness, increased penetration into a membrane and enhanced permeation are the various properties exhibited by the nanocrystals that could be useful for dermal applications[39].

Targetting

The particle size is the main factor that determines the uptake of nanoparticles. Targeting a particular system can be achieved by altering the in vivo behaviour which can be done by altering the surface properties. Surface hydrophobicity, presence and concentration of certain functional groups and charge are the surface properties of particles which are responsible for determining the organ distribution[40]. Brain targeting can be achieved by using Tween 80 coated nanocrystals.

CONCLUSION

Nanosuspensions appears to be a unique and peculiar and commercially feasible approach to overcome the problems such as poor bioavailability that arise during the delivery of hydrophobic drug and also those that are having poor solubility in aqueous and organic media. Production methods like high-pressure homogenization and media milling have been successfully used for the large-scale production of nanosuspension. The advancement in production methods includes using emulsion and microemulsion as templates possess few limitations over making it easier for manufacturing. The attractive characteristics like increased dissolution velocity and saturation solubility, versatility in surface modification, improved bio adhesiveness and ease of post-production processing, have enlarged the applications of nanosuspensions via several routes. The oral and parentral route applications of nanosuspensions have been very well established, but the ocular and pulmonary applications have to be evaluated. However, topical,

buccal and nasal applications are yet to be explored sizing is the wisest and finest method to enhance the solubility and dissolution rate of poorly water-soluble drugs. The major hurdle faced by the formulation scientist working on the oral drug delivery is the poor aqueous solubility which results in the employment of novel formulation technologies. A conventional approach to improve the overall therapeutic performance of poorly soluble drugs in any route of administration is by the use of drug nanocrystals.

The present research concludes the various nanosuspension formulation approaches and also highlights its alternative to the conventional methods of solubility and bioavailability enhancement techniques and requires further exploration for diverse, promising, existing and newly developed drugs belonging to BCS Class II category.

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