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Nanosuspension As An Innovative Nanotechnology Trend Drug Delivery System: A Review

Mustafa R. Abdulbaqi*[1], Hassanien S. Taghi[1], Zahraa M. Jaafar[2]

[1]Department of Pharmaceutics, College of Pharmacy, Al-Bayan University, Baghdad, Iraq
[2]Department of Pharmacology and Toxicology, College of Pharmacy, Al-Bayan University, Baghdad, Iraq
Corresponding author: Mustafa R. Abdulbaqi, E-mail: drmustafa1986@yahoo.com

ABSTRACT

Solubility, the freedom of the drug from its route of administration, is the key factor for drug efficacy. Most of recently discovered drugs are insoluble in water and hence poorly absorbed with reduced bioavailability that lead to more production efforts. Due to their flexible characteristics and specific advantages, nanosuspensions has introduced as promising technique for effective hydrophilic drugs delivery. The reduction into the submicron range of drug particles leads to a major increase in rate dissolution and thus improves bioavailability of the drug. Nanosuspension involves colloidal dispersed submicron particles of the pharmaceutical active drug ingredient in liquid-phase stabilized with a surfactant. By oral and non-oral route of administration, nanosuspensions can be administered. Study focuses on different preparation methods with advantages and disadvantages, characterization techniques, and implementations.

Keywords: Nanosuspension, Particle Size Reduction, Solubility Improvement, Bioavailability enhancement.

Correspondence:
Mustafa R. Abdulbaqi
Department of Pharmaceutics, College of Pharmacy, Al-Bayan University, Baghdad, Iraq

*Corresponding author: Mustafa R. Abdulbaqi email-address: drmustafa1986@yahoo.com

INTRODUCTION

The reduced solubility of the active drug component, during which almost 40 percent of newly formulated drugs were introduced as lipophilic compounds with low aqueous solubility and limited bioavailability, is one of the most prevalent goals for the production and formulation of new drugs. Nanosuspension is a colloidal dispersion of submicron drug particles. A pharmaceutical nanosuspension is characterized in an aqueous vehicle as a tiny finely colloid, biphasic, scattered, solid drug particles sized less than 1µm, with no matrix content, stabilized by polymers act as surfactants, prepared by various methods for different application administration routes such as topical, oral, pulmonary, parenteral and ocular routes (1, 2). In addition to solving the problem of low solubility and bioavailability, nanosuspension also modifies drug's pharmacokinetics and increases safeness and effectiveness. Compounds that have elevated log P value and freezing point are suitable candidates for nanosuspension formulation (3). It has been stated that nanosuspension would help to increase adsorption and bioavailability to reduce the convectional oral-dosage dose (4). As defined by the modified Noyes-Whitney equation, drug particle-size reduction results in an increase in surface area and thus the rate of dissolution. In addition, due to increased dissolution-pressure, as described by Ostwald-Freundlich, the increased saturated solubility of drug is hypothesized to induced by the reduced particle size (5, 6). Altered crystallinity of the drug structure may also arise depending on the assembly technique applied. Higher saturation solubility may be caused by a rising amount of amorphous drug fraction (7). Additionally, general tissue adhesiveness for nanoparticles has been identified. The present review discuss whether drug supply within nanosuspension form would improve the passage of drugs through biologic membranes as a result of steeply higher concentration crossing gradients. Nanosuspensions are different from nanoparticles, which are typically polymeric colloid medicine carriers, while solid-lipid nanoparticles are lipid medicine carriers (8). In nanosuspension approach, with reduced particle size, the drug is preserved within the crystalline state, resulting in enhanced rate of dissolution and thus optimized bioavailability. Nanosuspension-encapsulated drugs available in a pharmaceutically crystalline and amorphous form (9).

Benefits (2, 10, 11)

Improvement of the drug's dissolution velocity and saturation solubility
Biological efficiency improved
Ease of production and scale-up
Physical long-term stability
Versatile behavior.
Increase in oral absorption within the context of
Increased proportionality in dosage.
It is also applied to medications which are poorly water-soluble.
Sometimes it is supported by any path.
Decreased inflammation of the tissue only during subcutaneous/intramuscular administration.
Orally, nanosuspension administration display faster onset, lower fed/fast ratio with subsequent optimized bioavailability.
Due to a decrease in particle size, the extent of absorption is also expanded.
Only in the case of ocular administration and inhalation delivery, higher bioavailability and more consistent dosing.
In order to extend the bioavailability of such drugs, drugs with a higher log P value are also formulated as nanosuspensions.
Increase in biological efficiency thanks to the drug's high dissolution rate and solubility in saturation.
Nanosuspensions are also inserted into tablets, suitable for different routes of administration are pellets, hydrogel and suppositories.
Increased amorphous part among suspended particles, resulting in potential improvement and greater solubility within the crystalline structure.
Probability of nanosuspension surface-modification for site-specific delivery.

Drawbacks (12)

Difficulties may be caused by physical stability, sedimentation and compaction.
During handling and transport, adequate care must be taken because it is bulky.
Insufficient dosage.
Standardized and specific doses cannot be done at the same time.

Preparation Process

There are primarily two nanosuspension preparation techniques. The conventional precipitation methods (hydrosols) are termed as "Bottom-Up Technology", while "Top-Down Technologies" are disintegration methods and favoured excess precipitation. The Top-Down Technologies can be accomplished by several methods including Nanocrystals (media milling), Dissocubes (high-water homogenization), Nanopure (high non-aqueous media homogenization), and Nanoedge (combine precipitation with high-pressure homogenization).

1. Bottom-up technique
2. Top-down technique

Bottom-Up Technique

This term means one begin from the molecule level, then upgraded to the solid particle creation by molecular association, meaning that classical precipitation techniques are addressed by reducing the consistency of the solvent, such as pouring a solvent into non-solvent or increasing the temperature or a mixture of both. In pharmaceutical chemistry and technology, precipitation can be a classical technique (13, 14).

Benefit (14)

Basic and low-cost equipment is used.
Higher solubility in saturation is the advantage of precipitation relative to other nanosuspension preparation methods.

Drawbacks (15, 16)

The medicinal substance must, at least, display solubility in one solvent.
A solvent with a minimum of one non-solvent must be miscible.
Solvent residues have to be eliminated, thus increasing the cost of production.
Maintaining the particle character is a little tricky (i.e. size, especially the amorphous fraction).

Top-Down Technique

(A) Media-milling
(B) Homogenization with elevated pressure

(A) Milling-Media

Mills with high-shear or pearl mills were used, the nanosuspensions are made. Its parts include milling-chamber; milling-shaft; and re-circulation chamber. The mill containing tiny grinding balls/pearls is then fed with an aqueous suspension of the drug (17). As these balls rotate in raised shear rate (under controlled temperature), they fly within the grinding container jar and impact on the other grinding jar wall against the sample. A magnified particle size reduction is created by results in further reduction of particle size and optimized stability (26). By using Nanoedge technology, drawbacks of the precipitation method like crystal growing and longstanding stability are also overcome. The precipitated suspension is further homogenized during this procedure, resulting in particle size reduction and preventing crystal growth(27). Using water-miscible solvents including methanol, ethanol and isopropanol, precipitation is carried out in water (5). It is desirable to fully get rid of certain solvents, but inside the formulation, the combined forces of friction and impact (18, 19). The milling media or balls are made with high abrasion resistance from ceramic-sintered alumina or zirconia or strongly cross-linked polystyrene resin. One example of a kit, which will be utilized for grind size < 0.1 μm, is a planetary ball mill. Using the wet milling process, Zn-Insulin was prepared as a nanosuspension (mean particle size of 150 nm).

Benefits (20)

Simple process
Low-cost operation with respect to the milling itself
Large-scale manufacturing to any degree feasible (batch process).

Drawbacks (21, 22)

Milling beads may cause erosion and results in product impurity.
The period of the system is not very manufacturing friendly.
Potential germ development while milling for a prolonged duration within the water process.
This method require time and high cost to exclude the milling solids from drug nanoparticles within the prepared suspension, in particular in the manufacture of parenteral sterile products.

(B) Homogenization with High Pressure

Dissocubes

By this technique the drug suspension is shaped to be subjected via a small inlet orifice, resulting in static pressure depletion below water boiling pressure, causing the water to boil and the development of gas bubbles (22). The bubbles implode when the suspension exits the gap and normal atmospheric pressure is again reached, and then the drug particles in the surrounded portion urgent to the center and colloids throughout the process, thereby reducing particle size (23). Many cases necessate several re-cycling homogenization depending on hardness and desired particle size of drug. Pre-milling is sometimes advisable for better solid content nanosuspension (15).

Nanopure

Nanopure is homogenized suspensions in water-free media or mixes of water like oils, while the Disso-cubes technology the determining factor of the technique is cavitation caused by boiled water. Oils have minimum vapor-pressure and higher boiling-point than water (24). The decrease in static pressure would therefore not be sufficient enough to cause cavitation. Polymeric material disintegration by high-pressure homogenization suggest that disintegration has been promoted by higher temperatures of around 80 ˚C, while at 0 ˚C the suspended drug particles inside the non-aqueous medium have been homogenized and thus called deep-freeze" homogenization (25).

Nanoedge

Nanoedge principle concepts are similar to those of precipitation and homogenization, where a blend of these methods
they can be tolerated to a specific degree. An evaporation phase to supply a solvent-free modified beginning substance that followed by high-pressure homogenization is also included for the efficient development of nanosuspensions using this method.

Emulsion Diffusion

Emulsions can mediate the preparation of nanosuspension as a vehicle for drug delivering, and can be applied for medications with ultimate solubility in volatile organic-solvent or relatively miscile with water.

Such solvents are also used because the emulsion particles are dispersed (28). Over the aqueous phase, the organic-solvent (alone or in combination with other solvents) was added with stirring, which containing the dispersed drug plus suitable surfactants in order to create the emulsion. Further homogenization is applied to the prepared emulsion using high homogenization speed. The mixing of emulsion with aqueous phase was done during homogenization cycles for transformation of droplets into solid form. Since each emulsion droplet contain one particle, the particle size can be controlled by adjusting the emulsion dimensions, improving surfactant composition, raising organic phase intake; and eventually, the load of the drug inside the emulsion (29).

Benefits (30)

The use of specialized devices is not needed.

By adjusting the dimensions of the emulsion droplet, particle size can easily be managed.

Facilitated scale-up.

Drawbacks (31)

This system does not formulate drugs that are poorly soluble in both aqueous and organic media.

Safety issues related to the use of dangerous solvents within the procedure.

Di-ultrafiltration is needed for nanosuspension purification, which can make the process expensive.

In comparison to the assembly techniques mentioned earlier, large surfactant/stabilizer quantities are required.

Microemulsion Template

This technique is accompanied by an organic solvent or combination of solvent filled with an aqueous phase dispersed drug containing sufficient surfactants to create an emulsion. Under reduced pressure, organic phase was then evaporated allowing drug particles to precipitate form the nanosuspension, which stabilized using surfactants. Because of the scattered particles rather than toxic solvents, another approach makes use of partly water-miscible solvents such as butyl lactate, benzyl alcohol and triacetin (32)

Supercritical Fluid

By using this technology, drug nanoparticles can be generated from drug solutions. Rapid expansion of the supercritical solution process (RESS), supercritical anti-solvent process and compressed anti-solvent process (PCA) precipitation are the different methods attempted (33). The RESS requires expansion of the drug solution through a nozzle into supercritical fluid, resulting in a deprived solvent strength of the fluid leading to fine particles precipitation of drug. In which atomization of drug solution was performed into a compressed CO_2 chamber within the PCA phase. Drug solution is supersaturated caused by solvent extraction leading to fine crystals precipitation of drug. The drug is poorly soluble in supercritical fluid, while drug solvent is miscible with the fluid, therefore supercritical fluid act as anti-solvent phase (34). As drug solution is pumped into the supercritical fluid, the solvent is removed and the drug is precipitated as fine crystals (35).

Melt-Emulsification

Here the drug distributed inside stabilizer solution, then heated to temperature higher than drug's freezing point, and emulsion obtained after homogenization. A heating tape fitted with a temperature controller was wrapped in the sample holder during operation, so that the emulsion temperature was kept above the freezing point of drug. Then emulsion was cooled slowly down till equilibrium or within bath of ice (37).

Benefit

Absolute avoidance of organic solvents during the assembly process.

Dry Co-Grinding

Recently, dry milling also used to prepare nanosuspension. Beneficial addition of soluble polymers and/or copolymers to dispersed poorly soluble drug in liquid media prior dry grinding in order to prepare stable nanosuspensions. Soluble polymers such as PVP derivatives, hydroxypropyl methylcellulose (HPMC), polyethylene glycol (PEG) and finally cyclodextrin (30).

Consideration for Formulation

1. The Stabilizing Agent

The primary purpose of a stabilizer is to thoroughly wet the drug particles and to avoid the maturation and/or cluster of nanosuspensions by Ostwald so as to produce a physical stable preparation by creating a steric barrier (38). The physical stability and *in vivo* performance of nanosuspension is controlled by the quantity of stabilizer added. Poloxomers, polysorbates, cellulosics, povidones, and lecithin are stabilizers currently used. Lecithin is the stabilizer of choice for parenteral and autoclavable nanosuspension (39).

2. The Organic Solvent

In nanosuspension formulation, organic solvents are used when emulsion system (micro- or nano-) are template. Due to their less toxic effect, the water miscible solvent (like methanol, isopropanol, ethanol, etc.), and solvents that are partially miscible with water (like ethyl formate, triacetin, propylene carbonate, etc.) are pharmaceutically accepted and preferred for nanosuspension formulation over traditional hazardous solvents, such as dichloromethane (11).

3. The Co-Surfactants

When using microemulsions to formulate nanosuspensions, the option of co-surfactant is important. As cosurfactants can significantly influence phase behaviour, it is important to investigate the impact of co-surfactants on internal phase uptake for selected micro emulsion composition and drug loading. While the literature describes the use of bile salts and dipotassium glycerrhizinate as cosurfactants, different solubilizers are also safely used as cosurfactants within the microemulsion fabrication, for example transcutol-p and ethanol (40).

4. Miscellaneous Additives

Additives such as salts, polyols, buffers, osmogents and cryoprotectants may be present in nanosuspensions (41).

Processing in Post-Production

When drug molecule can undergo chemical degradation or cleavage, post-production processing of nanosuspensions becomes necessary (42). Processing might needed also when simplest stabilizer is unable to stabilize the formulation or there are acceptability restrictions with regard to the specified path. Lyophilization (spray drying) can also be used to provide nano scaled sized drug particles with a dry powder. Given the drug characteristics and economic aspects, fair selection must be made in these unit operations. Lyophilization is more costy and less effective than spray drying (5).

Characterization Techniques

Color, Odor, Taste Evaluations

In orally administered formulation, these attributes are particularly significant. Taste variation can result from alteration in particle size and crystal behavior leading to

modified dissolution. Chemical instability can reflected as an altered color, smell and taste (43).

Distribution of Particle Size

Particle size distribute in a manner that give indication to the formulation's physiochemical properties, as saturated solubility, dissolution tendency, and physical stability. Photon correlation spectroscopy (PCS), laser diffraction (LD), and coulter counter multi-sizer are also used to determine the particle size distribution (44). Within a size range between three nanometer to three micrometer, PCS technique will measure particles, while the LD method measure sizes between 0.05 and 80 µm. In comparison to the LD process, which offers only a relative size distribution, the coulter counter multi-sizer totally gives the number of particles (5). Particles should be less than 5µm for IV use, given that the capillary's smallest size is 5 to 6 µm and thus larger particle size might cause capillary occlusion and embolism (35).

Zeta Potential

A minimum zeta potential of ±30mV is needed when a stable nanosuspension stabilized merely via electrostatic repulsion, whereas a zeta potential of ±20 mV would be adequate when a blend of electrostatic and steric stabilizer is applied (45).

Morphology of the Crystal

Techniques such as X-ray diffractogram analysis along with differential scanning calorimetry or differential thermal analysis are also used to classify the polymorphic changes that attributed to the effect of high-pressure homogenization within the crystalline structure of the drug. Within the crystalline structure, nanosuspensions may undergo a transition that can be due to high-pressure homogenization to amorphous arrangement of particles, or to alternate polymorphic forms (3, 38).

Dissolution Tendency and Saturated Solubility

Nanosuspensions have a critical benefit over other methods, since optimized saturated solubility can also increase the dissolution velocity. In different physiological solutions, those two parameters should be determined. In evaluating the *in vitro* formulation performance, the assessment of saturation solubility and dissolution velocity is crucial. An increase in the dissolution pressure and velocity of nanosuspension could attributed to nanometer ranged particle size (46).

The Density

A critical parameter is the real gravity or density of the formulation. Density depletion indicates air-entrapment inside the formulation structure. A well-mixed, uniform formulation should be used to measure density at a given temperature; such measurements are supported by the precision hydrometer (40).

The value for pH

In order to attenuate the drift of pH and suspended particles surface coating with electrodes, pH value for aqueous formulations must taken at a certain temperature and after equilibrium settling is achieved. The external phase of the formulation should be free from electrolyte to establish pH stabilization (47).

The Size of Droplet

Light scattering or microscopic techniques also calculate the distribution of the droplet size for micro-sized emulsion carriers. A dynamic light dispersion spectrophotometer that uses a 632 nm wavelength neon laser (48).

Nanosuspension Stability

The excited nanosized particles due to elevated surface energy causes drug crystals to agglomerate. The stabilizer's most significant purpose is to thoroughly wet the drug particles to avoid the nanosuspension Ostwald ripening and/or agglomeration, which form a chemically stable preparation by supplying a steric and/or ionic barrier. Stabilizers like cellulosics, polysorbates, and lecithin are commonly used for nanosuspensions. In the production of parenteral nanosuspension, Lecithin may also be favored (49).

***In Vivo* Biological Efficiency**

An essential part of the analysis is to launch an *in vitro*/*in vivo* correlation and monitoring he drug's *in vivo* output irrespective of the route and hence the delivery system used. In the case of intravenously injected nanosuspension, it is of vital importance (2). Since the drug's *in vivo* behavior depends on the distribution of the organ, which successively depends on drug surface properties like surface hydrophobicity and plasma protein binding. In order to quantify the surface properties and protein interactions to promote a thought of *in vivo* behaviour, effective techniques must therefore be used (5).

Nanosuspension Applications

1. Orally

The most widely preferred method of medication administration is oral drug delivery. However, due to low solubility and absorption, certain medications possess limited bioavailability, which eventually limits their effectiveness. In such situations, nanosuspension should fix the matter because, attributed to increased area and increased adhesiveness; it aids to improve the dissolution rate and subsequent absorption (50). Increased muco-adhesion, which can increase transit time via GIT with raised bioavailability, may be induced by nanosuspension. Increased regional saturated solubility and thus drug nanosuspension adhesiveness result in improvement in oral bioavailability. Additionally, taste hiding is easy to perform (51).

2. Parenterally

Nanosuspensions also do not turn poorly soluble non-injectable drugs into an intravenous formulation. Despite the assembly of parenteral use of nanosuspension is important, current advances have demonstrated its usefulness as injectable formulations throughout this technology. Recently, the techniques used for nanosuspension preparation are highly controlled and ready to produce particles that uniformly sized with more convenient (52).

3. Ophthalmic

Nanosuspension can persuade drugs that display low solubility in lachrymal fluids to be a boon. Thanks to their intrinsic ability to increase the solubility of saturation of medication, nanosuspensions represent a great approach to ocular delivery of hydrophobic medicines (53).

4. Pulmonic

Nanosuspensions are also useful for the delivery of drugs that show low solubility within pulmonary fluids. Nowadays available pulmonary delivering methods (like aerosols, inhalers of dry powder, etc.) have some drawbacks, as restricted penetration or diffusion at the targeted spot, which might directed by nanosuspensions (54). For pulmonary transmission, fluticasone and budesonide are effectively formulated as nanosuspension (55).

5. Dermally

The nanosuspension has improved saturated solubility, and hence increased drug diffusion across skin. Nanocrystals also display diverse properties, for example

enhanced membrane penetration, increased permeation, and bio-adhesiveness that optimize dermal employment (56).

6. Targeted Distribution of Drugs

Drug nanoparticles absorption depends on the size of their particles, which further optimized with altered *in vivo* behavior by modifying the surface properties of the nanoparticles and utilized for targeted drug delivery (57). Stealth nanosized and smart crystals with drug particle sizes below 100nm approve their effectiveness as a targeting method for the prevention of phagocytic absorption of nanocrystals. Nanosuspension development could be a commercially viable alternative for targeted distribution due to the simplicity of the process (58).

7. Muco-adhesive Nanosuspension

The orally administered nanoparticles within nanosuspension tend to disperse into liquid dispersion and can find the mucosal-surface easily. The particles are immobilized by an adhesion mechanism referred to as "bio-adhesion" on the intestinal surface. The condensed suspension serves as a reservoir of particles from this moment on with fast adsorption process. The effort prior to particle absorption is the direct interaction of the particles with the intestinal cells *via* a bio-adhesive process (59).

CONCLUSION

Nanosuspension appears to be a novel and yet commercially feasible approach to addressing issues such as low bioavailability associated with hydrophobic drug delivery, including those with low aqueous as well as organic solubility. To improve drug absorption and bioavailability, the dissolution issues of poorly soluble drugs are largely resolved. Nanosuspension technology is also combined with conventional types of dosage: tablets, pills, pellets and parenteral products are also used.

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Conflict of Interest

Authors declare no conflicts present.

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