ISSN : 2320 4850

BI MONTHLY

Asian Journal of Pharmaceutical Research And Development

(An International Peer Reviewed Journal of Pharmaceutical Research and Development)

AJPRD

Volume - 01 Issue - 06 NOV-DEC 2013

website: www.ajprd.com
editor@ajprd.com

Asian Journal of Pharmaceutical Research and Development
(An International Peer-Reviewed Journal of Pharmaceutical Research and Development)
www.ajprd.com
ISSN 2320-4850

Review Article

NANOSUSPENSION: NEWER APPROACH FOR DRUG DELIVERY SYSTEM

Mittal Priyanka *, Singh Preeti, Verma Anamika, Khinchi M.P., Agarwal Dilip, Gupta M.K., Singh S.P.

Dept. of Pharmaceutics, Kota College of Pharmacy, Kota, Raj.

***Received:* 20 Nov. 2013** ***Revised and Accepted:* 23 Dec 2013**

ABSTRACT

Nanotechnology is defined as science and engineering carried out in a nanoscale that is 1-1000nm.Critical problem of poorly soluble drugs is low bioavailability and erratic absorption. The problem is even more complex for drugs belonging to biopharmaceutical classification system BSS CLASS2 category such as Carbamezepine and Intraconazole, as they are poorly soluble in both aqueous and non aqueous media. Nanosuspensions are biphasic systems consisting of pure drug particles dispersed in an aqueous vehicle, stabilized by surfactants. Nanosuspension technology can be used to improve the stability as well as bioavailability of poorly soluble drugs. It consists of pure poorly water soluble drug without any matrix material suspended in dispersion. Nanosuspensions can be delivered by oral, parental, pulmonary and ocular routes. A Nanosuspension not only solves the problems of poor solubility and bioavailability but also alters the pharmacokinetics of drugs and thus improves drug safety and efficacy. These are simple to prepare and are more advantageous than other approaches. Techniques such as wet milling, high pressure homogenization, emulsification-solvent evaporation and supercritical fluid have been used in the preparation of Nanosuspensions.

Key words: *Nanotechnology, nonosuspension, surfactants*

INTRODUCTION

A range of parameters like solubility, stability at room temperature, compatibility with solvent, excipient, and photostability play a critical role in the successful formulation of drugs. Till date, more than 40% of the new chemical entities being generated through drug discovery programs are lipophilic or poorly water-soluble compounds[1,2]. Many formulation approaches are available to solve the problems of low solubility and low bioavailability of drugs.

***For correscorespondence:**
Priyanka Mittal
Department of pharmaceutics
Kota College of Pharmacy
Kota, Rajasthan

Over the last decades, nanoparticle engineering has been developed and reported for pharmaceutical applications. Nanotechnology can be used to solve the problems associated with various approaches described earlier therefore; Nanosuspensions have emerged as a promising strategy for the efficient delivery of hydrophobic drugs because of their versatile features and unique advantages[3].

Nanotechnology is defined as the science and engineering carried out in the nanoscale that is 10^{-9} m. The drug microparticles/micronized drug powder is transferred to drug nanoparticles by techniques like Bottom-Up Technology and Top-Down Technology[4]. Nanosuspensions are submicron colloidal dispersions of nanosized drug particles stabilized by surfactants[5]. Nanosuspensions

consist of the poorly water-soluble drug without any matrix material suspended in dispersion[6]. These can be used to enhance the solubility of drugs that are poorly soluble in water as well as lipid media. As a result of increased solubility, the rate of flooding of the active compound increases and the maximum plasma level is reached faster. This approach is useful for molecules with poor solubility, poor permeability, or both, which poses a significant challenge for the formulators. The reduced particle size renders the possibility of intravenous administration of poorly soluble drugs without any blockade of the blood capillaries. The suspensions can also be lyophilized and into a solid matrix. Apart from these advantages, it also has the advantages of liquid formulations over others[3].

NANOSUSPENSION

Nanosuspensions are colloidal dispersions of nanosized drug particles stabilized by surfactants. They can also be defined as a biphasic system consisting of pure drug particles dispersed in an aqueous vehicle in which the diameter of the suspended particle is less than 1µm in size[7]. Reduction of drug particles to nanometer range leads to an enhanced dissolution rate not only because of increased surface area but also because of saturation solubility. The increase in the saturation solubility and solution velocity of nanoparticle is due to increase of vapour pressure of the particles. Nanosuspension have disclosed the problems associated with the delivery of poorly water soluble and poorly water and lipid soluble drugs and are unequalled because of their simplicity and rewards they confer over other strategies[8]. 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. An increase in the dissolution rate of micronized particles (particle size < 10 µm) is related to an increase in the surface area and consequently the dissolution velocity[9]. A Nanosuspension is a submicron colloidal dispersion of drug particles. A pharmaceutical

nanosuspension is defined as very finely colloid ,Biphasic ,dispersed, solid drug particles in an aqeous vehicle , size below 1*m ,without any matrix material , stabilized by surfactants and polymers, prepared by suitable methods for Drug Delivery applications, through various routes of administration like oral ,topical ,parenteral ,ocular9 and pulmanary routes[8].

INTERESTING SPECIAL FEATU

***Res of Nanosuspensions[10]*:**

- Increase in saturation solubility and consequently an increase in the dissolution rate of the drug.
- Increase in adhesive nature, thus resulting in enhanced bioavailability.
- Increasing the amorphous fraction in the particles, leading to a potential change in the crystalline structure
- higher solubility.
- Absence of ostwald ripening, producing physical long term stability as an aqueous suspension.
- Possibility of surface-modification of nanosuspensions for site specific delivery.

CRITERIA FOR SELECTION OF DRUG FOR NANOSUSPENSIONS[11]

Nanosuspension can be prepared for the API that is having either of the following characteristics-

- Nanosuspension can be prepared for the API that is having either of the following characteristics
- Water insoluble but which are soluble in oil (high log P) **or** API are insoluble in both water and oils
- Drugs with reduced tendency of the crystal to dissolve, regardless of the solvent
- API with very large dose

INTERNAL STRUCTURE OF NANOSUSPENSIONS :

The high-energy input during disintegration process causes structural changes inside the drug particles. When the drug particles are exposed to high-pressure homogenisation particles are transformed from crystalline state to amorphous state. The change in state depends upon the hardness of drug, number of

homogenisation cycles chemical nature of drug and power density applied by homogeniser.

ADVANTAGES OF NANOSUSPENSION[13]:

- Enhance the solubility and bioavailability of drugs
- Suitable for hydrophilic drugs
- Higher drug loading can be achieved
- Dose reduction is possible
- Enhance the physical and chemical stability of drugs
- Provides a passive drug targeting
- Provides ease of manufacture and scale-up for large scale production
- Long-term physical stability due to the presence of stabilizers
- Oral administration of nanosuspensions provide rapid onset, reduced fed/fasted ratio and improved bioavailability,
- Rapid dissolution and tissue targeting can be achieved by IV route of administration
- Reduction in tissue irritation in case of subcutaneous/intramuscular administration
- Higher bioavailability in case of ocular administration and inhalation delivery
- Drugs with high log P value can be formulated as nanosuspensions to increase the bioavailability of such drugs
- Improvement in biological performance due to high dissolution rate and saturation solubility of the drug
- Nanosuspensions can be incorporated in tablets, pellets, hydrogels and suppositories are suitable for various routes of administration
- The flexibility offered in the modification of surface properties and particle size, and ease of postproduction processing of nanosuspensions enables them to be incorporated in various dosage forms for various routes of administration, thus proving their versatility.

.

PREPRATION TECHNIQUES:

Mainly there are two methods for preparation of nanosuspensions. The conventional methods of

precipitation (Hydrosols) are called 'Bottom up

Bottom up technology

In Bottom up technology the drug is dissolved in a solvent, which is then added to non solvent that

causes precipitation of the fine drug particles. This technique is that during the precipitation procedure

the growing of the drug crystals needs to be controlled by addition of surfactant to avoid formation of microparticles[14].

Advantages

- Use of simple and low cost equipment and
- Higher saturation solubility is the advantage for precipitation technique compared to other methods of nanosuspension preparation.

Disadvantages

- Precipitation technique is not applicable to drugs which are poorly soluble in aqueous and non aqueous media.
- In this technique, the drug needs to be soluble in at least one solvent which is miscible with nonsolvent.
- Avoid crystal growth due to Ostwald ripening being caused by different saturation solubilities in the vicinity of differently sized particles.

Top down technology:

The top down technologies include

- Media milling
- High pressure homogenization
- Emulsion diffusion method
- Melt emulsification method and these are preferred over the precipitation methods.

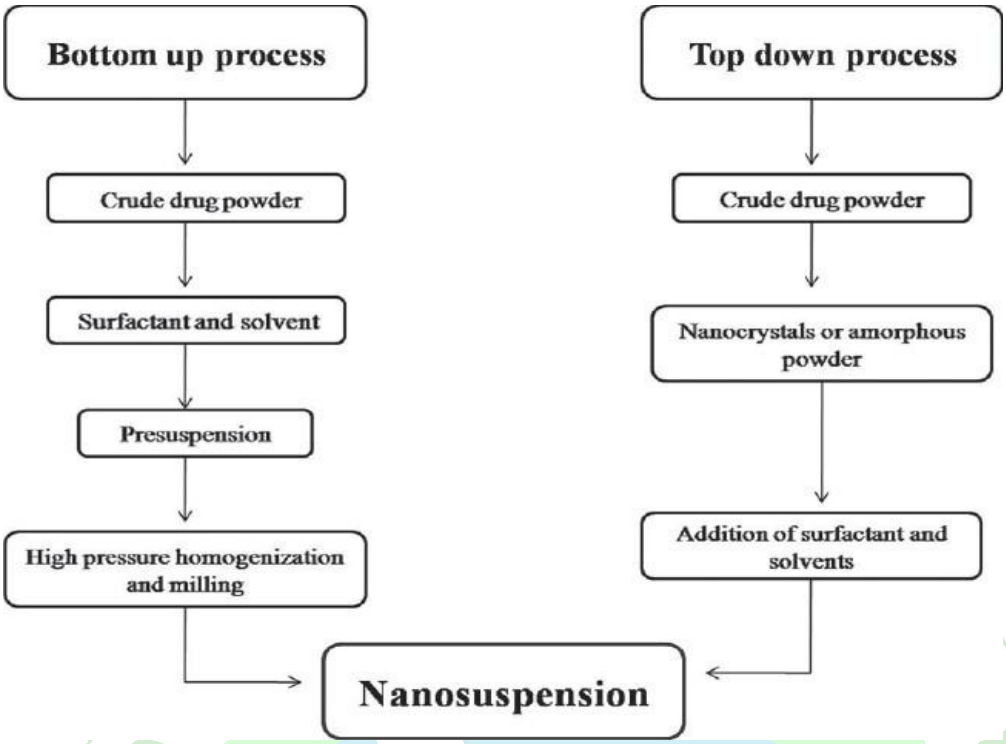

Fig.1: Two differing manufacture processes of Nanosuspensions 'bottom-up' process, 'top-down' process[15].

Media milling (nanocrystals or nanosystems)

The method is first developed and reported by Liversidge (1992). The nanosuspensions are prepared by using highshear media mills. The milling chamber charged with milling media, water, drug and stabilizer is rotated at a very high shear rate under controlled temperatures for several days (at least 2-7 days). The milling medium is composed of glass, Zirconium oxide or highly cross-linked polystyrene resin. The high energy shear forces are generated as a result of the impaction of the milling media with the drug resulting into breaking of microparticulate drug to nanosized particles[16].

Advantages

- Very dilute as well as highly concentrated nanosuspensions can be prepared by handling 1mg/ml to 400 mg/ml drug quantity.
- Nanosized distribution of final nanosized product.

Disadvantages

- The media milling technique is time consuming.
- Some fractions of particles are in the micrometer range.
- Scale up is not easy due to mill size and weight.

High pressure homogenization (Dissocubes)

It is the most widely used method for the preparation of nanosuspensions of many poorly water soluble drugs. Dissocubes are engineered using piston-gap-type highpressure homogenizers. A commonly used homogenizer is the APV Micron LAB 40. However,other piston-gap homogenizers from Avestin and Stansted can also be used Gap. A high-pressure homogenizer consists of a highpressure plunger pump with a subsequent relief valve (homogenizing valve). The task of the plunger pump is to provide the energy level required for the relief. The relief valve consists of a fixed valve seat and an adjustable valve. These parts form an adjustable radial precision gap. The gap conditions, the resistance and thus the homogenizing pressure vary as a function of the force acting on the valve[17].

Principle

In piston gap homogenizer particle size reduction is based on the cavitations principle. Particles are also reduced due to high shear forces and the collision of the particles against each other. The dispersion contained in 3 cm diameter cylinder; suddenly passes through a very narrow gap of 25 µm. According to Bernoulli's Law the flow volume of liquid in a closed system per cross section is constant. The reduction in diameter from 3 cm to 25 µm leads to increase in dynamic pressure and decrease of static pressure below the boiling point of water at room temperature. Due to this water starts boiling at room temperature and forms gas bubbles, which implode when the suspension leaves the gap (called cavitations) and normal air pressure, are reached. The size of the drug nanocrystals that can be achieved mainly depends on factors like temperature, number of homogenization cycles, and power density of homogenizer and homogenization pressure.

Advantages

- It does not cause the erosion of processed materials.
- Very dilute as well as highly concentrated nanosuspensions can be prepared by handling
- 1mg/ml to 400mg/ml drug quantity.
- It is applicable to the drugs that are poorly soluble in both aqueous and organic media.

Disadvantages

- Preprocessing like micronization of drug is required.
- High cost instruments are required that increases the cost of dosage form.

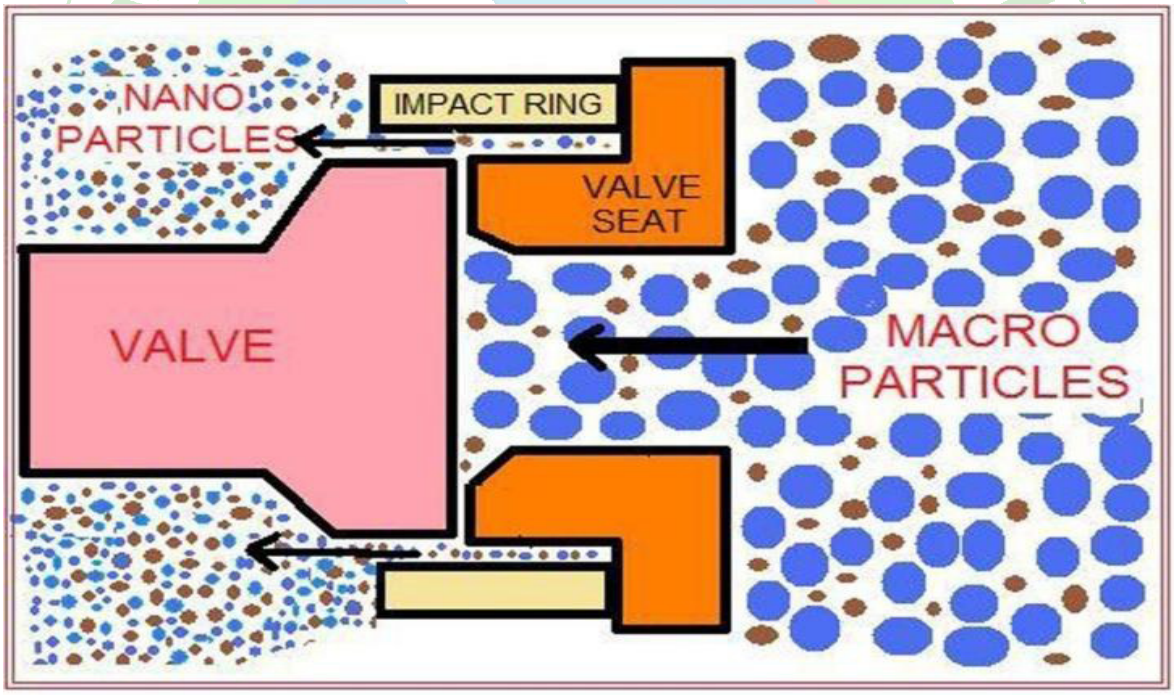

Fig:High Pressure Homoginization

Homogenisation in nonaqueous media (nanopure)

Nanopure is the water free media or water mixture. In nanopure technology the drug suspension in the non aqueous media when homonized at 0oC or even the freezing point and hence called as deep freeze homogenization[18].

- **Nanoedge**
  The precipitated drug nanoparticles have tendency to continue crystal growth to the size of microcrystal. They need to be processed with high-energy forces (Homogenisation).

The are in completely amorphous, partially amorphous or completely crystalline which create problems in long term stability as well as in bioavailability, so the precipitated particle suspension is subsequently homogenized which preserve the particle size obtained after the precipitation step[19].

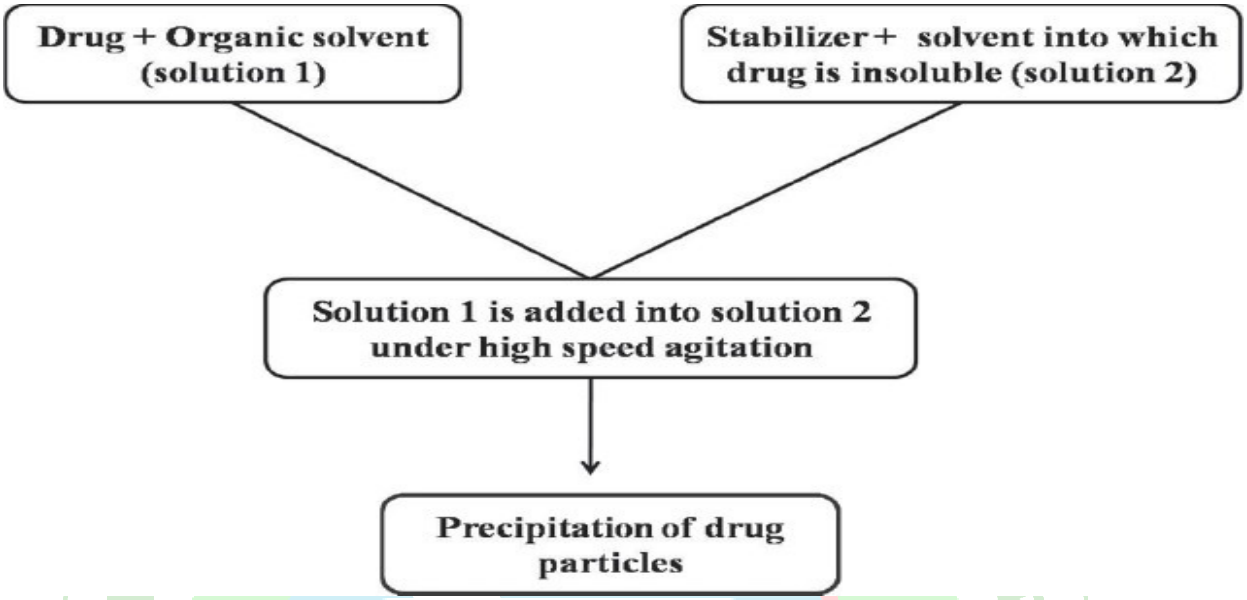

Fig : Method of prepration of nanoedge[19]

- **Co-grinding**

Recently, nanosuspensions can be obtained by dry milling techniques. Successful work in preparing stable nanosuspensions using dry-grinding of poorly soluble drugs with soluble polymers and copolymers after dispersing in a liquid media has been reported. It the colloidal particles formation of many poorly water soluble drugs; griseofulvin glibenclamide and nifedipine obtained by grinding with polyvinylpyrrolidone (PVP) and sodiumdodecylsulfate (SDS)16. Many soluble polymers and co-polymers such as PVP, polyethylene glycol (PEG), hydroxypropyl methylcellulose (HPMC) and cyclodextrin derivatives have been used. 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. Dry co grinding can be carried out easily and economically and can be conducted without organic solvents[14].

- **Precipitation**

The most common method of precipitation used is anti solvent addition method in which the drug is dissolved in an organic solvent and this solution is mixed with a miscible anti solvent. Mixing processes vary considerably. Precipitation has also been coupled with high shear precipitation of friable materials for subsequent fragmentation under conditions of high shear or thermal energy. Rapid addition of a drug solution to a solvent leads to sudden super saturation of the mixed solution, and generation of fine crystalline or amorphous solids[20].

- **Emulsification – solvent evaporation technique**

This technique involve the preparing the solution of drug by it emulsification in another liquid that is non-solvent for the drug. Evaporation of the solvent leads to precipitations of the drug. Crystal growth and particle aggregation can be controlled by creating high shear force using a high speed stirrer[19].

- **Supercritical fluid process**

Novel nanosizing and solubilization technology whose application has increased particle size reduction via supercritical fluid (SCF) processes. A supercritical fluid (SF) can be defined as a dense non condensable fluid. Supercritical fluids are fluids whose temperature and pressure are greater than its critical temperature (Tc) and critical pressure (Tp). A SCF process allows micronization of drug particles within narrow range of particle size, often to sub-micron levels. Current SCF processes have demonstrated the ability to create nanoparticulate suspensions of particles 5 to 2,000 nm in diameter. The low solubility of poorly water-soluble drugs and surfactants in supercritical CO_2 and the high pressure required for these processes restrict the utility of this technology in the pharmaceutical industry[20].

Formulation considerations

- **Stabilizer[21]**

Stabilizer plays an important role in the 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. The main functions of a stabilizer are to wet the drug particles thoroughly, and to prevent Ostwald's ripening and agglomeration of nanosuspensions in order to yield a physically stable formulation by providing steric or ionic barriers. The type and amount of stabilizer has a pronounced effect on the physical stability and in-vivo behaviour of nanosuspensions. In some cases, a mixture of stabilizers is required to obtain a stable nanosuspension. The drug-to-stabilizer ratio in the formulation may vary from 1:20 to 20:1 and should be investigated for a specific case. Stabilizers that have been explored so far include cellulosics, poloxamers, polysorbates, lecithins and povidones. Lecithin is the stabilizer of choice if one intends to develop a parenterally acceptable and autoclavable nanosuspension.

- **Organic solvents[21]**

Organic solvents may be required in the formulation of nanosuspensions if they are to be prepared using an emulsion or microemulsion as a template. As these techniques are still in their infancy, elaborate information on formulation considerations is not available. The acceptability of the organic solvents in the pharmaceutical arena, their toxicity potential and the ease of their removal from the formulation need to be considered when formulating nanosuspensions using emulsions or microemulsions as templates. The pharmaceutically acceptable and less hazardous water-miscible solvents, such as ethanol and isopropanol, and partially water-miscible solvents, such as ethyl acetate, ethyl formate, butyl lactate, triacetin, propylene carbonate and benzyl alcohol, are preferred in the formulation over the conventional hazardous solvents, such as dichloromethane. Additionally, partially watermiscible organic solvents can be used as the internal phase of the microemulsion when the nanosuspensions are to be produced using a microemulsion as a template.

- **Co-surfactants[22]**

The choice of co-surfactant is critical when using microemulsions to formulate nanosuspensions. Since co-surfactants can greatly influence phase behaviour, the effect of co-surfactant on uptake of the internal phase for selected microemulsion composition and on drug loading should be investigated. Although the literature describes the use of bile salts and dipotassium glycerrhizinate as co-surfactants, various solubilizers, such as Transcutol, glycofurol, ethanol and isopropanol, can be safely used as co-surfactants in the formulation of microemulsions.

Other additives[21]

Nanosuspensions may contain additives such as buffers, salts, polyols, osmogent and cryoprotectant, depending on either the route of administration or the properties of the drug moiety

CHARACTERIZATION OF NANOSUSPENSION

IN VITRO EVALUATION

- **Colour, odour, taste[14]**

These characteristics are especially important in orally administered formulation. Variations in taste, especially of active constituents, can offered be attributed to changes in particle size, crystal habit and subsequent particle dissolution. Changes in colour, odour and taste can also indicate chemical instability.

- **Particle size**[15]

The most important charecterization parameter for the nanosuspension are the mean particle size and width of particle size distribution (called polydispersity index) which governs the physiocochemical properties like saturation solubility, dissolution velocity, physical stability and even biological performance. It is proved that change in particle size changes saturated solubility and dissolution velocity.

Different methods for determining particle size distribution are:-

- Photon correlation spectroscopy (PCS),
- Laser diffraction (LD), and
- Coulter counter multisizer

PCS can even be used for determining the width of the particle size distribution (polydispersity index, PI). The PI is an important parameter that governs the physical stability of nanosuspensions and should be as low as possible for the long-term stability of nanosuspensions. A PI value of 0.1–0.25 indicates a fairly narrow size distribution where as a PI value greater than 0.5 indicates a very broad distribution.PCS determines the particle size in the range of (3nm to 3 µm) it becomes difficult to determine the possibility of contamination of the nanosuspension by microparticulate drugs (having particle size greater than 3µm)[15].

Laser diffractometry (LD)

Analysis of nanosuspensions should be carried out in order to detect as well as quantify the drug microparticles that might have been generated during the production process. LD determines the particle size in the range of 0.05-80µm up to 2000µm. The typical LD characterization includes determination of diameter 50% LD (50) and diameter 99% LD (99) values, which indicate that either 50 or 99% of the particles are below the indicated size. For parental use the particle size should be less than 5µm, considering that the smaller size of the capillaries is 5-6µm and hence a higher particle size can lead to capillary blockade and embolism[16].

For nanosuspensions that are intended for intravenous administration, particle size analysis by the

Coulter counter technique is essential in addition to PCS and LD analysis. Since the Coulter counter gives the absolute number of particles per volume unit for the different size classes[14].

- **Density**

Specific gravity or density of the formulation is an important parameter. A decrease in density often indicates the presence of entrapped air within the structure of the formulation. Density measurements at a given temperature should be made using well mixed, uniform formulation; precision hydrometer facilitate such measurements[7].

- **pH VALUE**

The pH value of aqueous formulation should be taken at a given temperature and only after settling equilibrium has been reached, to minimize "pH drift" and electrode surface coating with suspended particles. Electrolyte should not be added to the external phase of the formulation to stabilized the pH[23].

- **Droplet size**

The droplet size distribution of microemulsion vesicles can be determined by either light scattering technique or electron microscopy. Dynamic light scattering spectrophotometer which uses a neon laser of wavelength 632 nm[6].

- **Zeta potential**

The surface charge is determined using a zeta potential of the preparation. ZP characterizes the surface charge of particles and thus it gives information about repulsive forces between particles and droplets. To obtain stable nanoemulsion by preventing flocculation and coalescence of nano droplets. Zeta potential determines the physical stability of nanosuspenson. Zeta potential is an indirect

measurement of the thickness of the diffusion layer, i.e. can be used to predict long term stability. In order to obtain a nanosuspension exhibiting good stability, for an electrostatically stabilized nanosuspension a minimum zeta potential of ± 30mv is required whereas in the case of a combined electrostatic and steric stabilization, a minimum zeta potential of ± 20mV is desirable[14].

- **Viscosity measurement**

The viscosity of lipid based formulations of several compositions can be measured at different shear rates at different temperatures using Brookfield type rotary viscometer. The sample room of the instrument must be maintained at 37°C by a thermo bath and the samples, for the measurement are to be immersed in it[11].

- **Powder x-ray diffraction**

Powder X-ray diffraction (PXRD) diffractograms of each of the excipients, and all of the un-milled and milled atorvastatin formulations were recorded using a Siemens Cu Kα radiation. The 2θ scan range was 5-60° with a step size of 0.02° and the scan speed was 3° per min. X-ray diffraction analysis in combination with differential scanning calorimetry, scanning electron microscopy is used to determine the polymorphic changes due toimpact of high pressure homogenization in the crystalline structure of the drug. Nanosuspension can undergo a change in the crystalline structure, which may be to an amorphous form or to other polymorphic forms because of high pressure homogenization[23]

In Vivo Evaluation

Particular drug and route of administration requires the specific in vivo evaluation of the nanosuspensions. Generally the formulations are administered by required route and the plasma drug concentrations are determined by HPLC-UV visible spectrophotometry. Surface hydrophilicity/hydrophobicity (which determines interaction with cells prior to phagocytosis), adhesion properties and the interaction with body proteins are generally evaluated by in vivo parameters. The monitoring of the in-vivo performance of the Nanosuspensions and the establishment of relationship between in-vitro release and in-vivo absorption are required in order to prepare a successful preparation, irrespective of the route of the administration and the delivery systems. Rate of dissolution influences the in-vivo biological performance of oral nanosuspensions. Size of nanoparticle and surface properties of the particles determine the organ distribution for intravenously injected nanosuspensions. The in-vivo organ distribution behavior of the nanosuspension is affected by hydrophilicity/hydrophobicity and interactions of particles with plasma proteins. Surface hydrophobicity is determined by hydrophobic interaction chromatography and absorption of protein is determined by 2-D PAGE quantitatively and qualitatively after intravenous injection of nanosuspensions of drug in animals[16].

APPLICATION OF NANOSUSPENSION

- **Pulmonary drug delivery**

Nanosuspensions may be considered to be an ideal approach for delivering drugs that exhibit poor solubility in pulmonary secretions. Aqueous nanosuspensions can be nebulized using mechanical or ultrasonic nebulizers for lung delivery. The nanoparticulate nature of the drug allows the rapid diffusion and dissolution of the drug at the site of action. At the same time, the increased adhesiveness of the drug to mucosal surfaces offers a prolonged residence time for the drug at the absorption site[24].

- **Nanoparticle mucoadhesion**

Nanoparticles orally administered in the form of a suspension diffuse into the liquid media and rapidly encounter the mucosal surface. The direct contact of the particles with the intestinal cells through a bioadhesive phase is the first step before particle absorption. The adhesiveness of the nanosuspensions not only helps to improve bioavailability but also improves targeting of the parasites persisting in the gastro-intestinal tract[12].

- **Oral drug delivery**

The oral route is the preferred route for drug delivery because of its numerous well-known

advantages. .Orally administered antibiotics such as atovaquone and bupravaquone reflect this problem very well25. Nanosizing of such drugs can lead to a dramatic increase in their oral absorption and subsequently bioavailability26. Oral administration of the gonadotrophin inhibitor Tronazol as a nanosuspension leads to an absolute bioavailability of 85.4 and the conventional dispersion (Danocrine) only to 4.3%[25].

- **Parental drug delivery**

The most important applications of nanosuspension technology are the formulation of intravenously administered products. IV administration results in several advantages, such as administration of poorly soluble drugs without using a higher concentration of toxic co-solvents, improving the therapeutic effect of the drug available as conventional oral formulations and targeting the drug to macrophages and the pathogenic microorganisms residing in the macrophages[26].

- **Targeted drug delivery**

The engineering of stealth nanosuspensions (analogous to stealth liposomes) by using various surface coatings for active or passive targeting of the desired site is the future of targeted drug delivery systems. Nanosuspensions can be used for targeted delivery as their surface properties and in-vivo behavior can easily be altered by changing either the stabilizer or the milieu[16].

- **Ocular drug delivery**

Nanosuspensions, by their inherent ability to improve the saturation solubility of the drug, represent an ideal approach for ocular delivery of hydrophobic drugs and Nanoparticulate nature of the drug allows its prolonged residence in the cul-desac, giving sustained release of the drug. The nanosized drug particles had shown a prolonged residual time giving sustained release of drug[27].

- **Bioavailability enhancement.**

The poor oral bioavailability of the drug may be due to poor solubility, poor permeability or poor stability in the gastrointestinal tract (GIT). Nanosuspensions resolve the problem of poor bioavailability by solving the twin problems of poor solubility and poor permeability across the membrane[17].

- **Topical formulations**

Drug nanoparticles can be incorporated into creams and water-free ointments.The nanocrystalline form leads to an increased saturation solubility of the drug in the topical dosage form, thus enhancing the diffusion of the drug into the skin[28].

REFERENCES:

1. *Sharma P,Danny WA,Garg S. "Effect of wet milling process on the solid state of indomethacin and simvastatin" , International journal pharm 2009,380*
2. *Kakrana M, Sahooa NC,Judeh LZ, Wang Y, Chong K,Loh L "FABRICATION OF DRUG NANOPARTICLES BY EVAPORATIVE precipitation of nanosuspension" international journal pharm 2010,383*
3. *Vishal R.Patel, Y.K.Agarwal "Nanosuspension: An approach to enhance solubility of drugs", journal of advanced pharmaceutical technology and research, apr-jun 2011, vol-2, issue-2.*
4. *Nagarjuna P,Krishnachaithanya K, Srinivas VD, Padma SV "Nanosuspension:A promising drug delivery systems" Int J Pharm Sci Nano 2010,vol 2, 679-84*
5. *Barret ER, "Nanosuspension in drug delivery",nat rev 2004,vol 3,785-96*
6. *.Muller RH, Ghosla S, Dingler A,Schneppe T, "large scale production of solid lipid nanoparticles and nanosuspension", handbook of pharmaceutical controlled release technology,2000,pg 359-375*
7. *Dubey R. Pure drug nanosuspensions-Impact of nanosuspension technology on drug discovery and development. Drug Del Tech 2006; 6:65-71.*
8. *Vishvajit A. Kamble, Deepali M. Jagdale and Vilasrao J.Kadam "Nanosuspension A Novel Drug Delivery System" , International Journal of Pharma and Bio Sciences , Vol.1/Issue-4/Oct-Dec.2010.*
9. *Chingunpituk, J (2007), "Nanosuspension technology for drug delivery", Walailak J Sci & Tech,, 4(2), 139-153.*
10. *Dhiman S., Thakur GS, Dharmila. Nanosuspension: A recent approach for nano drug delivery system. International Journal of Current Pharmaceutical Research. 2011;3(4):96-101.*
11. *Patil SA, Rane BR, Bakliwal SR, Pawar SP. Nano Suspension: At a glance. Int J Ph Sci. 2011; 3(1): 947-960.*
12. *Prabhakar . Ch "A Review on nanosuspension in drug delivery" , International Journal of Pharma and Bio Sciences,jan – mar 2011,vol-2,issue-1, pg 1-10*
13. *Paun J.S. and Tank H.M. "Nanosuspension: An Emerging Trend for Bioavailability Enhancement of Poorly Soluble Drugs", Asian J. Pharm. Tech. 2012; Vol. 2: Issue 4, Pg 157-168*
14. *Kalpesh S. Wagh*, Satish K. Patil, , Anup K. Akarte, Dheeraj T. Baviskar "Nanosuspension- A new approach of bioavailability enhancement" , International Journal of Pharmaceutical Sciences Review and Research, Volume 8, Issue 2, May – June 2011.*
15. *Toshi Chaurasia, Divya Singh, Nimisha, Dipti Srivastava " A Review on Nanosuspensions: promising Drug Delivery Strategy" , Current Pharma Research., Vol. 3(1), 2012, 764-776.*

16. H Banavath, Sivarama Raju K, Md. Tahir Ansari, Md. Sajid Ali and Gurudutta Pattnaik " Nanosuspension an attempt to enhance bioavailability of poorly soluble drugs", International journal of pharmaceutical sciences and research,2010 ,vol-1, issue-9,pg 35-40.
17. Prasanna Lakshmi, Giddam Ashwini Kumar "Nanosuspension Technology :A Review" , International Journal of Pharmacy and Pharmaceutical Sciences , Vol 2, Suppl 4, 2010.
18. Sourav Das "Nanosuspension: An Assuring Novel Drug Delivery System" , International Journal of Pharmaceutical Sciences Review and Research , May – Jun 2013; no 38, 228-231.
19. Hintz RJ, Johnson KC, "The effect of particle size distribution on dissolution rate and oral absorption", Int J Pharm 1989,51,pg 9-17
20. Kipp JE et al. Microprecipitation method for preparing submicron suspensions. US Patent 6,607,784 2003.
21. Date, AA; Kulkarni, RM and Patravale, VB (2004),"Nanosuspensions: A promising drug delivery", Journal of Pharmacy & Pharmacology, 56: 827–840
22. Bhargavi, R (2001), "A technical review of nanosuspensions", International Journal of Pharmacy &Technology, Vol. 3, Issue No.3, 1503-1511.
23. Mitesh Patel*, Arpit Shah, Dr. N.M. Patel, Dr. M.R. Patel, Dr. K.R. Patel " NANO Suspension: A Novel Approch For Drug Delivery System", journal of pharmaceutical science and bioscientific research, Volume 1, Issue 1: July-August 2011 (1-10)