Review Article

Versatility of nanosuspension formulation in various drug delivery systems: A brief review

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Abstract

Nano suspension formulations are attractive, encouraging and consist purely poor water soluble drugs without any matrix material. Nano suspension technology solved the problem of poorly aqueous soluble and less bioavailability is also overcome by using this technology. Nanosuspension formulation is applicable to all aqueous insoluble drugs. The objective behind this study is to review the work done on nanosuspensions and recent drugs used to formulate this dosage form with their uses. The formulation of nanosuspensions include drugs, stabilizers, organic solvents and other additives such as buffers, salts, polyols, osmogens and cryoprotectant. Nanosuspension formulations are synthesized by using wet mill, high-pressure homogenizer, emulsion-solvent evaporation, melt emulsification method and supercritical fluid techniques. Nanosuspensions can be administered by oral, parenteral, pulmonary and ocular routes. It can also be used for targeted drug delivery when incorporated in the ocular inserts and mucoadhesive hydrogels. This review article describes the nanosuspensions, their preparation methods, characterization, and recent applications of the nanosuspension.

Keywords: Nanosuspension, solubility, solvent evaporation, recent applications

Introduction

In the development of new molecular entities one of the main problems responsible for the low production is poor solubility and poor permeability of the lead compounds in drug formulation. More than 40% of the new chemical entities being generated through drug discovery programs are poorly water-soluble or lipophilic compounds. Formulating a poorly water soluble drug has always been a challenging problem faced by the scientist. In a biphasic nanosuspension formulation, insoluble solid drug particles are uniformly dispersed in an aqueous vehicle. The colloidal nature of doses is stabilized by surfactant and polymers (Kumar et al., 2009). To increase the solubility, formulation of nano-sized particles can be implemented to all drug compounds belonging to the biopharmaceutical classification system (BCS) classes II and IV. The micronization and solubilization are methods for

increasing the solubility of poorly soluble drugs. Other techniques are like liposomes, emulsions, micro-emulsion, solid dispersion and inclusion complexation using cyclodextrins (Yadollahi et al., 2013). For the drugs which are insoluble in water and organic solvents nanosuspension technology can also be used. Hydrophobic drugs such as Atorvastatin, Famotidine, Simvastatin, Revaprazan, Aceclofenac, are formulated as nano suspension. The micronization of poorly soluble drugs was preferred for long period of time by using colloid mill (Bhowmik et al., 2013). About 0.1 μ m to 25 μ m is overall particle size ranges. In this biphasic system, the suspended pure drug's particles are less than 1 μ m in size. The nanosuspension formulation can also be lyophilized or spray dried and the nano particles of a nanosuspension can also be incorporated in a solid matrix (Shid et al., 2013).

Advantage of Nano Suspension

Nanosuspensions have emerged as a promising strategy for the efficient delivery of hydrophilic drugs because of their versatile features & unique advantages. The reduction of drug particles into submicron range leads to a significant increase in dissolution rate & therefore enhances

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Figure 1. Advantage of Nano Suspension (Kumar et al., 2009)

bioavailability. More advantages are depicted in figure 1 (Xiaohui and Jin, 2009; Goel et al., 2019).

Disadvantage of Nanosuspension (Van et al., 2018)

- 1) Physical stability, sedimentation and compaction can causes problems.
- 2) It is bulky sufficient care must be taken during handling and transport.
- 3) Uniform and accurate dose cannot be achieved unless suspension.

Preparation method of nanosuspensions

Technically preparations of nano suspensions are simpler alternative than liposome's and other conventional colloidal drug carriers but reported to be more cost effective. It is particularly for poorly soluble drugs and to yield a physically more stable product (Jacob et al., 2020).

Figure 2. Manufacturing of Nano suspensions

Classification is given in figure 2. The top-down process follows disintegration approach from large particles, micro particles to Nano sized particles (Vaneerdenbrugh et al., 2008).

Examples are; High pressure homogenization, Nano edge, Nano pure, Media milling (Nano crystals).

Bottom-up process is an assembly method forms nano particles from molecules (Dewaard et al., 2008). Examples includes; Solvent-Anti solvent method, Supercritical fluid process.

Emulsification solvent evaporation technique

Lipid emulsion /Micro-emulsion template. The principle techniques used in recent years for preparing nano suspensions are:

(A) High pressure homogenization

It is most commonly used technique for preparing nanosuspension of many poorly aqueous soluble drugs (Keck and Muller, 2006). It involves three steps. Firstly drug powders are dispersed in stabilizer solution to form pre-suspension, and then the pre-suspension is homogenized in high pressure homogenizer at a low pressure for pre milling, and finally homogenized at high pressure for 10 to 25 cycles until the nano suspensions of desired size are formed. Different methods like Disso cubes, Nano pure, Nano edge and Nano jet are depend on this principle (Nash et al., 2002).

Homogenization in aqueous media (Disso cubes)

This technology was developed by R.H. Muller using a piston-gap type high pressure homogenizer in 1999. In this method, the suspension containing a drug and surfactant is forced under pressure through a nano sized opening valve of a high pressure homogenizer.

The principle of this method is based on cavitations. The dispersion present in 3cm diameter cylinder is suddenly passed through a very narrow gap of 25 μ m. According to Bernoulli's law the flow volume of liquid in a closed system per cross section is constant. Due to reduction in diameter from 3cm to 25 μ m it leads to increase in dynamic pressure and decrease of static pressure below the boiling point of water at room temperature. Then water starts boiling at room temperature and forms gas bubbles which implode when the suspension makes the gap (called cavitations) normal high pressure is obtained and to convert the drug's micro particles into nano particles, the particles cavitations forces are sufficiently high (Mullar et al., 2000).

Advantages

1. It is applicable to the drugs that are poorly soluble in both aqueous and organic media
2. It does not cause the erosion of processed materials.

Disadvantages

1. Micronization of drug is required.
2. Cost of dosage form are increases because High cost instruments are required

Homogenization in non aqueous media (Nano pure)

Nano pure is suspensions homogenized in water-free media or water mixtures like PEG 400, PEG 1000 etc. The homogenization can be done at, 0°C and below freezing point (-20°C), hence it is known as "deep freeze" homogenization. The homogenization can also be done at room temperature (Cornelia et al., 2006).

Nano-edge

Nano-edge technology is the combination of both precipitation and homogenization as given in figure 3 (Dearn, 2000). By the use of this technology The major drawback of precipitation technique such as crystal growth and long term stability can be overcome. The better stability and smaller particle size can be achieved in short time.

Nano-jet

It is also known as opposite stream technology which uses a chamber where a stream of suspension is divided into two or more parts, which colloid with each other at high pressure and particle size is reduced due to the high shear forces produced during the process (Prassanna and Giddam, 2014).

(B) Milling techniques

Media Milling

The principle of this method is high shear media mill

Figure 3. Illustration of the high-pressure homogenization process (Sutradhar et al., 2013)

(Liversidge et al., 1998). The milling chamber was charged with the milling media, water, drug and stabilizer and rotated at a very high shear rate under controlled temperature for 2-7 days (Patravale et al., 2004). The milling medium contain of glass, Zirconium oxide or highly cross linked polystyrene resin as shown in figure 4. As a result of impactation of milling media with the drug high energy shear forces are formed which cause breaking of drug micro particles to nano sized particles.

Advantages

1. Very dilute as well as highly concentrated nano suspensions can be prepared
2. The final product as Nano sized distribution.

Disadvantages

1. This technique is time consuming.
2. Some fractions of particles are in the micro meter range.
3. Due to mill weight and size scale up is not easy.

Dry-Co-grinding

Recently dry milling techniques are used in most of nano suspension preparation. Dry-co-grinding can be carried out easily and economically and can be conducted without organic solvents. Physicochemical properties and dissolution of poorly water soluble drugs are improved by Co-grinding because of an improvement in the surface polarity and transformation from a crystalline to an amorphous drug (Bodmeier and Ginity, 1998).

Advantages

1. Easy and safe process.
2. No organic solvent required.
3. Require short grinding time.

Figure 4. Illustration of the high-pressure homogenization process (Sutradhar et al., 2013)

Disadvantages

Generation of residue of milling media

(C) Emulsification-solvent evaporation technique

This method involves preparing a solution of drug followed by its emulsification in another liquid that is a non solvent for the drug. Evaporation of the solvent leads to precipitation of the drug. By using a high-speed stirrer, Crystal growth and particle aggregation can be controlled by creating high shear forces.

(D) Precipitation

For the poorly soluble drugs, precipitation has been applied to prepare submicron particles. Firstly drug is dissolved in a solvent, followed by miscible anti solvent in the presence of surfactants. Rapid addition of a drug solution to the anti solvent leads to sudden super saturation of drug and formation of ultrafine crystalline or amorphous drug solids (Trotta et al., 2003).

Advantages

Simple process Ease of scale up and Economical production.

Disadvantages

Growing of crystals needs to be limit by surfactant addition. Drug must be soluble at least in one solvent

(E) Supercritical fluid process

In this process through solubilization and nano- sizing technologies the particle size reduction was achieved. Super critical fluids (SCF) are those which have temperature and pressure are greater than its critical temperature (T_c) and critical pressure (T_p). This process allows the micronization of drug particles to submicron level. Recent advancement in this process

are to create nano particulate suspension having particle size of 5 to 2000nm in diameter (Young et al., 2000).

(F) Melt emulsification method

Melt emulsification 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. Finally emulsion was cooled down room temperature or on an ice bath (Moneghini et al., 2001).

Advantages

This technique relative to the solvent evaporation method is total avoidance of organic solvents during the production process.

Disadvantages

Formation of larger particles

(G) Lipid emulsion/microemulsion template

This technique works for volatile organic solvents or partially water miscible solvents. In this method, the drug was dissolved in suitable organic solvent and then it is emulsified in aqueous phase using suitable surfactants. Under reduced pressure the organic solvent was slowly evaporated to form drug particles precipitating in the aqueous phase and aqueous suspension of the drug in the required particle size was formed. And suspension can be diluted to form nano suspensions. Moreover, micro emulsion as templates can produce nano suspensions

.Micro emulsions 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. The drug can be either loaded into the internal phase or the pre-formed micro emulsion can be saturated with the drug by intimate mixing. . The advantages of lipid emulsions as templates for nano suspension formation are that they easy to produce by controlling the emulsion droplet and easy for scale up (Serajuddin, 1999).

Advantages

- High drug solubilization
- Long shelf life
- easy to manufacture

Disadvantages

- Use of hazardous solvent
- High amount of surfactant and stabilizers are used

(H) Solvent evaporation

In the method the polymer solutions are prepared in volatile solvents and emulsions. But from past years dichloromethane and chloroform was replaced by ethyl acetate which has a better profile of toxicology .on evaporation of solvent emulsion is converted into a nano suspension particle. In the conventional technique, two main method, single-emulsions example; oil-in-water (o/w) or double-emulsions, e.g., (water-in-oil) of in-water, are used . These methods require high-speed homogenization or Ultra-sonication, followed by evaporation of the solvent, either by continuous magnetic stirring at room temperature or under reduced pressure the solidified nano particles are collected. By ultracentrifugation and then washed with distilled water to remove the additives like surfactants, and then it was lyophilized. The concentration of polymer stabilizer and the speed of homogenizer (Jadhav and Gwandar, 2018).

Characterization of nanosuspension

The characterization generally include chemical, physical, and biological tests. However, mean particle size and particle size distribution, crystalline state and particle morphology, nanosuspension charge, saturation solubility and dissolution velocity, stability and in vivo biological performance are the essential characterizations for the nanosuspension.

Mean particle size and particle-size distribution

The mean particle size and particle-size distribution are of great significance for nano suspensions since these two key parameters usually determine some critical properties of nano suspensions, such as the physical stability, dissolution velocity, saturation solubility, as well as their biological performance

(Serajuddin, 1999) reported that different particle sizes of the drug display significant variation of saturation solubility and dissolution velocity. Photon correlation spectroscopy (PCS) is a powerful technique that can be applied to quickly and accurately determine the mean particle size of nano suspensions. Furthermore, the width of the particle-size distribution (poly dispersity index (PI)) can also be determined by the PCS technique. It should be noted that the PI is another important parameter that controls the physical stability of nano suspensions. To make nano suspensions of long-term stability, the PI should be as low as possible (Arias et al., 1997).

Unfortunately, due to the low measuring range of PCS technique, it is still challenging to detect the possible contamination of nano suspensions with particle size greater than 3 μ m. Therefore, laser diffractometry (LD) analysis is necessary because it can quantify the possible drug micro particles of nano suspensions. Laser diffractometry can be carried out to measure particles with the size ranging from 0.05 to 80 μ m. In addition, LD has become critical for characterizing nano suspensions since even a minor fraction of particles greater than 5–6 μ m (the size of the smallest blood capillary) would probably lead to emboli formation or capillary blockage. For the PCS or LD analysis, de-ionized water can be used to dilute the nano suspensions. Regarding some nano suspensions intended for intravenous administration, the Coulter counter technique is also used for particle size analysis. This technique usually yields the absolute number of particles per volume unit, therefore, it has been considered more appropriate for determining the contamination of nano suspensions (Müller et al., 1999).

Particle morphology and crystalline state

The characterizations of the particle morphology and crystalline state can help us better understand the possible morphological or structural changes of drugs when subjected to nano-sizing. It is important to study the amount of amorphous drug nano particles within the nano suspensions since they are likely to be produced during the preparation of nano suspensions. The amorphous form is thermodynamically unstable and tends to transform into a crystalline form during storage. Such transformation over storage should be taken into consideration when preparing or formulating nano suspensions. Therefore, X-ray powder diffraction (XRD) and scanning electron microscopy (SEM) are usually used to determine the crystalline structure and particle morphology of drugs, respectively. In addition, differential scanning Calorimetry (DSC) is

another useful technique for characterizing the crystalline structure and determining the amorphous fractions of drugs (Müller et al., 1999).

Particle surface charge

Particle surface charge is important for the stability ensurance of nano suspensions. Particle surfaces charges provided electrostatic repulsion which can prevent drug nano particles from precipitation. Directly the surface charge cannot measured, hence the zeta potential of a nanosuspension can be utilized as an indicator of the stability of the nanosuspension technique and can be controlled by the drug and stabilizer. Zeta potential is the electrical potential at between the Stern layer and the diffusion layer of oppositely charged ions (Nel et al., 2009). Electrostatically stabilized nanosuspension required minimum zeta potential of ± 30 mV. However, ± 20 mV is sufficient if a satiric stabilizer was added to the nanosuspension formulation (Jacobs, 2002). Zeta potential maintenance of nanosuspension important during storage and production. A Zeta potential can be measured by using zetasizer. The drug is dissolved in Milli-Q water to give a suitable concentration in which the electrophoretic cell can be dipped (Sameut et al., 2013). The measurement of zeta potential is usually performed in the original dispersion medium, physiological salt solutions, or buffers with different molarities (Nagelreiter et al., 2013). It can also be performed by diluting the drug in water. Such dilution may slightly alter the surface charge and give a zeta potential different from the true value (Eldridge et al., 2014). The extent of adsorption and binding strength of stabilizer molecules to the particle surface are also measured by the zeta potential. The zeta potential can be measured by laser light scattering (Deshiikan and Papadopoulos, 1998) or by electro acoustic means (O'brien et al., 1995). In these technologies, the measurement of the electro phoretic mobility of the particles in an electric field was performed. The electro acoustic method has an advantage over laser the light diffraction by not being restricted to measurements in diluted dispersions

Saturation solubility and dissolution velocity

The saturation solubility and dissolution velocity are two essential parameters that can be used to analyze changes in the in vivo performances of drugs, such as bioavailability, plasma peak, and blood profile (Sutradhar et al., 2013). Nanosuspension is commonly used to improve the saturation solubility of the drug; therefore, it is necessary to investigate the saturation solubility of a nanosuspension. Dissolution velocity is also important parameter for a nano suspension. Therefore it is necessary to assess the saturation solubility and dissolution velocity of the drug nano suspensions under different conditions, such as in different physiological buffers and at different temperatures (Ayash, 2018).

Stability

The particle size is reduction increased surface energy during the preparation of nanosuspension. This increased surface energy destabilizes the colloidal suspension. Ostwald ripening is used to minimize the particle agglomeration (Chaurasia et al., 2012). To stabilize the nanosuspension Polysorbates, povidones, poloxamer, lecithin, polyoleate, and cellulose polymers are used. The mixture of surfactants and polymers are useful for long-term stabilization of nano-suspensions. The stabilizers play the role as an ionic barrier and inhibit the close interaction between particles. The surfactants can change the zeta potential and increase the electrostatic repulsion between the nano particles, thus giving better stability. For stability of nano-suspension, the precipitation of particles should be considered. According to Stoke's law, the decrease in precipitation velocity can be achieved by decreasing particle size, reducing the density difference of solid phase, and increasing the viscosity of the medium. Increasing the uniformity of particle sizes can also increase the stability of nanosuspension (Liu et al., 2012).

In-vivo biological performance

The study of in vivo biological performance of the drug is of particular importance without considering the delivery system or route employed. For intravenously injected nano suspensions, it is very important to study the in vivo biological performance because it usually depends on the organ distribution. The protein absorption pattern can be observed after the intravenous injection of drug nano particles and its composition can yield the information of organ distribution (Blunk et al., 1993; Blunk et al., 1996). Therefore, to better understand the in vivo behavior, appropriate techniques, such as hydrophobic interaction chromatography and 2D PAGE are commonly used to investigate the surface hydro phobicity and measure the qualitative and quantitative composition of protein absorption respectively (Wallis, 1993; Patravale and Kulkarni, 2004).

Pharmaceutical application of nanosuspension

Oral drug delivery

Due to smaller particle size and much larger surface to volume ratio, oral nano suspensions are specially used to increase the absorption rate and bioavailability of poorly soluble drugs (Boedeker et al., 1994). The nanosuspension have advantages like improved oral absorption, dose proportionality, and low inter subject variability (Jia, 2002). By using standard manufacturing techniques, drug nano suspensions can be simply incorporated into various dosage

Figure 5. Applications of Nano suspensions (Kumar et al., 2009)

forms like tablets, capsules, and fast melts. The nanosuspension of Ketoprofen was successfully incorporated into pellets for the sustained release of drug over the period of 24 hours (Liversidge, 1996). Various applications are shown in figure 5.

Parental drug delivery

Nanosuspension technology are used to overcome the problem of solubilization capacity, parental acceptability, high manufacturing cost in other doses form. Nanosuspensions are administered through various parental routes such as intra articular, intraperitoneal, intravenous, etc., nano suspensions increase the efficacy of parenterally administered drugs (Liversidge et al., 2003). Clofazimine nanosuspension showed an improvement in stability as well as efficacy above the liposomal Clofazimine in Mycobacterium avium-infected female mice (Peters et al., 2002). Rainbow et al. showed that intravenous nanosuspension of itraconazole enhanced efficacy of antifungal activity in rats relative to the solution formulation.

Pulmonary drug delivery

For pulmonary delivery, nano suspensions can be delivered through mechanical or ultrasonic nebulizers. Due to the presence of many small particles, all aerosol droplets contain nano particles drug (Hernandez et al., 2005). As the particle size is very small, aqueous suspensions of the drug can be easily nebulized and given by pulmonary route. For administration of liquid nano suspension formulations different types of nebulizers are used. Drugs like budesonide, ketotifen, ibuprofen, indomethacin, nifedipine,

itraconazole, interleukin-2, p53 gene, are successfully tried with pulmonary route (Heidi et al., 2009).

Ocular drug delivery

For sustained release nano suspensions are used in ocular delivery. Experiment showed higher availability of drug in aqueous humor of rabbit eye. Thus, nanosuspension formulation improving the shelf-life and bioavailability of drug after ophthalmic application. Liang and co-workers prepared cloricromene nanosuspension for ocular delivery using Eudragit (Kumari, 2018).

Targeted drug delivery

Nanosuspensions are suitable for targeting particular organs due to their surface properties. By changing the stabilizer it is easy to alter in vivo behavior. The drug will be taken up by the mononuclear phagocytic system which allows region-specific delivery. This can be used for targeting antifungal, antimycobacterial, or antileishmanial drugs to macrophages if the pathogens persist intracellularly (Kayser et al., 2005; Kayser, 2000). More recent applications of nanosuspension formulations are given in table 1. It has been described an enhanced drug targeting to brain in the treatment of toxoplasmic encephalitis using an atovaquone nanosuspension (Scholer et al., 2001).

Conclusion

This review presents the recent progress in therapeutic

Table 1. Recent applications of nanosuspensions

Drugs	Categories	Methods	Results	References
Tamoxifen	Antiestrogens	High pressure	Fine solution and	Somasekhar
		homogenization	Dissolution properties	Et al., 2018
Cisapride	Gastroprokinetics agent	Nanoprecipitation	Improve solubility and	Gopinath
			Bioavailability	Et al., 2017
Itraconazole	Antifungal	Acid base	Poor aqueous solubility	Daebis et al., 2015
Oral		Neutralization Technique	Hinders consist bioavailability	
Amoxicillin	Antibiotic	Solvent evaporation technique	Improvement of solubility	Jadhav et al., 2018
Fluometholone	Corticosteroids	High pressure	Improve solubility of drug	Saudagar and Pradnya, 2016
		homogenization		
Nebivolol	Beta-blockers	Precipitation Method	Increase drug solubility and to overcome bioavailability	Shekhar and Vijaya, 2017
Pitavastatin	HMG CoA	Precipitation	Overcome Bioavailability	Kumar and Ali, 2014
	Reductase Inhibitors	Method		
Zeltoprofen	Non steroidal	Nanoprecipitation technique	Enhance solubility and dissolution rate	Papdiwal et al., 2014
	Antiinflammatory drug			
Aceclofenac	Non steroidal	Sonoprecipitation method	Improve therapeutic Efficacy of poor soluble Drug	Kumar et al., 2016
	Antiinflammatory drug			
Nifedipine	Calcium channel Blockers	Nano precipitation technique	Improve dissolution of poor soluble drug	Yasmin et al., 2017
Rosuvastatin	Cardiovascular	Nano precipitation technique	Improve dissolution and Solubility	Raturi et al., 2013
Calcium				
Simvastatin	HMG CoA Reductase inhibitors	Emulsification	Improvement of solubility and dissolution velocity	Rupali, 2014
		Solvent diffusion method		
Celecoxib	Non steroidal	Nanoprecipitation	Improve solubility and Bioavailability	Sunder et al., 2019
	Antiinflammatory drug			
Etoricoxib	Non steroidal	High pressure	Enhance saturation solubility and	Vasava et al., 2015
	Antiinflammatory drug	Homogenization Technique	Increase dissolution	

nanosuspensions produced by various techniques such as wet mill, high-pressure homogenizer, emulsion-solvent evaporation, melt emulsification method and supercritical fluid techniques. To solve the problems of hydrophobic drug such as poor solubility and poor bioavailability nano suspensions have unique and commercially possible approach. Media milling and high-pressure homogenization technology have been successfully used for large scale production of nanosuspension. Characteristics, like improvement of dissolution velocity, increased saturation solubility, improved bio adhesivity, versatility in surface modification, and ease of postproduction processing, have widened the applications of nano suspensions for various routes of administration. The applications of nano suspensions in oral and parental routes have been very well established, although applications in pulmonary and ocular delivery have to be evaluated. The aim of future studies is to combat the challenges associated with poorly soluble drugs in order to improve bioavailability, enhance dissolution velocity and bioadhesion of the drug.

Conflict of Interest

The authors declare that there is no conflict of interest.

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