Available online on 15.05.2019 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Review Article

Nanosuspension: An emerging trend to improve solubility of poorly water soluble drugs

S. B. Vedaga[1*], S.B. Gondkar[1], R.B. Saudagar[2]

[1] Department of Pharmaceutics, R.G. Sapkal College of Pharmacy, Anjaneri, Nashik-422213, Maharashtra, India.

[2] Department of Pharmaceutical Organic Chemistry, R. G. Sapkal College of Pharmacy, Anjaneri, Nashik-422213, Maharashtra, India

ABSTRACT

There are various parameters like solubility, stability, compatibility, excipient, and photostability which affects formulation of drugs, but solubility plays an important role for drug formulation. Most of newly discovered drugs are poorly water soluble. The poor water solubility of drugs always create major problem during drug formulation. There are many conventional techniques available for increasing the solubility of poorly soluble drugs such as micronization, solubilisation using co-solvents, salt form, precipitation technique etc. Other newer methods are also available such as liposomes, emulsions, microemulsion, solid dispersion but they lack in general applicability to all drugs. These techniques are not applicable for those drugs which are not soluble in aqueous and organic solvents. Poorly water-soluble compounds are difficult to develop as drug products using conventional formulation techniques. Nanotechnology is emerging trend to develop the formulation of those drugs which are poorly water soluble. Nanotechnology involves particle size ranges from 1–1000 nm. The reduction of drug particle size into the submicron range automatically leads to increase in the dissolution rate and therefore enhances bioavailability. Nanosuspension technology is effective new way that can be used for enhancing the dissolution of poorly water soluble drugs. A nanosuspension solves the problems of poor solubility and bioavailability as well as alters the pharmacokinetics of drug and this will improve drug safety and efficacy. Another additional feature of nanosuspensions is that they may induce changes in the crystalline structure, increasing the amorphous fraction in the particle or even sometimes creating completely amorphous particles.

Keywords: Nanotechnology, Solubility, Nanosuspension, methods, bioavailability

Article Info: Received 24 March 2019; Review Completed 30 April 2019; Accepted 02 May 2019; Available online 15 May 2019

Cite this article as:

Vedaga SB, Gondkar SB, Saudagar RB, Nanosuspension: An emerging trend to improve solubility of poorly water soluble drugs, Journal of Drug Delivery and Therapeutics. 2019; 9(3):549-553 http://dx.doi.org/10.22270/jddt.v9i3.2635

***Address for Correspondence:**

S. B. Vedaga, Department Of Pharmaceutics, R.G. Sapkal College of Pharmacy, Anjaneri, Nashik-422213, Maharashtra, India.

INTRODUCTION

Nanotechnology is defined as the science and engineering carried out in the nanoscale that is 10^{-9} m[1]. Nanotechnology is the science and technology of precisely describes the structure of matter at the molecular level. Nanosuspensions are colloidal dispersions and biphasic system consisting of particles dispersed in an aqueous vehicle in which the diameter of the suspended particle is less than 1um in size[2]. The unique features of nanosuspensions have enabled their use in various dosage forms[8]. The nanosuspensions can be used to formulate compounds that are insoluble in both water and oils[12]. The particle size distribution of the solid particles in nanosuspensions is usually less than one micron with an average particle size ranging between 200 and 600 nm[5]. Nanosuspensions vary from nanoparticles and solid lipid nanoparticles. Nanoparticles are usually polymeric colloidal transporters of drugs whereas solid lipid nanoparticles are lipid carriers of drugs. In nanosuspension technology, the drug is continued in the required crystalline state with reduced particle size, leading to an improved dissolution rate and therefore enhanced bioavailability[7]. Nanosuspensions consist of the poorly water soluble drug which is frequently suspended in dispersion. These can be used to enhance the solubility of drugs that are poorly soluble in aqueous as well as lipid media[3]. The nanosuspension formulation can be applied to all drug compounds belonging to biopharmaceutical classification system (BCS) classes II andIV to increase their solubility[4]. Preparation of nanosuspension is simple. There are various techniques available to prepare nanosuspensions such as wet mill, high pressure homogenizer, emulsion solvent evaporation, melt emulsification and supercritical fluid techniques[7]. Nanosuspensions differ from nanoparticles which are polymeric colloidal carriers of drugs[4]. Nanosuspensions can be applied by parenteral, oral, ocular and pulmonary routes. Currently, efforts are being directed to extending their applications in site-specific drug delivery[8].

Advantages of nanosuspension

- It enhances the solubility and bioavailability of drugs
- By nanosuspension approach higher drug loading can be achieved

- It enhances the physical and chemical stability of drugs
- It provides a passive drug targeting
- It is suitable for hydrophilic drugs
- Dose reduction is possible
- Larger drug loading can also be done

When to go for nanosuspension approach?

- Nanosuspension is preferred for the compounds that are insoluble in water.
- Compounds with high log P value.
- Compounds having high melting point and high dose[2].

FORMULATION CONSIDERATIONS FOR NANOSUSPENSIONS:

Nanosuspension formulation requires basically stabilizer or surfactant, proper solvent system and others ingredients for its preparation[7].

a) Stabilizers:

Use of stabilizers is essential in formulation of nanosuspensions. In the absence of an appropriate stabilizer, the high surface energy of nano-sized particles can induce agglomeration or aggregation of the drug crystals. This will provide high physical instability therefore use of stabilizer is required in nanosuspension formulation. Eg. Polysorbate, (Tween/Span series), povidone, poloxomers and lecithin[3,5,7].

b) Organic solvent:

Organic solvents are generally used in preparation of nanosuspension if basic technologies such as emulsion or microemulsions are used as template for this.These solvents are very hazardous in physiologic and environmental means but still some less hazardous water miscible solvents like methanol, ethanol are used.The use of organic solvents in the pharmaceutical area depends upon their toxicity potential and the ease of their removal from the formulation [3,7,10].

c) Surfactants:

Surfactants are incorporated to reduce interfacial tension of particles and thereby to produce a smooth dispersion.They also used as wetting or deflocculating agents e.g. Tweens and Spans - widely used surfactants[5, 6].

d) Co-surfactants:

The choice of co-surfactant becomes critical when using microemulsions to formulate nanosuspensions. Co-surfactants greatly influence phase behavior. Therefore the effect of co-surfactant on uptake of the internal phase for selected microemulsion composition and on drug loading should be investigated.e.g. Transcutol, glycofurol, ethanol and iso-propanol - safely used as co-surfactants. Also, bile salts and Dipotassium glycerrhizinate can be used as co-surfactants[3,5,6].

e) Other additives:

Uses of other ingredients mainly depends upon either the route of administration or physicochemical properties of drug candidate but some additives such as buffers, salts, polyols, osmogent and cryoprotectant are normally used.Other additives such as buffers, salts, polyols, osmogent and cryoprotectant, depending on either the route of administration or the properties of the drug moiety[5,7].

METHODS OF PREPARATION OF NANOSUSPENSION

Technically nanosuspensions preparations are simpler than liposome's preparation and other conventional colloidal drug carriers but they are more cost effective. Nanosuspension approach is used particularly for poorly soluble drugs and to yield a physically more stable product. For manufacturing nanosuspensions there are two converse methods available viz. "Top-down process technology" and "Bottom-up process technology".

The top -down process follows disintegration approach from large particles, microparticles to Nanosized particles.

Examples are following;

High pressure homogenization
Nanoedge
Nanopure
Media milling (Nanocrystals).

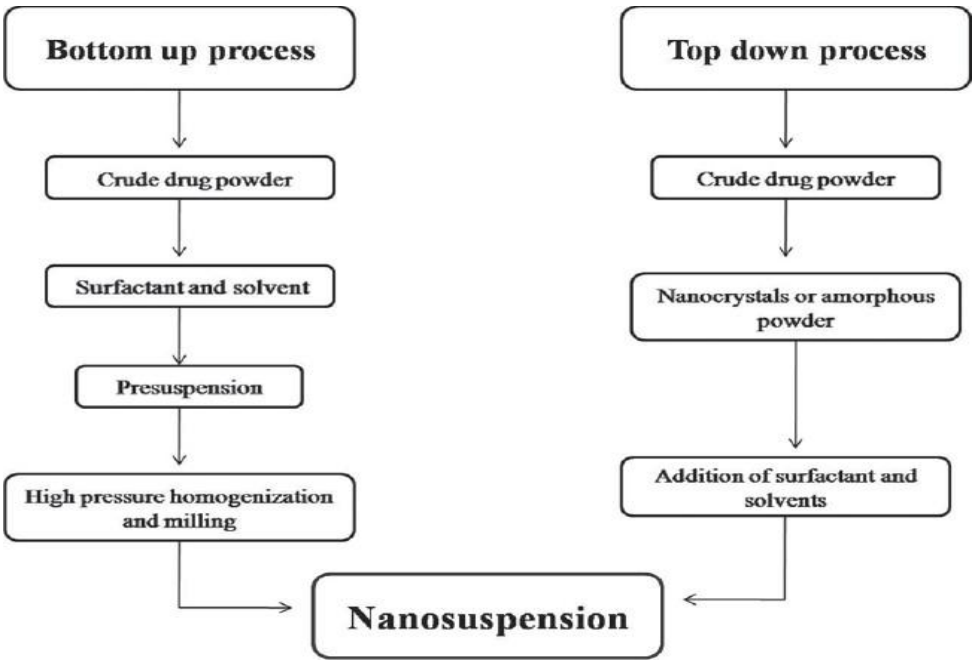

Figure 1: Approaches for preparation of nanosuspensions

Bottom-up process is an assembly method which also forms nanoparticles from molecules. Examples includes

Solvent-Antisolvent method

Super critical fluid process

Emulsification Solvent evaporation technique

Lipid emulsion/Micro-emulsion template.

1. BOTTOM UP TECHNIQUES

The principle techniques generally used in recent years for preparing nanosuspensions are:

A .High pressure homogenization:

This technique has been used to prepare nanosuspension of many poorlywater soluble drugs.It involves three steps. First drug powders are dispersed in stabilizer solution to form presuspension, and then the presuspension. International is homogenized in high pressure homogenizer at a low pressure for premilling, and finally homogenized at high pressure for 10 to 25 cycles until the nanosuspensions of desired size are formed. Different methods are developed based on this principle for preparations of nanosuspensions are Disso cubes, Nanopure, Nanoedge and Nanojet[5,7].

a. Homogenization in aqueous media (Disso cubes):

Disso cubes technology was developed by R.H.Muller. He used a piston-gap type high pressure homogenizer in 1999. The suspension containing a drug and surfactant is forced under high pressure through a Nanosized aperture valve of a high pressure homogenizer.The instrument can be operated at pressure ranging from 100-1500 bars (2800-21300 psi) and up to 2000 bars with volume capacity of 40 ml (for laboratory scale).

Principle:

This method is based on cavitation principle. In this method the dispersion containing drug and surfactant present in 3cm diameter cylinder is suddenly passed through a very narrow gap of 25µm.According to Bernoulli's law the flow volume of liquid in a closed system per cross section is constant. This results in increase in dynamic pressure and decrease of static pressure below the boiling point of water at room temperature due to reduction in diameter from 3cm to 25µm, then water starts boiling at room temperature which results in formation of gas bubbles, which implode when the suspension leaves the gap (called cavitation) and normal air pressure is reached. The particles cavitation forces are sufficiently high to convert the drug micro particles into nanoparticles[5, 7].

Advantages

1. It prevents erosion of processed materials

2. The method can be applied to the drugs that are poorly soluble in both aqueous and organic media.

Disadvantages

1. Pre-processing like micronization of drug is required.

2. High cost instruments are required that will also increases cost of dosage form.

b. Homogenization in nonaqueous media (Nanopure):

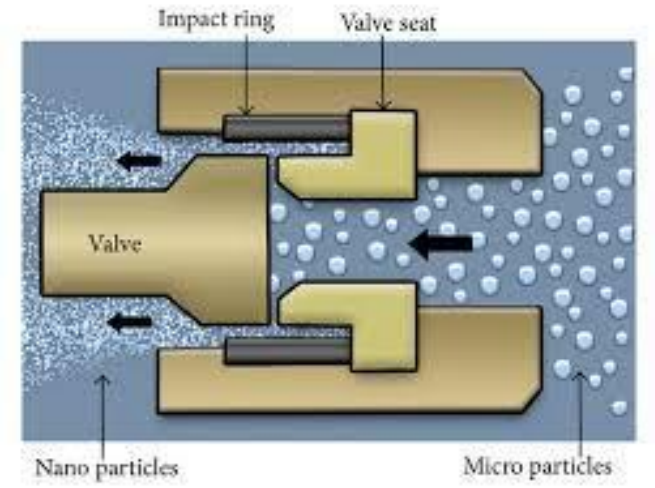

Figure 2: Schematic Cartoon of the High-Pressure Homogenization Process.

Nanopure is nothing but suspensions that are homogenized in water-free media or water mixtures like PEG 400, PEG 1000 etc. The homogenization can be done at room temperature and sometimes at 0^0C and below freezing point that is -200C, hence it is known as "deep freeze" homogenization. The results obtained were comparable to Disso Cubes and hence can be used effectively for thermolabile substances at milder conditions[5,7].

c. Nanoedge:

The basic principles of Nanoedge are the same as that of precipitation and homogenization.The drug is dissolved in an organic solvent and this solution is mixed with a miscible anti-solvent for precipitation. In the water-solvent mixture, because of low solubility the drug precipitates.Nanoedge technology involves the combination of both precipitation and homogenization. The basic principle of this method is same as that of precipitation and homogenization. The major disadvantage of precipitation technique such as crystal growth and longterm stability can be minimized by using the Nanoedge technology. Particles of smallersize and better stability in short time can be achieved[5, 7].

d. Nanojet:

It is also known as opposite stream technology, uses a chamber where a stream of suspension is divided into two or more parts, which colloid with each other at high pressure, due to the high shear forcesproduced during the process particle size is reduced[7]. Due to high shear force produced during the process which results in particle size reduction. The M110L and M110S microfluidizers (Microfluidics) equipments used for this purpose[1,5,7].

B. Dry cogrinding:

Since last years, nanosuspensions are prepared through wet grinding processes by using pearl ball mill. Nowadays, various technologies has beendeveloped for preparation of nananosuspensions such as dry milling methods.Stable nanosuspensions are prepared by using dry grinding of poorly soluble drug with soluble polymers and copolymers after dispersing in liquid medium[1,7].

C. Precipitation Method:

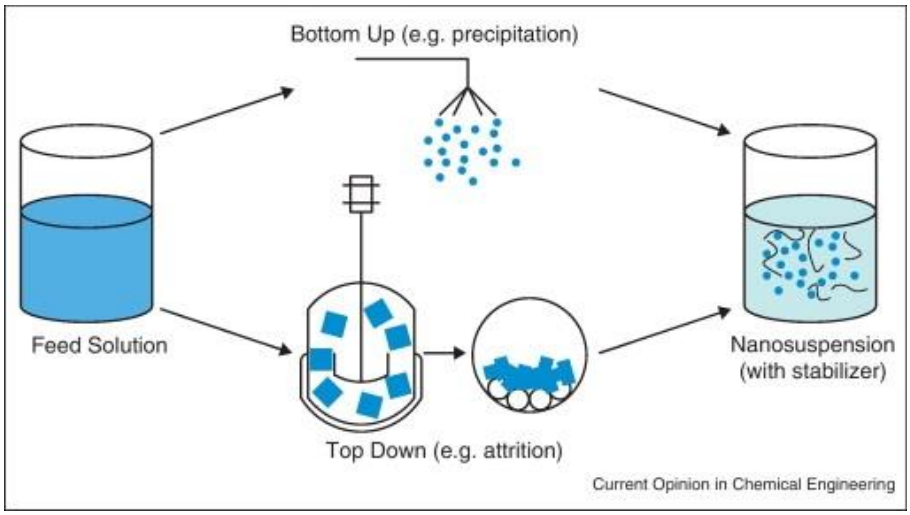

Figure 3: schematic diagram for precipitation method

Precipitation method is a common method used to prepare submicron particles of poorly soluble drugs. In this method, firstly the drug is dissolved in solvent and then solution is mixed with solvent to which drug is insoluble in the presence of surfactant which will results in precipitation. Rapid addition of solution to such solvent (generally water) leads to rapid supersaturation of drug in the solution, and formation of ultrafine amorphous or crystalline drug. This method involves formation of nuclei and crystal growth which are mainly dependent on temperature. High nucleation rate and low crystal growth rate are primary requirements for preparing a stable suspension with minimum particle size[1,7].

APPLICATINS OF NANOSUSPENSIONS

1. Nanosuspension for pulmonary drug delivery

Pulmonary drug delivery to the lung represents a non-invasive possibility for local and systemic therapies. Direct pulmonary delivery in humans can be achieved using an aerosol generated by either an inhaler or nebulizer. The local application of therapeutic agents to the lungs has the advantages of an increased selectivity and high local concentration over other routes of administration, thus being the prevalent approach for the treatment of respiratory diseases. On the other hand, pulmonary route has gained growing attention as a potential way for systemic drug delivery, due to the large alveolar surface area, the thinness of the epithelial barrier and extensive Vascularization suitable for drug absorption[13].

2. Nanosuspension for ocular drug delivery

The nanocrystalline form leads to an increased saturation solubility of the drug in thetopical dosage form, thus enhancing the diffusion of the drug into the skin.The topical ocular administration of drugs is the most common route to provide treatment for both superficial and intraocular diseases. Depending on the target sites of the different ocular pathologies, drugs either need to be retained at the cornea and/or conjunctiva(e.g. conjunctivitis, blepharitis, keratitis sicca) or cross these barriers and reach the internal structures of the eye (e.g., glaucoma, uveitis). For ocular delivery of poorly soluble drugs, because the organic solvents and extreme pH should be avoid when considering the high sensitivity of the eye tissue, preparations such as microsuspensions and ointments have been developed to meet the therapeutic requires[13,14].

3. Nanosuspension for topical/dermal drug delivery

Dermal nanosuspensions are mainly of interest if conventional formulation approaches fail.The nanocrystalline form leads to an increased saturation solubility of the drug in thetopical dosage form, thus enhancing the diffusion of the drug into the skin. The increased saturation solubility leads to “supersaturated” formulations, enhancing the drug absorption through the skin. This effect can further be enhanced by the use of positively charged polymers as stabilizers for the drug nanocrystals. The opposite charge leads to an increased affinity of the drug nanocrystals to the negatively charged stratum corneum. Among the various strategies for enhancing dermal application, nanocrystals can be considered a rather new but highly interesting approach[13,14].

4. Distinct Drug Delivery

Nanosuspensions are compatible for targeting precise organs considering that of their surface houses. Along with this, it is anything but difficult to modify in vivo conduct by altering the stabilizer. The drug will probably be taken up by the mononuclear phagocytic method which allows area-particular delivery. This can be utilized for focusing on antifungal, antimycobacterial, or antileishmanial pharmaceuticals to macrophages[6, 13].

5. Target Drug Delivery

The need to target drugs to specific sites is increasing day by day as a result of therapeutic and economic factors. Nanosuspensions can also be used for targeted delivery as their surface properties and *in vivo* behavior can easily be altered by changing the stabilizer. Their versatility, ease of scale up and commercial product enable the development of commercial viable nanosuspensions for targeted delivery [8, 13, 14].

6. Parenteral Administration

The parenteral route is an invasive route. Parenteral administration of drugs is critical and often associated with the problems such as the limited number of acceptable excipients, restrictions on the quantities of excipients approved for parenteral use, the stringent requirements of the aseptic production process, safety issues, patient noncompliance and biological problems such as allergic reactions and thrombophlebitis. Nanosuspensions can be administered via different parenteral administration routes ranging from intra-articular via intraperitonal to

intravenous injection. For administration by the parenteral route, the drug either has to be solubilized or has particle/globule size below 5 µm to avoid capillary blockage[8, 14].

REFERENCES

1. Patel VR, Agrawal YK, Nanosuspension: An approach to enhance solubility of drugs, Journal of Advanced Pharmaceutical Technology & Research, 2011; 2(2).
2. Prasanna Lakshmi, Giddam Ashwini Kumari, Nanosuspension Technology: A Review, International Journal of Pharmacy and Pharmaceutical Sciences, 2010; 2(4).
3. Jaiswal P, Kesharwani S, Kesharwani R, Patel D, Ethosome: A New Technology Used As Topical & Transdermal Delivery System. Journal of Drug Delivery and Therapeutics, 2016; *6*(3):7-17.
4. Sneha B. Garasiya, Nanosupension: an attempt to enhance the bioavailability of poorly water soluble drugs, International journal of advances in pharmacy, Biology and Chemistry, vol. 2012; 1(1),
5. Shah DP, Patel B, Shah C, Nanosuspension technology: A innovative slant for drug delivery system and permeability enhancer for poorly water soluble drugs, Journal of Drug Delivery and Therapeutics, 2015; 5(1):10-23
6. Roshan Kumar B., Nikitha I., Shiva Sharma, Nishikant D, Rishi T., Nanosuspension: A review, Research & Reviews: Journal of Journal of Pharmaceutics and Nanotechnology, 2016; Special Issue 2,
7. Geetha G, Poojitha U, Khan KAA, Various Techniques for Preparation of Nanosuspension- A Review, International Journal of Pharma Research & Review, Sept 2014; 3(9):30-37 ISSN: 2278-6074
8. Patravale VB, Date AA, Kulkarni RM, Nanosuspensions: a promising drug delivery strategy, Journal of pharmacy and pharmacology JPP 2004, 56: 827–840_ 2004
9. Kalvakuntla S, Deshpande M, Attari Z, Koteshwara K B. ,Preparation and Characterization of Nanosuspension of Aprepitant by H96 Process, Adv Pharm Bull, 2016; 6(1):83-90 doi:15171/apb.2016.013
10. Sahu BP, Das MK, Nanosuspension for enhancement of oral bioavailability of felodipine, ApplNanosci (2014; 4:189–197, DOI 10.1007/s13204-012-0188-3
11. Yong Li, Xiuhua Zhao, Yuangang Zu, Yin Zhang, Preparation and characterization of paclitaxel nanosuspension using novel emulsification method by combining high speed homogenizer and high pressure homogenization, International Journal of Pharmaceutics 2015; 490:324–333
12. P. Kocbek, S. Baumgartner, J. Kristl, University of Ljubljana, Preparation and evaluation of nanosuspensions for enhancingthe dissolution of poorly soluble drugs, International Journal of Pharmaceutics 2006; 312:179–186
13. Nangare KA, Powar SD, Kate VK, Patwekar SR And Payghan SA, Therapeutics Applications of Nanosuspension in Topical/ Mucosal Drug Delivery, Journal of Nanomedicine Research, 2018; 7(1).
14. Prajapati S, Maurya S, Das M, Tilak V, Verma K, & Dhakar R. Dendrimers in Drug Delivery, Diagnosis and Therapy: Basics and Potential Applications. Journal of Drug Delivery and Therapeutics, 2016; *6*(1):67-92.
15. Nilesh Jain, Ruchijain, Navneet Thakur, Brahmprakash Gupta, Deepak Kumar Jain, Jeethendra Banveer, Surendra Jain, Nanotechnology: A Safe And Effective Drug Delivery System, Asian Journal of Pharmaceutical and Clinical Research, 2010 ; 3(3),
16. Mitesh Patel, Arpit Shah, Dr. N.M. Patel, Dr. M.R. Patel, Dr. K.R. Patel, Nanosuspension: A Novel Approach For Drug Delivery System, Journal of pharmaceutical science and bioscientific research, Volume 1, Issue 1: July-August 2011; 1-10.