ISSN: 0975-766X
CODEN: IJPTFI
Review Article

Available Online through
www.ijptonline.com

A TECHNICAL REVIEW OF NANOSUSPENSIONS

R.Bhargavi*
Hindu College of Pharmacy, Amaravathi Road, Guntur, A.P.
Email: rompicharlabhargavi@gmail.com

Received on 25-07-2011 *Accepted on 14-08-2011*

Abstract

Nanosuspensions are the colloidal dispertions of nano sized drug. Most of the drugs are hydrophobic and poorly soluble. Nanosuspension technic can be used to resolve the problems associated with those poorly soluble drugs i.e poor extent of release (bioavailability) and absorption of drugs. Nanosuspensions contain a pure poorly water soluble drug of nano size range (1-1000nm) in dispersion. Nanosuspensions are used in various dosage forms, including specialized delivery systems like mucoadhesive hydrogels. Nanosuspensions also alters the pharmacokinetic parameters of drug & thus improves drug efficacy & safety. Currently, researchers are being directed to extend their applications in targeted drug delivery systems.

Introduction

One of the critical problems associated with most of the drugs is low bioavailability and erratic absorption[1]. There are number of formulation approaches to resolve the problems of low solubility and low bioavailability[2]. The approaches include micronization cosolvency, solid dispersions[3], solid solutions oily solutions, salt formation, precipitation, liposomes[4], micro emultions[5] and inclusion complexes[6] with cyclodextrins show reasonable success. But they lack in universal applicability to all drugs. Nanosuspensions is the efficient approach for resolving those problems associated with poorly soluble drugs[7]

Nanosuspension is submicrone colloidal dispersion of pure particles of drug stabilized by surfactants. Nanosuspensions consists of pure poorly water soluble drug without any matrix material suspended in dispersion[8].

Formulation of Nanosuspensions

Formulation of Nanosuspensions includes stabilizers, solvents, surfactants, co-surfactants and other additives.

Stabilizers

Stabilizer can be incorporated for improving the stability by reducing the agglomeration or aggregation of drug particles. It acts by wetting the drug particles thoroughly and prevents ostwald's ripening [9,10] and agglomeration. The drug to stabilizer ration in the formulation may vary from 1:20 to 20:1.

Examples of stabilizers include Poloxamers,polysorbates,cellulosics,lecithins,povidones etc.

Solvents

The pharmaceutically acceptable and less hazardous water miscible solvents like ethanol, isopropanol and partially water miscible solvents like ethyl acetate, ethyl formate, butyl acetate, triacetin propylene carborate and benzyl alcohol are preffered in the formulation of Nanosuspensions.

Surfactants

Surfactants are incorporated to improve the dispersion by reducing the interfacial tension. They also act as wetting or deflocculating agents. Tweens and Spans are widely used surfactants in Nanosuspensions.

Co-Surfactants

Co-Surfactants are critical when using microemulsions to formulate Nanosuspensions. Literature describes the use of bilesalts and dipotassium glycerrhizinate as co-surfactants. Transcutol, glycofurol, ethanol and isopropanol etc can be used as co-surfactants.

Other additives

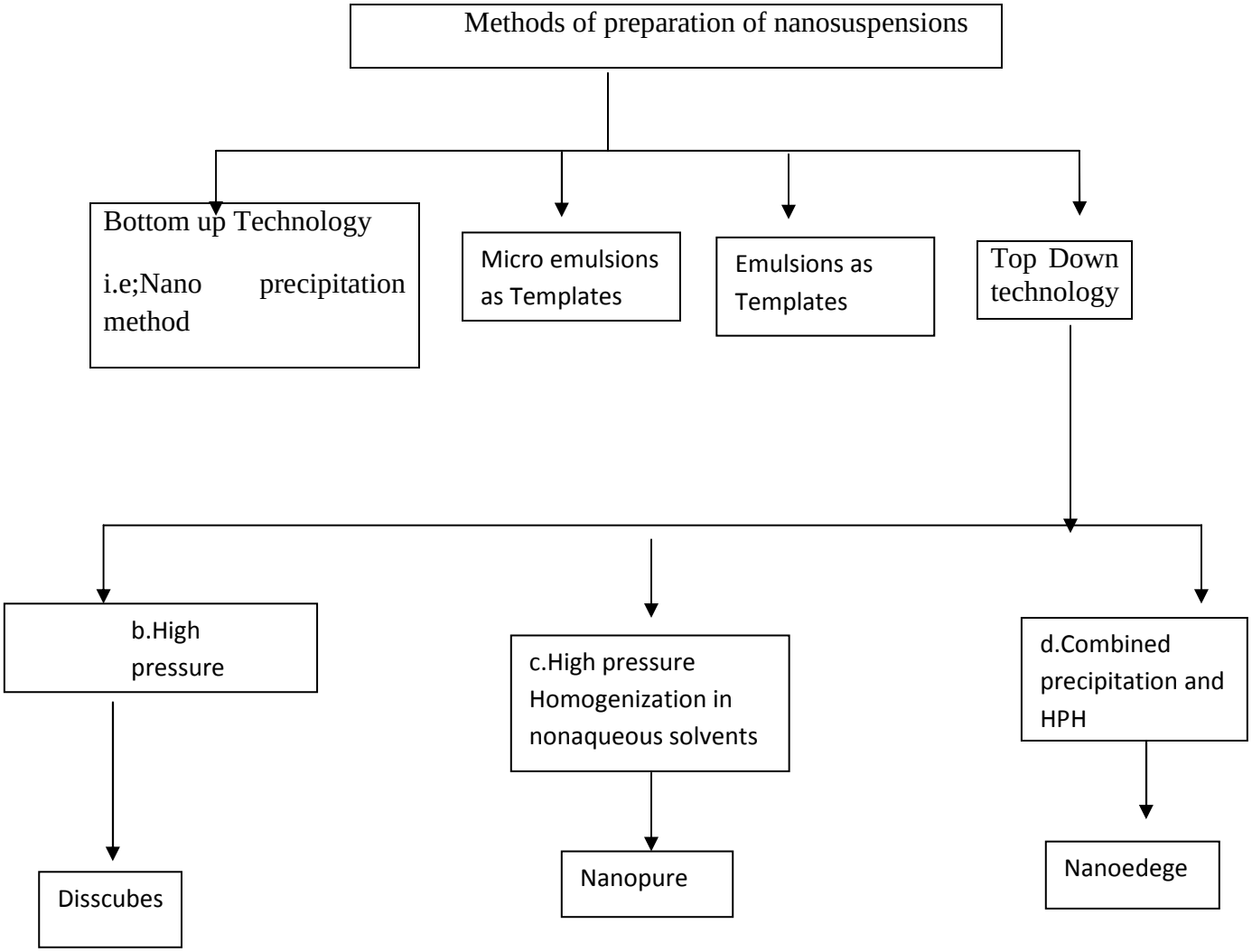
Nanosuspensions may also content additives such as Buffer salts, polyols, osmogent and cryoprotectants based on their route of administration or on the properties of the drug moiety.

Methods of Preparation of Nanosuspensions

Mainly there are two methods for the preparation of nanosuspensions

1. Bottom up technology in which the drug is dissolved in a solvent which is then added to nonsolvent to precipitate the crystals[11] .
2. Top down technology-which includes media milling(nano crystals) and high pressure homogenization in water (dissocubes), High pressure homogenization in nonaqueous media (nanopure)

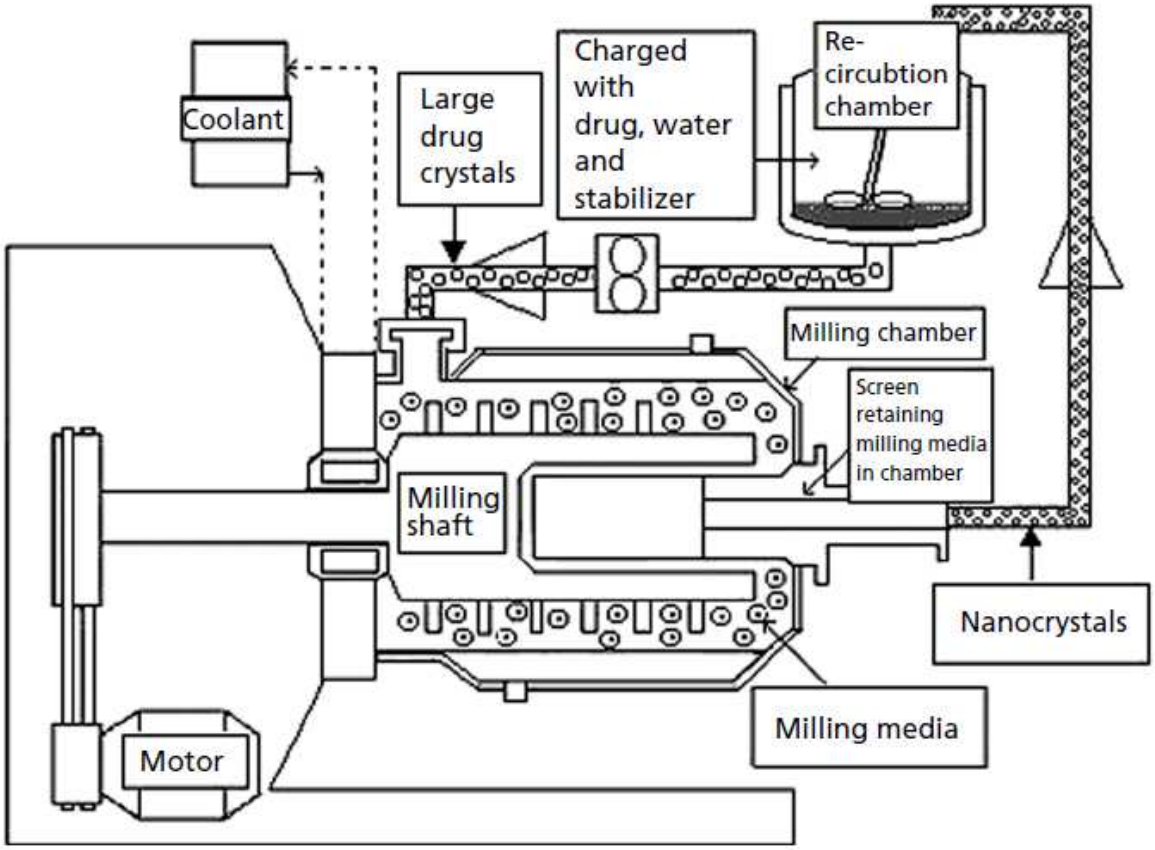
Fig1: Methods of preparation of nanosuspensions.



a. Media milling(nano crystals)

This method was developed by liversidge[12]. In this Nanosuspensions are prepared by using high shear media mills.

Fig2: Schematic representation of Media milling process.

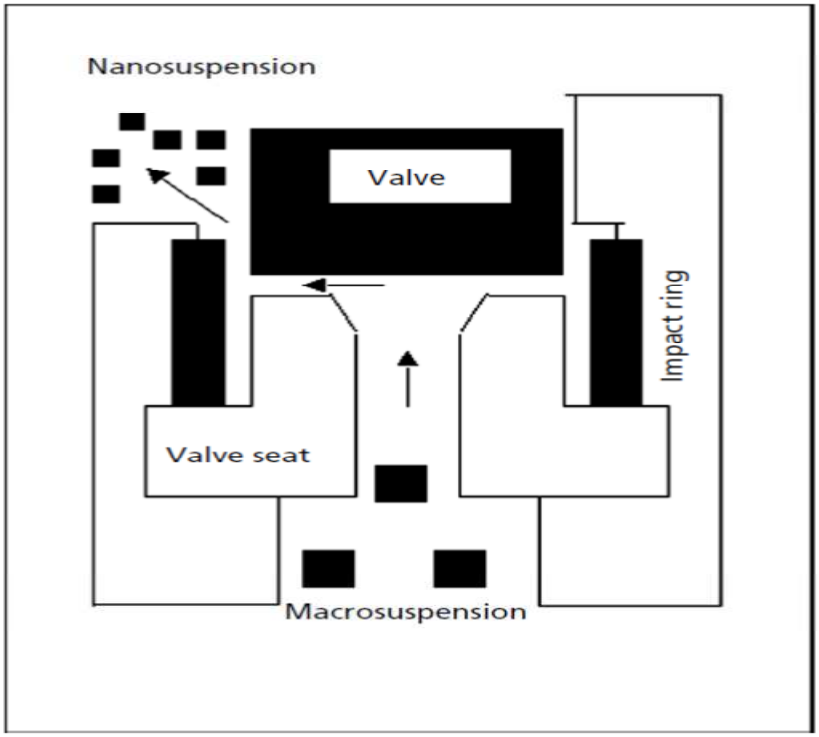


The media mill consists of a milling chamber, a milling shaft and a recirculation chamber. The milling chamber is charged with the milling media, water, drug and stabilizer as described in fig 2 and the milling media then rotated at a very high shear rate. The high energy and shear forces generated as a result of the impaction of the milling media with the drug provide the energy input to break the microparticulate drug in to nano sized particles.

b. High pressure homogenizers(dissocubes/nanopure)

This technique was first developed by R.H Muller[13] **.** Dissocubes and nanopures are engineered using piston gap type hgh pressure homogenizers.

Fig3: Schematic representation of high pressure homogenization process.



A high pressure homogenizer consists of a high pressure plunger pump with a subsequent relief valve. The relief valve consists of a fixed valve seat and an adjustable valve. These parts form and adjustable radial precision gap. It is advisable to start with micronized drug particles (<25µm)for production of nanosuspension in order to prevent blocking of homogenization gap. Hence generally a jet milled drug is employed as the starting material for producing dissocubes.

Homogenization can be performed in water(dissocubes)or alternatively in nonaqueous media(nanopure)[14] . Here the particles are disintegrated by cavitation and shearforces. The static pressure exerted on the liquid causes the liquid to boil forming gas bubbles. When exiting from the gap, gas bubbles collapse under normal air pressure. This produces shock waves which make the crystals collide , leading to particle disintegration. The instrument can be operated at pressures varying from 100-1500bars. High pressure homogenizers are available with different capacities ranging from 40ml (for laboratory purpose)to a few thousand litres(for large scale production)

C. Combined precipitation and homogenization(nanoedege)

The precipitated drug nano particles have a tendency to continue crystal growth to the size of micro crystals. They need to be processed with high energy forces (homogenization). So the precipitated particles suspension is subsequently homogenized.

3. Microemulsions as templates

Microemulsions are thermodynamically stable and isotropically clear dispersions of two immiscible liquids, such as oil and water. Surfactants and cosurfactants[15] are incorporated for stabilizing the dispersion.

4. Emulsions as templates

Apart from the use of emulsions as a drug delivery vehicle, they can also be used as templates to produce nanosuspensions. The use of emulsions as templates is applicable for those drugs that are soluble in either volatile organic solvent or partially water miscible solvent. Relatively safer solvents such as ethyl acetate and ethyl formate are mainly used solvents[16,17] .

Evaluation and Characterization of Nanosuspensions

Evaluation and characterization of nanosuspensions includes both In-vitro and in-vivo evaluation methods

In-Vitro Evaluation Methods

1. Mean particle size and particle size distribution
2. Particle charge (zeta potential)
3. Saturation solubility and dissolutuion velocity.
4. Crystalline state and particle morphology.

1. Mean particle size and particle size distribution

Mean particle size of drug particles effects the saturation solubility, dissolution velocity, physical stability and biological performance of nanosuspensions. The mean particle size and width of particle size distribution (poly dispersity index) are determined by photon correlationspectroscopy(PCS).

PCS measures the particle size in the range of 3nm-3µm only. It is a versatile technique but has low measuring range. In addition to pcs analysis, nanosuspensions are analysed by Laser Diffractometry (LD). LD yields a volume size distribution and can be used to measure particle sranging from 0.05-80µm upto 2000µm. Atomic forœ microscopy[18] is used for visualization of particle shape.

2. Particle charge (zeta potential)

The physical stability of a nanosuspension is governed by the particle charge (zeta potential) is effected by the stabilizer and the drug itself.

For electrostatically stabilized nanosuspension a minimum zeta potential of ±30mv is required.

For combined steric and electrostatic stabilized nanosuspensions a minimum of ±20mv is required.

3. Saturation solubility and dissolution velocity

Nanosuspension increase the saturation solubility as well as dissolution velocity. Saturation solubility is compounds specific constant depending upon the temperature and properties of dissolution medium.

4. Crystalline state and particle morphology

Crystalline morphology was determined by differential scanning calorimetry (DSC). When nanosuspensions are prepared, drug particles are converted to amorphous form. Hence it is essential to measure the extent of amorphous drug generated during the production of nanosuspensions. X-Ray Diffraction (XRD) is used for determining the physical state and extent of amorphous drug.

In-Vivo Biological Performance

The in-vitro-in-vivo correlation have utmost importance in the case of intravenously injected nanosuspensions. Suitable techniques have to be used in order to evaluate the surface properties and protein interactions to get an idea od invivo behavior. Surface hydrophibicity, qualitative and quantitative measurement of protein adsorption are important incase of in-vivo studies. Surface hydrophobicity was determined by hydrophobic interaction chromatography.

Table-1: Potential benefits of nanosuspension technology over other conventional formulations technologies for poorly soluble drugs.

Route of administration	**Potential benefits**
Oral	Rapid onset Reduced fed/fasted ratio Improved bioavailability
Intravenous	Rapid dissolution, Tissue targeting
Ocular	Higher bioavailability, More consistent dosing
Inhalation	Higher bioavailability, More consistent drug
Subcutaneous/intramuscular	Higher bioavailability, Rapid onset, Reduced tissue irritation

Conclusion

Nanosuspension technique is unique approach to resolving the problems associated with the delivery of drugs with poor solubility and low bioavailability (brick dust). Nanosuspensions due to its wide range of applicability in oral, parentral, pulmonary, ocular drug deliveries, they are more advantageous. Nanosuspensions can also improves the safety and efficacy of a drug by altering its pharmacokinetic parameters. The applications of nanosuspensions in buccal, nasal and topical delivery are still awaiting exploration.

References

1. Dubey R, Pure drug nanosuspensions impact of nanosuspensions technology on discovery and development. Drug Del.Tech 6, 2006, 65-71.
2. Aboofazeli R, Barlow DJ, Lawrence MJ. Particle size analysis of concentrated phospholipids microemulsions: II. Photon correlation spectroscopy. AAPS Pharm. sci.2, 2000, 1–10.
3. Agnihotri SM, Vavia PR. Diclofenac-loaded biopolymeric nanosuspensions for ophthalmic application. Nanomed, Nanotech. Biol. Med. 5, 2009, 90–95.
4. Rao GCS, Satish KM, Mathivnan N, Rao EB. Advances in nanoparticulate drug delivery systems. Ind.Drugs. 7, 2004, 389-95.
5. Akers MJ. Excipient–drug interactions in parenteral formulations. J. Pharm.Sci. 91, 2005, 2283–2300.

6. Allen TM. Liposomes, opportunities in drug delivery. Drugs 54,1997, 8–14.

7. Muller RH, Bohm BHL, Grau J. Nanosuspensions: a formulation approach for poorly soluble and poorly bioavailable drugs. In D.Wise (Ed.) Handbook of pharmaceutical controlled release technology. 17, 2000, 345-57.

8. Chowdary KPR, Madhavi BLR. Novel drug delivery technologies for insoluble drugs. Ind.Drugs. 42(9), 2005, 557-563.

9. Cornelia MK, Rainer H, Muller. Drug nanocrystals of poorly soluble drugs produced high-pressure homogenizations. Eur. J. Pharm. Biopharm 62, 2006, 3–16.

10. Patravale B, Abhijit AD, and Kulkarni RM, Nanosuspensions: a promising drug delivery strategy. J.Pharm.Pharcol. 56, 2004, 827-40.

Corresponding Author:

R.Bhargavi*

Email: *rompicharlabhargavi@gmail.com*