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Review Article

Pharmaceutics for enhanced drug delivery

Nanosuspension as Promising and Potential Drug Delivery: A Review

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Abstract: In the last decade, nanosuspensions have gained considerable interest as a method for formulating poorly soluble drugs. Because of their cost-effectiveness and technological simplicity compared to liposomes and other colloidal drug carriers, nanoscale systems have recently received a lot of attention as a way of solving problems of solubility. Nanosuspensions are biphasic systems comprising of pure drug particles dispersed in an aqueous vehicle, stabilized by surface active agents. Fabrication of nanosuspension is simple and more advantageous than other approaches. Nanosuspension is a very finely single solid drug particle in an aqueous vessel, stabilized by surfactants for either oral or topical use or for parenteral and pulmonary administration, it can also be used for targeted drug delivery when incorporated in the ocular inserts and mucoadhesive hydrogels, with reduced particle size resulting in increased dissolution rate. This article covers the preparation of nanosuspension by bottom up technology, top down technology, melt emulsification, emulsification- solvent evaporation and supercritical fluid with their advantages and disadvantages, aspects of structure, classification and their drug delivery applications. Nanosuspension can be processed for the drugs which are of hydrophobic in nature quite easily employing stability enhancers, solvents that are of organic and additional ingredients including buffering agents, salts, PEG, osmotic agents and anti-freeze compounds.

Keywords: Nanosuspension, Solubility, Surfactants, Fabrication techniques, Bioavailability

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1. INTRODUCTION

Apparently poorly water-soluble drugs show many problems such as poor dissolution, low bioavailability for drugs of BCS -II namely piroxicam, naproxen, cyclosporine[1] in conventional dosage forms when formulating them. Conventional methods include micronization, use of fatty solutions, use of penetration enhancer or co solvents, process of surfactant diffusion, salt forming, precipitation, etc., but these techniques have limited utility in enhancing solubility for poorly soluble drugs. They can be used to enhance the solubility of drugs that are poorly soluble in both aqueous and lipid media. Nanosuspension is intended to improve absorption and bioavailability, may help to decrease the dose of traditional oral dosage types. Nanosuspension vary from nanoparticle in that nanoparticles are generally polymeric colloidal carriers of drugs whereas in nanosuspension technology, the drug is maintained in the required crystalline state with reduced particle size leading to an increased dissolution rate and therefore improved bioavailability. These can be used to increase the solubility of drugs that are poorly soluble in both aqueous and lipid media. Nanosuspensions are colloidal dispersions of nanosized drug particles stabilized by surfactants.[2] They can also be described as a biphasic system consisting of pure drug particles dispersed in an aque ous vehicle in which the suspended particle has a diameter of less than 1µm.The nanosuspensions can also be lyophilized or sprayed, and the nanoparticles of a Nanosuspension can also be embedded in a solid matrix.[3] For all drug compounds belonging to Biopharmaceutical Classification System Classes II and IV the formulation of nanosized particles can be applied to improve the dissolution rate and thus partition into the gastrointestinal barrier.[4]

1.1 *Nano Suspension Advantages*

1) Reduced tissue irritation in the case of subcutaneous/intramuscular administration
2) Enhanced dissolution rate and saturation solubility of the drug.[5]
3) Long-term physical firmness.
4) Higher drug loading can be attained.
5)
Higher bioavailability for ocular administration and drug deliv ery by inhalation.
6)
Nanosuspension can be used in creams, gel, pellets, capsules and tablets.

1.2 *Nano Suspension Disadvantages*

1) Physical constancy, sedimentation & compaction can cause problems.
2) Improper dose.
3) Uniform & accurate dose cannot be accomplished.
4) It is bulky sufficient care to be taken during handling and transport.
5) Uniform and specific doses cannot be achieved unless suspended.[6]

1.3 *Norms for choice of drug for nanosuspensions*

Nanosuspension can be prepared and designed for the API that is having either of the following features:
1.Water-insoluble but which are soluble in oil (high log p) or API are insoluble in both water and oils.
2. Drugs with focused predisposition of the crystal to dissolve, regardless of the solvent.[7]

2. FORMULATION CONSIDERATION

2.1 *Stabilizer*

A stabilizer is used to wet the drug particles systematically and to prevent the maturing and agglomeration of nanosuspension by providing a stearic or ionic barrier to yield a physically stable formulation.[8] Some of the stabilizers are poloxamers, polysorbate, cellulosic, povidones, and lecithin. Drug particles dispersed within a liquid continuous medium are stabilized by steric, electrostatic mechanisms, or by a combination of both via polymers and/or Surfactants. Steric stabilization is usually imparted by nonionic polymers and nonionic surfactants, e.g., cellulose derivatives, poloxamers (also considered as polymeric surfactants), polysorbates, and povidones, preventing particles from getting into the range of attractive Vander Waals forces. Electrostatic stabilization is usually imparted by ionic surfactants, e.g., sodium dodecyl sulfate (SDS), dioctyl sulfosuccinate sodium salt (DOSS) and benzethonium chloride (BKC) providing mutual repulsion of similar charged particles.[9]

2.2 *Organic Solvents*

Toxicity potential and the ease of their removal after formulation are the two vital aspects that decide the suitability of organic solvents in the pharmaceutical area during the formulation of nanosuspension by using emulsion or microemulsion as templates. Ethanol and isopropanol are watermiscible solvent, whereas ethyl acetate, ethyl formate, butyl lactate, triacetin, propylene carbonate and benzyl alcohol are partially water-miscible, less hazardous and pharmaceutically acceptable.[10]

2.3 *Surfactants*

In order to illuminate the dispersion, it is incorporated into a formulation surfactant which performs its action as wetting or deflocculating reducing the tension of the interfaces. Commonly used surfactants are polysorbate (Tween/Span series), povidone, cellulosics, poloxomers and lecithin.[11]

2.4 *Co-Surfactants*

This describes other co-surfactants for specific stabilizers that can be used safely in microemulsion formulation, co-surfactants such as salts (dipotassium glycyrrhizinate) can be used safely with stabilizers such as glycerol, ethanol, and isopropanol.[12]

2.5 *Other Additives*

The composition of nanosuspensions such as osmogen, cryoprotectant, polyols, buffers and salts depend on either the route of administration or the properties of the product moiety.[13]

3. METHODS OF NANOSUSPENSION

Technically preparations of nanosuspensions are simpler alternative than liposomes and other conventional colloidal drug carriers but reported to be more cost-effective.[14] It is particularly for poorly soluble drugs and to yield a physically

more stable product. For manufacturing nanosuspensions, there are two converse methods, "Top-down process technology" and "Bottom-up process technology".[15] Top-down approaches start from a larger element of material, slicing or milling this bulk material, to obtain smaller units of the desired shape. Bottom-up approaches arrange smaller subunits or components (e.g., atoms or molecules) into larger and functionally richer, complex structures. Examples for drugs prepared as nanosuspensions by these methods include griseofulvin, nabilone, atorvastatin.[16] The following methods are used to prepare nanosuspension,

3.1 *Bottom Up Technology*

This approach starts from the bottom i.e. start from molecular level and lastly goes to a molecular association for the formulation of small solid particles.[17] It is generally utilized for the manufacturing of nanosuspensions both in bulk solutions or in single droplets. In this technique, the drug is entirely dissolved in a solvent. Then the solvent solution is added to a non-solvent, causing precipitation of the drug.

3.1.1 Precipitation method

The drug is first dissolved in a solvent, then this solution is mixed with a miscible antisolvent in the presence of surfactants. Rapid addition of a drug solution to the antisolvent leads to sudden super saturation of drug and formation of ultrafine crystalline or amorphous drug solids.[18]Advantages include simple process, ease of scale up and economical production. Disadvantages include growing of crystals needs to be limit by surfactant addition. Drug must be soluble at least in one solvent.

3.2 *Top Down Technology*

Top down methods include techniques such as grinding (media milling), high pressure homogenization, neosporosis, combined precipitation and homogenization (nano edge), nano jet technology, emulsification-solvent evaporation techniques, hydrosol process, supercritical fluid method, precipitation technique, dry-co-grinding.[19]

3.2.1 *Milling Technique*

3.2.1.1 *Media Milling (Nan crystal or Nano systems)*

Nanosuspension is formed in this technique by reducing particle size using pearl and media milling. This milling technique consists mainly of tube, milling cabinet, and recirculation cabinet. This method is very simple, cost-effective and it can possible to scale up.[20,21]

Advantages
1. Simple Approach
2. Low cost process with regarding the milling itself.

Disadvantages
1. Potential erosion from the milling material leading to contamination of the product.
2. Potential germ development during long periods of milling in the water phase.

3.2.1.2 Dry Co-grinding

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. The co-grinding technique can reduce particles to the submicron level.[22]
1.This method helps improve the polarity of drugs on the surface.
2. This process is mostly used because it is simple and cheap, and without any organic solvent being used.

3.2.2 *High Pressure Homogenization*

This method is used for those drugs which show poor solubility. The suspension is used through as small area with a high pressure up to 1500 bar, which raises the dynamic pressure with a corresponding decrease in the static pressure, which reduces the boiling pint of the water to normal (room temp).[23]

3.2.2.1 *Homogenization in water (Disso cubes)*

The suspension of the drug is allowed to move through a sm all orifice which results in a reduction of the static pressure b elow the boiling water pressure which leads to water boiling and gas bubbles forming.[24] The bubbles burst and the outer portion containing the product particles rushes towards the middle and in the process colloids, causing particle size reduction. The main advantage of high-pressure homogenization over media friction is that it can be used for both condensed and concentrated suspensions and enables aseptic processing as well.[25]

3.2.2.2 *Homogenization in Nano aqueous media (Nano pure)*

It involves homogenization in water mixtures or water free media and is prepared for the thermolabile compound. Nano pure is also called as deep freezing because homogenization of drug suspension is carried out in non-aqueous media at 0°C.[26]

3.2.2.3 *Combined Precipitation and Homogenization (Nano Edge)*

Nano edge's basic principles are similar to those of precipitati on and homogenization. A combination of these techniques results in smaller particle size and better stability in a shorter time. The precipitated suspensions further homogenized in this technique; resulting in reduced particle size and preventing growth of the crystals. Precipitation is performed in water using water-miscible solvents such as methanol, ethanol and isopropanol.[27]

3.2.2.4 *Nano jet technology*

Nano jet is the most frequently used technology in which high force pressure is applied to the suspension which is divided into at least two parts and which is affected by the high shear forces generated throughout the process to reduce particle size.[28] Microfluidizers are availed in this technology to reduce the size. The major limitation of this technique is the high number of passes through the microfluidizer (up to 75 passes) and that the product obtained contains a relatively larger fraction of microparticles and consumes large production time.

3.3 *Melt Emulsification Method*

The material is dispersed in the stabilizer's aqueous solution and heated overhead the drug's melting point, and homogenized to produce an emulsion. Throughout this procedure the sample container was encased with a heating tape tailored with a temperature regulator and the emulsion temperature was detained above the drug's melting point.[29] The emulsion was then gradually cooled down to room temperature or on an ice bath.

Advantage

Melt emulsification technique comparative to the solvent diffusion method is the whole evasion of solvents which are organic in nature throughout the manufacturing method.[30]

Disadvantage

Formation of larger particles and some compliant objects than solvent evaporation

3.4 *Emulsification-Solvent Evaporation Technique*

This technique involves preparing a solution of drug followed by its emulsification in another liquid that is a nonsolvent for the drug. Evaporation of the solvent leads to precipitation of the drug. Crystal growth and particle aggregation can be controlled by creating high shear forces using a high-speed stirrer.[31]

3.5 *Super Critical Fluid (Scf) Method*

Supercritical fluid technology can be used to produce nanoparticles from drug solutions. The various methods attempted are the rapid expansion of supercritical solution process (RESS), supercritical anti-solvent process and precipitation with compressed anti-solvent process (PCA). The RESS involves an expansion of the drug solution in supercritical fluid through a nozzle, which leads to loss of solvent power of the supercritical fluid resulting in precipitation of the drug as fine particles. In the PCA method, the drug solution is atomized into a chamber containing compressed CO_2.[32]As the solvent is removed, the solution gets supersaturated and thus precipitates as fine crystals.

3.6 *Other Methods*

3.6.1 *Micro emulsions as templates*

This method uses an organic solvent or combination solvent f illed with the product distributed in an aqueous phase containing suitable surfactants to form an emulsion.[33]

Advantages

1. Use of specific equipment is not required.
2. Particle size can easily be controlled by controlling the size of the emulsion droplet.

Disadvantages

1.Drugs which are poorly soluble in both organic and aqueous media cannot be formulated using this process.

3.6.2 *Hydrosol method*

This method is similar to that of emulsification solvent evaporation approach with minor difference in which drug solvent is totally miscible in drug anti-solvent. High shear forces can face the challenges like ostwald ripening and crystal growth.[34]

4. Characterization Of Nanosuspensions

Characterization of nanosuspensions is done by various methods with different parameters like size of particles, particle size distribution and also zeta potential, because these parameters are mainly affected on safety, efficacy and stability of formulation.

4.1 *Particle Size*

The particle size distribution can be determined by photon correlation spectroscopy (PCS), laser diffraction (LD) and coulter counter multisizer. The PCS method can measure particles in the size range of 3 nm to 3µm and the LD method has a measuring range of 0.05-80µm. The coulter counter multisizer gives the absolute number of particles, in contrast to the LD method, which gives only a relative size distribution. Particle size and polydispersity index (PI) are some of the most critical parameters of nanosuspensions. The size of particles governs the numerous features of nanosuspensions.[35] PI provides the physical stability of nanosuspensions. The stability of nanosuspensions can be maintained for longer period provided the PI should be low. A PI value of 0.1 to 0.25 represents a fairly narrow size distribution, and PI value greater than 0.5 indicates a very broad distribution. For IV use, particles should be less than 5µm, considering that the smallest size of the capillaries is 5-6µm and hence a higher particle size can lead to capillary blockade and embolism.

1.The rate and extent of drug (bioavailability)

2. Dissolution rate

The Noyes and Whitney equation showed, when the particles size reduces, the surface area of the particles, solubility and dissolution rate of drug will increase.[36]

4.2 *Crystalline State and Particle Morphology*

Since nanosuspension requires high-pressure homogenization, there is a shift in the crystalline formulation structure that can be transformed into either amorphous or other polymorphic forms.[37] Changes in the solid state of the product particles and the size of the amorphous component are calculated by the X-ray diffraction analysis and followed by a differential calorimetry scanning analysis.

4.3 *Particle Charge (Zeta Potential)*

The principal role of particle size in nanosuspension is critical to maintaining nanosuspension stability. The electrical charge on a particle surface induces electrostatic repulsion between the nanoparticles and prevents accumulation and precipitation of particles, demonstrating the double electrical coating around a charged particle. The double layer is composed of a stern layer and an opposite diffusion layer. For a stable suspension stabilized only by electrostatic repulsion, a minimum zeta potential of ±30 mV is required whereas in case of a combined electrostatic and steric stabilizer, a zeta potential of ±20 mV would be sufficient. Particles charge is typically determined by measuring electrophoretic mobility upon application of an electric field which is then converted to zeta potential.[38]

4.4 *In vitro drug release*

Studies of the release of drugs *in vitro* were formed in a dissolution apparatus using paddle method at 50 rpm rotational speed.[39] The dissolution medium volume and temperature were 900 ml, and 37.0±0.2 ° C, respectively. Samples were collected at fixed times and were filtered using filter of 0.45µm. The amount of drug dissolved can be determined by measuring absorbance using UV spectroscopy or HPLC. Establishment of an IVIVC, described as a correlation between in vitro release and in vivo behavior, enhances the utility of an in vitro study.[40] Water, aqueous surfactant solutions, buffer solutions(P^H 6.8,7.4) or other simulated biological fluids can be chosen as dissolution media.[41]

4.5 *pH*

Using a digital pH meter at 20±1 C, the pH values were measured at 25°C. The formulation was brought into contact with the pH-meter electrode and equilibrated for 1 min.[42] This method was done in triplicate, calculating the mean along with standard deviation.

4.6 *Stability*

Reduction in particle size results in increased surface energy due to the greater number of unstable surface atoms and molecules. The estimation of the saturation solubility helps to investigate any change in the *in vivo* performance (blood profiles, plasma peaks, and bioavailability) of the drug. The use of stabilizers is to avoid the cluster making of particle and reduce the chances for Ostwald ripening.[43] The mixture of surfactants and polymers is beneficial for the long-term stabilization of nanosuspensions.[44]

4.7 Total Drug content

Take the required aliquot (0.5ml) of nanosuspension and subject to evaporation. The obtained residue is dissolved in suitable organic solvent and filtered using 0.45µm filter. The total drug content is estimated employing suitable analytical technique.[45]

Total drug content = (Total volume of nanosuspension× Amount of drug in aliquot)/Volume of aliquot

5. APPLICATIONS OF NANOSUSPENSION

5.1 *Oral Drug Delivery*

There are a number of problems in the traditional dosage method (i.e. oral drug administration), and they cause poor solubility, inadequate absorption and insufficient effectiveness.[46] So, in order to overcome the problem oral nanosuspension has been formulated. Due to small particle size and large surface area, oral nanosuspension helps to increase the oral bioavailability and increase in solubility of poorly soluble drugs (BCS class-II) as illustrated in Fig 1.

5.2 Parenteral Drug Delivery

Nanosuspensions can be used to transform poorly soluble non-injectable drugs into a formulation suitable for intravenous administration. Although the production of nanosuspension for parenteral use is critical, current developments in this technology have proved its utility as injectable formulation.[47]

5.3 Pulmonary Drug Delivery

For pulmonary delivery, nanosuspensions can be nebulized through mechanical or ultrasonic nebulizers. Due to the presence of many small particles, all aerosol droplets contain drug nanoparticles. Aqueous suspensions of the drug can be easily nebulized and given by pulmonary route as the particle size is very small.[48] Some of the drugs successfully tried with pulmonary route are budesonide, ketotifen, ibuprofen, indomethacin, nifedipine, itraconazole.

5.4 Ocular Drug Delivery

Nanosuspensions are used in ocular delivery of the drugs for sustained release, an ideal approach for ocular delivery of hydrophobic drugs due to their inherent ability to improve saturation solubility of drugs.[49]

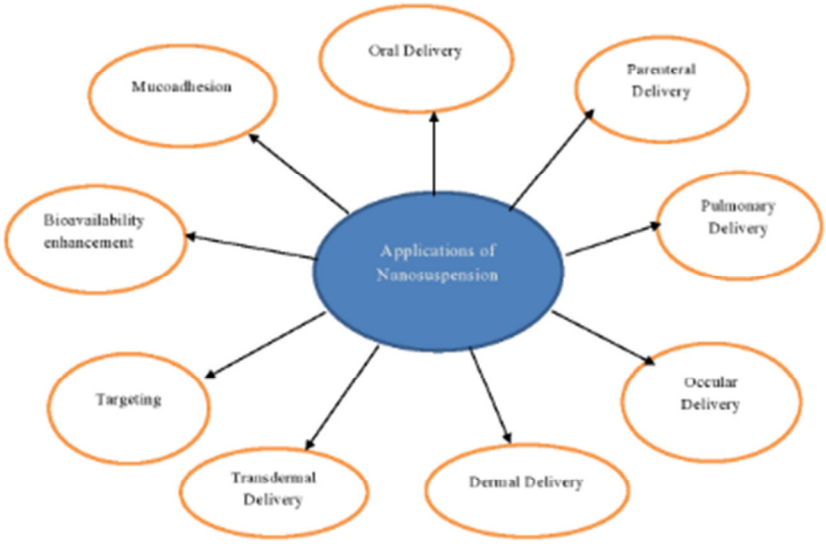

Fig 1. Application of Nanosuspension

5.5 Dermal

The nanocrystalline form possesses to increased saturation solubility resulting in enhanced diffusion of the drug into the skin, such as increased penetration into a membrane,

enhanced permeation and bio adhesiveness which could be very useful for dermal application.[50] Some of the marketed products include Rapamune, Emend, TriCor, Megase, Silver.

5.6 Transdermal Drug Delivery

Nanonization is a technique that is converting the drug particle into a nano size. The slow permeation of many drugs across the skin layer is the main disadvantages of transdermal route. In these techniques to cross the skin barrier such as penetration enhancers in the topical formulation.[51]

5.7 Drug Targeting

Nano suspension can also be used to target their surface properties and modify the stabilizers behavior can be easily altered in vivo. Mono nuclear phagocytic system must absorb the drug to allow regional specific delivery.[52] This may be used to target macrophages with anti microbacterial, leishmanial drugs if the infectious pathogen persists intracellularly.

5.8 Bioavailability Enhancement

Nanosuspensions determination the problem of poor bioavailability by solving the twin problems of poor solubility and poor permeability across the membrane. The therapeutic effect was significantly enhanced due to the faster dissolution (90% in 20 min) of the Lyophilized Nanosuspensions powder when compared with the dissolution from a coarse powder (15% in 20 min) and thus bioavailability.[53]

5.9 Mucoadhesion Of the Nanoparticles

Nanoparticles orally administered in the form of a suspension diffuse into the liquid media and rapidly encounter the mucosal surface. The particles are immobilized at the intestinal surface by an adhesion mechanism referred to as bio adhesion and represented in FIG 1.The direct contact of the particles with the intestinal cells through a bio adhesive phase is the first step before particle absorption, to improve bioavailability and targeting of the parasites persisting in the GIT.[54]

6 CONCLUSION

Nanosuspensions appear to be unique & yet commercially viable approach to combating problems such as poor bioavailability that are associated with the delivery of hydrophobic drugs. Fabrication methods like media milling and high-pressure homogenizer are utilized for large scale fabrication of nanosuspensions, including those that are poorly soluble in aqueous as well as organic media. The administration of nanosuspensions can be done through different routes including oral, ocular, topical, parenteral, pulmonary. Thus, nanosuspension technology can bring considerable benefits to the patients as well as research scope in the discipline of pharmacy.

7 AUTHORS CONTRIBUTION STATEMENT

Pushpalatha drafted the manuscript. Haranath collected the literature related to the applications and edited the manuscript and arranged in sequence. Abdul Ahad collected literature about the methods of preparation of nanosuspensions. Kalpana gathered literature on formulation aspects of nano suspension. Devika and Priyanka collected the information related to characterization. All authors read and approved the final manuscript.

8 CONFLICT OF INTEREST

Conflict of interest declared none.

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