NANOSUSPENSION TECHNOLOGY IN PHARMACEUTICALS

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ABSTRACT:

Nanotechnology deals with the process that occurs at molecular level and of nanolength scale size. Nanosuspension is a part of nanotechnology. Nanosuspensionis colloidal dispersions of nanosized drug particles stabilized by surfactants.Nanosuspensions can be used to enhance the solubility of drugs that are poorly soluble in aqueous as well as lipid media thus increasing the rate of flooding of the active compound and the maximum plasma level is reached faster. This review article includes preparation of nanosuspensions by various techniques with their advantages and disadvantages, formulation considerations, Characterization and their applications in drug delivery. Nanosuspensions solves the problem of poor solubility, bioavailability and alter the pharmacokinetics of the drug there by improving its safety and efficacy.

Keywords: Nanotechnology, Nanosuspensions, Bioavailability, BCS Class II, solubility, polymers, drugs

INTRODUCTION:

Nanosuspension technology has been used for drugs which are insoluble in both water and organic solvents. Thistechnique solve the problems related with conventional approaches for improving solubility and bioavailability. A pharmaceutical nanosuspensions is defined as very finely colloid,biphasic,dispersed,solid drug particles in an aqueous vehicle, size below 1um, 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,ocular and pulmonary routes.

Average particle size of nanosuspension ranges from 200-600nm. Nanosized particles, increases solution velocity,saturation solubility because of the vapor pressure effect and also decreases the diffusional distance on the surface of drug nanoparticles thus leading to an increased concentration gradient result to a much more pronounced increase in the dissolution velocity as compared to a micronized product. In nanosuspension technology, the drug is maintained in the required crystalline statewith reduced particle size, leading to an increased dissolution rate and therefore improvedbioavailability [1].

NEED OF NANOSUSPENSION:

BCSclass-II drugs are poorly water soluble andtheir pharmacokinetic studies shows low oral bioavailability. To solve this problems, techniques like dissolution in aqueous mixtures with an organic solvent, formation of ß-cyclodextrin complexes, soliddispersions, drug in salt formand micronization, has been developed to increase drug dissolution rate. As per Noyes–Whitney equation, drugs with smaller particle size have enlarged surface areas which lead to increase dissolution velocity and faster dissolution rate together with the resulting higher concentration gradient between gastrointestinal lumen and systemic circulation thus increasing the oral bioavailability of drugs. A pharmaceutical nanosuspension is an as very fine dispersion of solid drug particles in an aqueous vehicle stabilized by surfactant. 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. In nanosuspension technology, the drug is maintained in the required crystalline state with reduced particle size, leading to an increased dissolution rate and therefore improved bioavailability [1].

Fig.1- Various Nanosuspensions

ADVANTAGES OF NANOSUSPENSION DRUG DELIVERY SYSTEM:-

- Generally applicable to most drugs & simplicity
- Can be applied for poorly water-soluble drugs.
- Can be given by any route
- Reduced tissue irritation in case of subcutaneous/intramuscular administration.
- Rapid dissolution & tissue targeting by IV route of administration.
- Oral administration provides rapid onset, reduced fed/fasted ratio & improved bioavailability.
- Occular administration & inhalation delivery provides higher bioavailability & more consistent dosing.
- Due toreduced particle size of nanosuspension,the absorption form absorption window can be enhanced.
- Improvement in biological performance due to high dissolution rate &saturation solubility of the drugs.
- Long-term physical stability (due to absence ofOstwald ripening).
- Nanosuspensions can be incorporated in tablets, pellets, hydrogel &suppositories are suitable for various routes of administration.
- Increasing the amorphous fraction in the particlesleading to a potential change in the crystalline structure & higher solubility.
- Surface-modification of nanosuspension possible, for site specific delivery [2].

DISADVANTAGES FOR NANOSUSPENSION DRUG DELIVERY SYSTEM

- Physical stability, sedimentation & compaction can cause problems.
- It is bulky sufficient care must be taken during handling & transport.
- Improper dose [2].

CRITERIA FOR SELECTION OF DRUG FOR NANOSUSPENSIONS:

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

- Water insoluble but which are soluble in oil (high logP) 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 [2].

FORMULATION CONSIDERATIONS:

- ***Stabilizers:*** The main function of stabilizer is to wet the drug particles thoroughly and to prevent Ostwald's ripening and agglomeration of nanosuspension in order to yield a physically stable formulation by providing steric or ionic barriers.The drug-to-stabilizer ratio in the formulation may vary from 1:20 to 20.1Stabilizers that have been used so far are poloxomers, polysorbate, cellulosic, povidones, and lecithins. Lecithin is the stabilizer of choice to develop a parentally acceptable and autoclavable Nanosuspensions.
- ***Surfactants:*** Surfactants are incorporated to improve the dispersion by reducing the interfacial tension. They also act as wetting or deflocculating agents.
  Eg: Tweens and Spans - widely used surfactants.
- ***Co-Surfactants:***The selection of co-surfactant is important when using microemulsion to formulate. Since co-surfactants can greatly influence phase behavior, the effect of co-surfactant on uptake of the internal phase for selected microemulsion composition and on drug loading should be investigated. Eg: Bile salts, DipotassiumGlycerrhizinate, Transcutol, Glycofurol, Ethanol, and Isopropanol.
- ***Organicsolvent:*** Nanosuspensions, when prepared by using emulsion or microemulsion template, then organic solvents are used in formulation pharmaceutically acceptable lesshazardous solvents are used for the preparation offormulation.eg: Methanol, Ethanol, Chloroform, Isopropanol, Ethyl acetate, Ethyl formate, Butyl lactate, Triacetin, Propylene carbonate, Benzyl alcohol.
- ***Other additives:*** Selected according to the requirement ofthe route of administration or the properties of thedrug moiety. Eg: Buffers, Salts, Polyols, Osmogens, and Cryoprotectant [3].

METHOD OF PREPRATION

Method of preparation of nanosuspensions

- Bottom Up process-form nanoparticles from precipitation, microemulsion, melt emulsification method
- Top down process-nanoparticles obtained by high-pressure homogenization and milling methods [3].

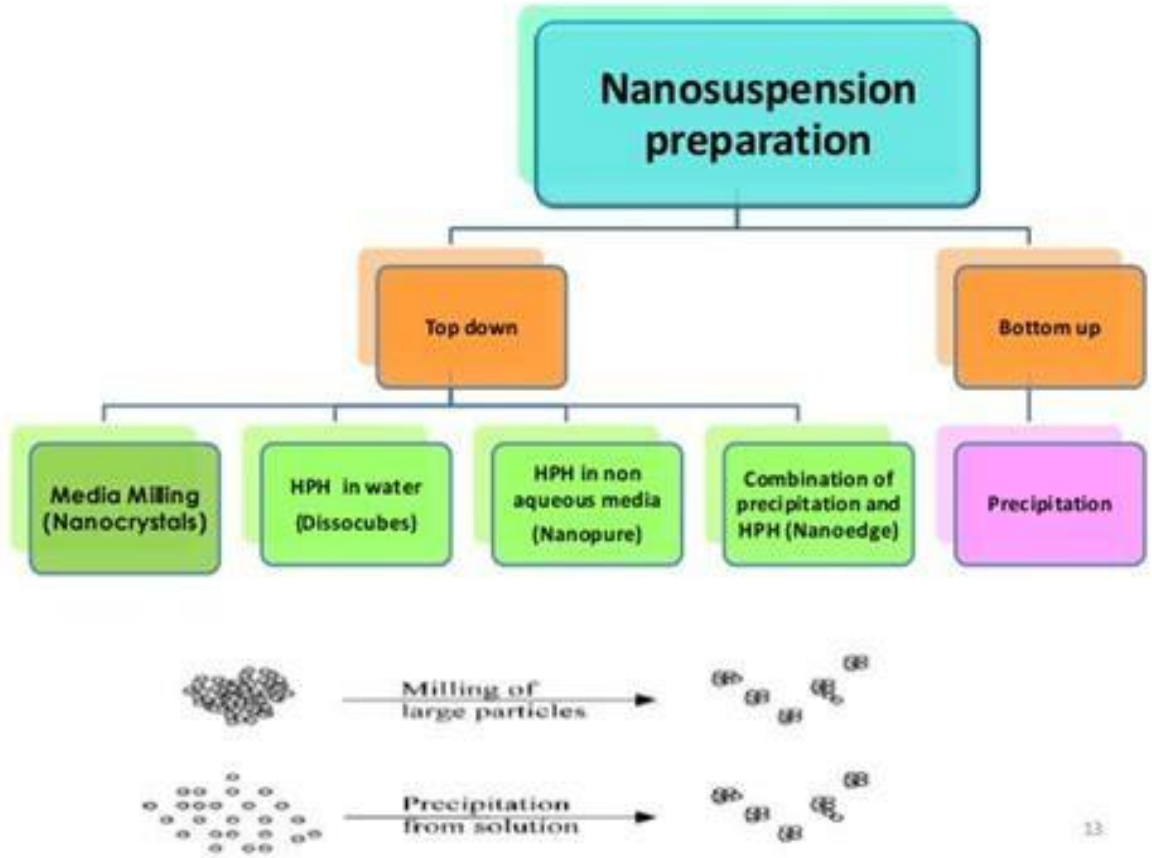


Fig .2- Method of Preparation of Nanosuspension

A) Bottom up Technology:

The conventional methods of precipitation (Hydrosols) are called Bottom Up technology. Precipitation method is a general method used to prepare submicron particles of poorly soluble drugs. In this method, drug is dissolved in solvent and then solution is mixed with solvent to which drug is insoluble in the presence of surfactant. Rapid addition of solution to such solvent (generally water) leads to rapid super saturation of drug in the solution, and formation of ultrafine amorphous or crystalline drug. This method involves nuclei formation 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. The limitation of this precipitation technique is that the drug needs to be soluble in at least one solvent and this solvent needs to be miscible with nonsolvent.

Bottom-up process is an assembly method forms nanoparticles from molecules.

Examples includes

- Solvent-Antisolvent method
- Super critical fluid process
- Emulsification- Solvent evaporation technique
- Lipid emulsion/Micro-emulsion template [4].

Precipitation (solvent-antisolvent method) method:

Precipitation has been applied to prepare submicron particles, especially for the poorly soluble drugs. The drug is first dissolved in a solvent, then this solution is mixed with a miscible antisolvent in the

presence of surfactants. Rapid addition of a drug solution to the antisolvent leads to sudden super saturation of drug and formation of ultrafine crystalline or amorphous drug solids. Precipitation method involves two phases - nuclei formation & crystal growth. When preparing a stable suspension with the minimum particle size, a high nucleation rate and but low growth rate is necessary. Both rates are depending on temperature. In this technique the drug needs to be soluble in at least one solvent which is miscible with non-solvent.

Advantages: Simple process, Ease of scale up and Economical production.

Disadvantages: Growing of crystals needs to be limit by surfactant addition. Drug must be soluble at least in one solvent [4].

Supercritical fluid process:

This method utilizes solubilization and nanosizing technologies through the super critical fluid process for particle size reduction. Super critical fluids (SCF) are noncondensable dense fluids whose temperature and pressure are greater than its critical temperature (Tc) and critical pressure (Tp).This process allows the micronization of drug particles to submicron level. Recent advances in SCF process are to create nanoparticulate suspension of particle size of 5 to 2000nm indiameter. The low solubility of poorly water-soluble drugs and surfactants in supercritical CO2 and the high pressure required for these processes restrict the utility of this technology in the pharmaceutical industry [4].

Solvent evaporation:

Here the solutions of polymer are prepared in volatile solvents and emulsions. The emulsion is converted into a nanoparticle suspension on evaporation of the solvent for the polymer, which is allowed to diffuse through the continuous phase of the emulsion. Conventionally, two main strategies are being used for the formation of emulsions, the preparation of single-emulsions, e.g., oil-in-water (o/w) or double-emulsions, e.g., (water-in-oil)-in-water, (w/o)/w. These methods require high-speed homogenization or ultrasonication, followed by evaporation of the solvent, by continuous magnetic stirring at room temperature or under reduced pressure. The solidified nanoparticles are collected which was washed with distilled water to remove the additives like surfactants, and then it was lyophilized [4].

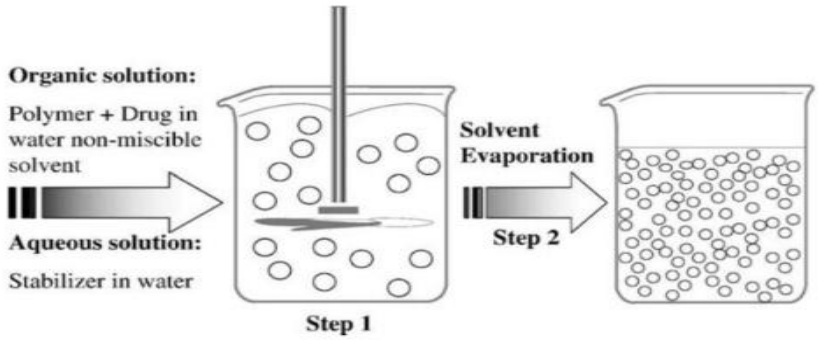


Fig.2- Schematic representation of Solvent evaporation process

Lipid emulsion/microemulsion template:

This method applicable for drugs that are soluble in either volatile organic solvents or partially water miscible solvents. Here the drug was dissolved in suitable organic solvent and it is emulsified in aqueous phase using suitable surfactants. Then the organic solvent was slowly evaporated under reduced pressure to form drug particles precipitating in the aqueous phase forming the aqueous suspension of the drug in the required particle size. The suspension formed can be suitably diluted to get nanosuspensions. Moreover, microemulsions as templates can produce nanosuspensions.Microemulsions are thermodynamically stable and isotropically clear dispersions of two immiscible liquids such as oil and water stabilized by an interfacial film of surfactant and co-surfactant. The drug can be either loaded into the internal phase or the pre-formed microemulsion can be saturated with the drug by intimate mixing. Suitable dilution of the microemulsion yields the drug nanosuspension.

Advantages:-High drug solubilization, long shelf life and easy to manufacture

Disadvantages:

-Use of hazardous solvent

-Use of high amount of surfactant and stabilizers [5].

1. **Melt emulsification method:**

In this method drug is dispersed in the aqueous solution of stabilizer and heated above the melting point of the drug and homogenized to give an emulsion. During this process, the sample holder was enwrapped with a heating tape fitted with temperature controller and the temperature of emulsion was maintained above the melting point of the drug emulsion was then cooled down either slowly to room temperature or on an ice- bath.

Advantages: Melt emulsification technique relative to the solvent evaporation method is total avoidance of organic solvents during the production process.

Disadvantages: Formation of larger particles and few compliant objects than solvent evaporation [5].

2. **Emulsification-solvent evaporation technique:**

This technique involves preparing a solution of drug followed by itsemulsification in another liquid that is a nonsolvent for the drug. Evaporation of the solvent leads to precipitation of the drug. Crystal growth and particle aggregation can be controlled by creating high shear forces using a high-speed stirrer [5].

B) Top down process:

The top down process involves the disintegration from large particles, microparticles to nanosized particles. The techniques used area's follows:

- High pressure homogenization
- Nanoedge
- Nanopure
- Media milling
- Dry-co-grinding

1. **High pressure homogenization:**

This method is most widely used for preparing nanosuspensions of many poorly aqueous soluble drugs. The process involves three steps.

- Drug powders are dispersed in stabilizer solution to form presuspension,
- The presuspension is homogenized in high pressure homogenizer at a low pressure for premilling
- Finally homogenized at high pressure for 10 to 25 cycles until the nanosuspensions of desired size are formed [6].

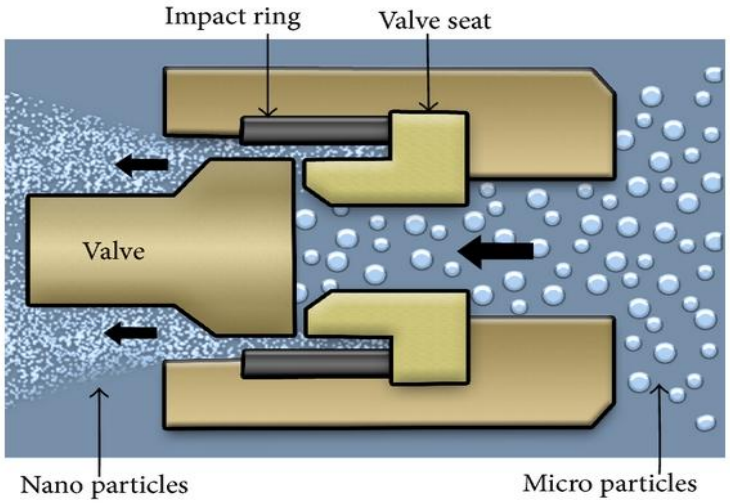


Fig.3-High-pressure homogenizer process

Different methods are developed based on this principle for preparations of nanosuspensions
are Disso cubes, Nanopure, Nanoedge and Nanojet

a) Homogenization in aqueous media (Disso cubes):

This technology was developed by R.H.Muller using a piston-gap type high pressure homogenizer in 1999. In this method, the suspension containing a drug and surfactant is forced under pressure through a nanosized aperture valve of a high pressure homogenizer.

Principle:

This method is based on cavitation principle. The dispersion 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. It leads to 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 and forms 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.

Advantages:

1) It does not cause the erosion of processed materials.

2) It is applicable 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 increases the cost of dosage form [6].

b) Homogenization in nonaqueous media (Nanopure):

Nanopure is suspensions homogenized in water-free media or water mixtures like PEG 400, PEG 1000.Temperature will be room temperature, 0 degree or even atfreezing point. So it is known as deep freezehomoginisation. It is the best method for thethermolabile substances at milder conditions.In this technologythe nanocrystals of the drug dispersed in liquid polyethylene glycol (PEG) or various oils can be directly filled as drug suspensions into HPMC capsules or gelatin [6].

c) Nanoedge:-

The principle involved in Nanoedge technology is the combination of both precipitation and homogenization.

***Principle*:**

In this technique drug is dissolved in an organic solvent and this solution is mixed with the miscible anti-solvent for precipitation .Drug precipitates due to low solubility in the water solvent mixture. Precipitation is coupled with high shear processing, which is accomplished by combination of rapid precipitation and high pressure homogenization.

Advantage:

1) The disadvantage of precipitation technique such as crystal growth and long term stability can be overcome by using the Nanoedge technology

2) Particles of smaller size and better stability in short time can be achieved [7].

d) Nanojet:

It is also called 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, up to 4000 bar at high velocity of 1000m/s.The high shear forces produced in this process leads to reduction in particle size.

Limitation:

1) High numbers of passes (nearly about 75) are required through the microfluidizer, and the product obtained contains a relatively large fraction of micro particles.

2) This process requires large production time [7].

2. Milling techniques

a) Media Milling:

This method was first developed and reported by Liversidge (1992). The nanosuspensions by this method are prepared by high shear media mill. The milling chamber was charged with the milling media, water, drug and stabilizer and rotated at a very high shear rate under controlled temperature at least 2-7 days. The high energy shear forces are formed as a result of impaction of milling media with the drug which results in breaking of drug micro particles to nanosized particles.

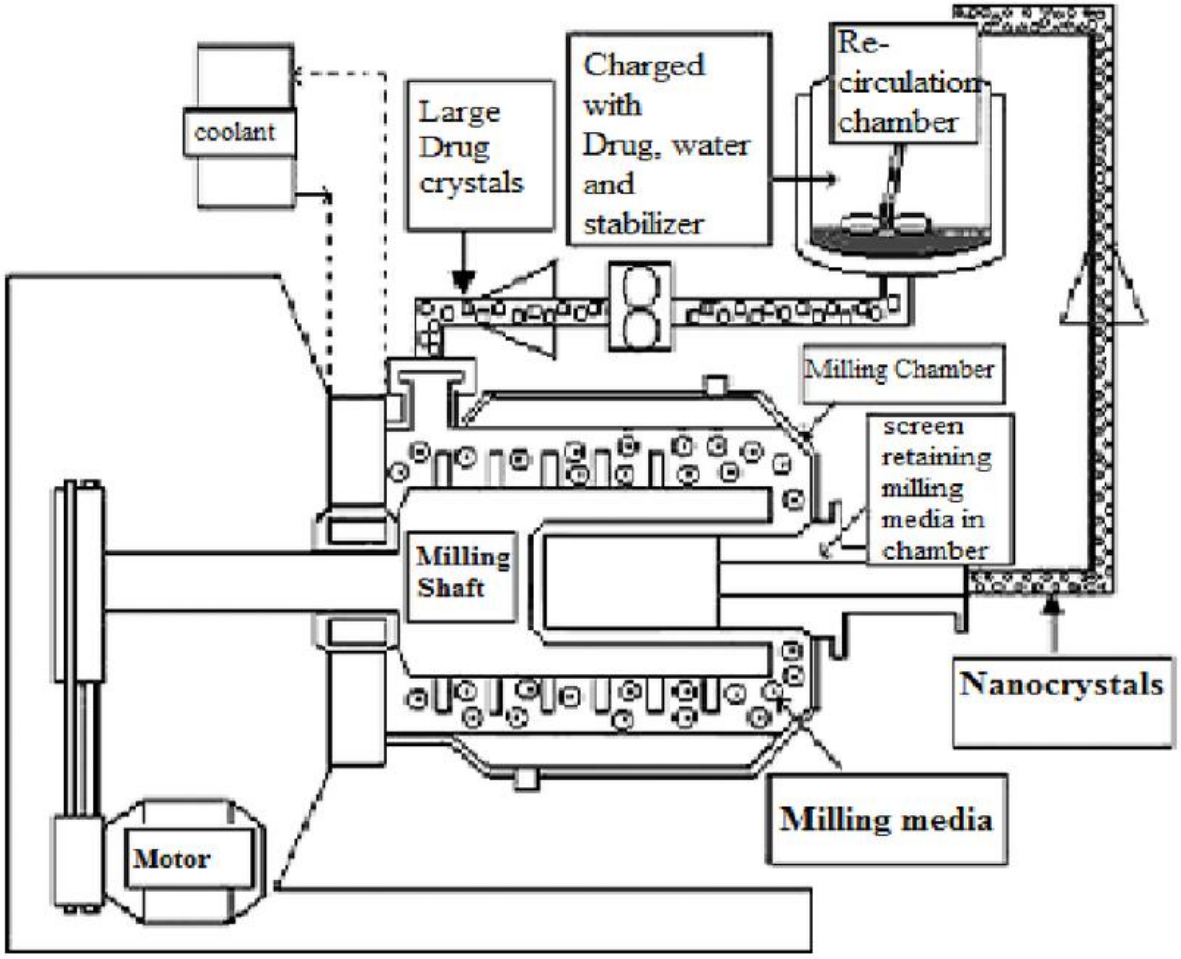


Fig.4- Schematic representation of media milling process

Principle:

The high energy and shear forces generated as a result of the impaction of the milling mediawith the drug provide the energy input to break the microparticulate drug into nano-sizedparticles. The milling medium is composed of glass, zirconium oxide or highly cross-linkedpolystyrene resin. The process can be performed in either batch or recirculation mode. Inbatch mode, the time required to obtain dispersions with unimodal distribution profiles andmean diameter <200nm is 30–60 min.

Advantages:

1) Very dilute as well as highly concentrated nanosuspensions can be prepared by handling 1 mg/ml to 400 mg/ml drug quantity.
2) Nanosized distribution of final nanosized product.
3) Drugs that are poorly soluble in both aqueous and organic media can be easilyformulated into nanosuspensions.
4) Ease of scale-up and little batch-to-batch variation.

Disadvantages:

1) Generation of residues of milling media, which may be introduced in the final product as a result of erosion
2) The media milling technique is time consuming.
3) Some fractions of particles are in the micrometer range.
4) Scale up is not easy due to mill size and weight [8].

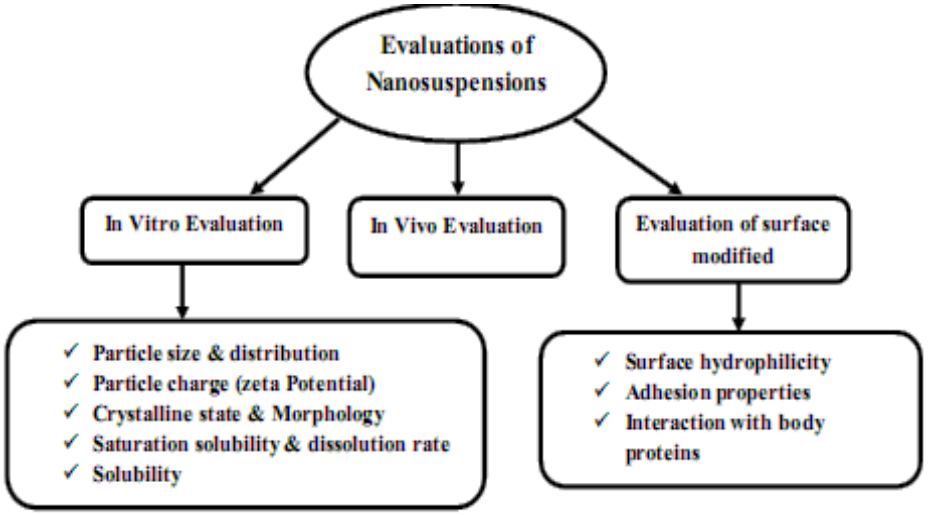
ii) Dry-Co-grinding:

Recent technique, dry- co-grinding can be carried out easily and economically and can be conducted without organic solvents. Physicochemical properties and dissolution of poorly water soluble drugs are improved by Co-grinding because of an improvement in the surface polarity and transformation from a crystalline to an amorphous drug.

Advantages

1. Easy process and no organic solvent required.
2. Require short grinding time [8].

EVALUATION PARAMETERS



A) In vitro Evaluations:

1. **Mean particle size and size distribution:**

The mean particle size and the width of particle size distribution called Polydispersity Index. Particle size and polydispersity index (PI) governs the saturation solubility, dissolution velocity and biological performance. PolydispersityIndex and the particle size distribution can be determined by photon correlation spectroscopy (PCS). A PI value of 0.1-0.25 indicates a fairly narrow size distribution, if PI value greater than 0.5 indicates a very broad distribution. The particle size distribution can also be determined by laser diffraction (LD) and Coulter counter multisizer. The coulter-counter gives the absolute no. of particles per volume unit for the different size classes and it is more efficient and appropriate technique than LD for quantifying the contamination of nanosuspensions by micro particulate drugs.LaserDiffractometry (LD) measures volume size distribution and measures particles ranging from 0.05- 80µm upto 2000µm. Atomic Force microscope is used for visualization of particle shape [9].

2. **Particle charge (Surface Charge or Zeta Potential):**

Particle charge determines the stability of nanosuspension. The zeta potential of ananosuspension is governed by both the stabilizer & the drug itself. For electrostaticallystabilized nanosuspension a minimum zeta potential of ±30mV and for combined stericand electrostatic stabilization it should be a minimum of ± 20Mv [9].

3. **Crystalline state and particle morphology:**

High pressure homogenization nanosuspensions can undergo a change in the crystalline structure, which may be to an amorphous form or to other polymorphic forms. The evaluation of the crystalline state and particle morphology

helps in understanding the polymorphic or morphological changes that a drug may undergo when subjects to nanosizing. The changes in the solid state of the drug particles and extent of the amorphous fraction can be determined by X-ray diffraction analysis and supplemented by DSC. To get an actual idea of particle morphology, scanning electron microscopy (SCM) ispreferred [10].

4. **Saturation solubility and dissolution velocity:-**

The assessment of saturation solubility and dissolution velocity helps in determining the in vitro behavior of the formulation. Nanosuspensions have an important advantage that it can increase the dissolution velocity as well as the saturation solubility. The saturation solubility of the drug in different physiological buffer as well as at different temperature should be assessed using methods described in theliterature. The investigation of the dissolution velocity of nanosuspensions reflects the advantages that can beachieved over convectional formulations, especially when designing the sustained-release dosage formsbased on nanoparticulate drugs [10].

5. **Stability:**

Stability of nanosuspensions depends on the particle size of the suspended particles.Decrease in the particle size to the nanorange increases the surface energy of theparticles, and the tendency of the particles to agglomerate increases. Therefore thestabilizers are used to decrease thechances of Ostwald ripening and to improve thestability of the suspension by providing a steric or ionic barrier. Stabilizers like cellulosic, Poloxamers, Polysorbates, lecithin, polyoleate andPovidones are generally used in thenanosuspensions. Nanosuspensions can be stored at different stress conditions like different temperature (15, 25, 35, 45°C), thermal cycling, and mechanical shaking and change in their meanparticle size can be followed for three months. Differentconcentrations of small moleculesurfactants (likesodium lauryl sulfate (SLS) and dowfax 2A1 (DF)) and polymeric stabilizer likeHydroxypropyl methylcellulose (HPMC)) can be evaluated to determine theeffect of stabilizer type and micellar solubilized drug on Ostwald ripening [11].

6. **pH:**

Prepared nanosuspension was taken in 10ml beaker and pH was measured using pHmeter.

7. **Osmolarity:**

Osmolarity of nanosuspension can be measured by using Osmometer [11].

8. **Drug content:**

Drug content of nanosuspension formulation was carried out by taking lyophilizedpowder (weigh equivalent to 5mg of drug) appropriate solvent mixture like Methanol: THF (1:1) mixture, shake well centrifuge. The supernatants are separated and diluted with same solvent mixture and absorbance is measured at suitable λmax. The drug content is calculated using the calibration curve.

Total volume of nanosuspention = total volume of nanosuspention x amount of drug in aliquot/volum of aliquot [11].

B) In-Vivo Pharmacokinetic correlation:

Establishing the relationship between in-vitrorelease and in-vivoabsorption and the monitoring of the in-vivoperformance of the Nanosuspensions are essential to a successful preparation. For oral Nanosuspensions, the drug dissolution rate can influence in-vivobiological performance of formulations. For intravenously injected Nanosuspensions, the organ distribution in part depends on the nanoparticle size and surface property.

Surface hydrophilicity/ hydrophobicity and interactions with plasma proteins are considered as important factors affecting the in-vivoorgan distribution behavior after i.v injection of Nanosuspensions. There are many techniques to evaluate the surface properties and protein interactions like 2-D PAGE, employed for the quantitative measurement of protein adsorption to nanoparticle surface after i.v. injection of drug Nanosuspensions to animals.

1. **Surface hydrophilicy:**

Surfacehydrophilicy is considered as one of the importantparameters affecting the in vivo organ distribution after i.v. injection. Adsorption of plasma proteins which is akey factor for organ distribution and the interaction with cells before phagocytosis can be determined by surface hydrophobicity. Surface hydrophobicity must be determined in the aqueous dispersion medium. The best technique used earlier was hydrophobic interaction chromatography (HIC), to determine the hydrophobicity of bacteria, & then shifted to the characterization of nanoparticulate drug carrier [12].

2. **Adhesion properties:**

Bioadhesive studies are conducted in Male Wistar rats. Generally each rat receives single dose of 10 mg of nanoparticles which are combined with drug (approx.45 mg particles/kg body weight).Abdominal cavity of the animal cut opened, the stomach, small intestine and cecum is removed and rinsed with phosphate saline buffer. The stomach, small intestine and cecum is cut into 2cm length and digested in alkali for 24hr .Then added 2ml of methanol and centrifuged. 1 ml sample of supernatant is assayed by spectroflurimetry to estimate the number of nanoparticles of drug adhered to mucosa. If necessary standard curves can be prepared for calculation [12].

3. **Interaction with body proteins:**

In-vitro interaction between body protein - mucin and the nanoparticles can be studied by incubating nanoparticles and mucin (4:1 weight ratio) either in neutral or acidic medium. The incubation is processed at 370C temperature with stirring. The dispersion is then centrifuged, in test plate 150µl of each supernatant taken and added with 150µl BCA Protein Assay Reagent Kit. The plate is then incubated for 2 h at 37° C. By following this procedure absorbance of mucin is measured at λmax of the drug. Total amount of mucin absorbed to nanoparticles is determined by taking the difference between its initial concentration and the concentration in dispersion after incubation and centrifugation [12].

APPLICATIONS OF NANOSUSPENSION:

1. **Oral Drug Delivery:**

Oral route is the most preferable route for many of the drugsespecially in the case of orally administering antibiotics such as atovaquone and bupravaquone. Nanosizing of drugs can lead to a dramatic increase in their oral absorption and subsequent bioavailability. Improved bioavailability can be explained by the adhesiveness of drug nanoparticles to the mucosa, the increased saturation solubility leading to an increased concentration gradient between gastrointestinal tract lumen and blood and the increased dissolution velocity of the drug. The oral administration of naproxen nanoparticles leads to an area under the curve (AUC) (0-24 h) of 97.5 mgh/ l compared with naproxen nanosuspensions and naproxen tablets. In the case of danazole (gonadotrophin inhibitor) nanosuspensions has absolute bioavailability of 82.3 and the conventional dispersion only 5.2 %.Amphotherin B is an anti-parasitic drug with poor solubility whose intravenous injection and infusion can be related with

considerable fluctuation of drug concentrations in the blood. Oral administrationof Amphotherin B nanosuspension, produced by high pressure homogenization potentially reduced parasite numbers by maintaining constant blood levels in plasma. In addition, AmB nanosuspension showed good stability and good shelf life characteristics. Milk thistle plant (Silybum marianum) isolate-Silybin, used as a therapeutic agent for human colon cancer and prostate cancer. The effectiveness of silybin as antitumor drug was limited due to its poor water solubility and low bioavailability after oral administration. Nanonozing the drug particle to a size ranging from 100 to 1000 nm could improve the solubility and bioavailability. The study of Silybin nanosuspensionfor its antitumor activity against human prostatic carcinoma PC-3 cell line (in vitro model) indicated that silybin nanosuspension could be a potential source of medicine for the treatment of human prostate cancer [13].

2. Parentral Drug Delivery:

Nimodipine is used in patients with subarachnoid hemorrhage related vasospasm. Oral administration of nimodipine showed low bioavailability due to the high first-pass metabolism in the liver. Intravenous administration is an alternative to oral administration which could give better bioavailability. Nimodipine nanosuspension prepared by high-pressure homogenization, showed less local irritation and phlebitis risks which indicated that nimodipine nanosuspension is a promising new drug formulation for intravenous therapy of subarachnoid hemorrhage related vasospasm.The drug clofazimine is given as iv, the concentration in the liver, spleen and lungs reached ahigh level i.e.; greater than minimum inhibitory concentration, for most of the mycobacterium avium strains. Tarazepide is formulated as nanosuspension in order to overcome the use of surfactants and cyclodextrins to improve the bioavailability [14].

3. Pulmonary Drug Delivery:

Drugs that are inadequately dissolvable in pulmonary secretions may be formulated with the help of the nanosuspensions. These medications are conveyed as suspension aerosols or as dry powders by method for dry powder inhalers. Nebulization is generally achieved with the use of ultrasonic s or mechanical nebulizer.

Advantages of nanosuspension over conventional pulmonary formulations:-

1) Increase in diffusion and dissolution rate at the site of action leading to increase in bioavailability of the drug.
2) Drug has affinity to mucosal surfaces.
3) Drug gets evenly distributed in the lungs as all the droplets of aerosols contains nanoparticles as compared to the macro particulate form of the drug.

Here we are using nano-preperations for the drugs which have poor solubility in pulmonary
Secretions. For the lung delivery mechanical or ultrasonic nebulizer nebulizes it. Eg.budenoside [15]

4. Occular Drug Delivery:

Nanosuspensions plays a vital role for drugs that exhibit poor solubility in lachrymal fluids. The nano-size drug particles showed higher solubility, higher dissolution rate, higher bio adhesion, corneal penetration and increases the residence time in a cul-de-sac and avoidance of high tonicity created by water-soluble drugs. It indicated that diameter of the particles size less than 10 µm will reduce particle irritation to the eye, diminish tearing and therefore increase the efficacy of an ocular treatment.

E.g:The nanosuspensions of hydrocortisone, prednisolone and dexamethasone was developed using high pressure homogenizer showed enhanced rate and extent of ophthalmic drug absorption as well as the intensity of drug action.[16]

Table: 1. Advantages of Nanosuspensions over conventional formulations

Route of administration	*Disadvantages of conventional formulations*	*Benefits of Nanosuspensions*
Oral	Slow onset of action/ poor absorption	Rapid onset of action/ improved solubility so improved bioavailability
Ocular	Lacrimal wash off/ low bioavailability	Higher bioavailability/ dose consistency
Intravenous	Poor dissolution/ nonspecific action	Rapid dissolution/ tissue targeting
Intramuscular	Low patient compliance due to pain	Reduced tissue irritation
Inhalations	Low bioavailability due to low solubility	Rapid dissolution/ high bioavailability/

Target Drug Delivery:

Nanosuspensions can be used for targeted delivery as their surface properties andin vivo behavior can easily be altered by changing the stabilizer. Their versatility and ease of scale up enable the development of commercial viable nanosuspensions for targeted delivery especially in the brain targeting. The engineering of stealth nanosuspensions by using various surface coatings for active or passive targeting of the desired site is the future of targeted drug delivery systems [16].

Eg.Targeting of Cryptosporidium parvum, the organism responsible for cryptosporidiosis was achieved by using surface modified mucoadhesive nanosuspensions.

5. **Bioavailability enhancement:**

Nanosuspensions resolve the problem of poor bioavailability by solving the twin problems of poor solubility and poor permeability across the membrane. Bioavailability of poorly soluble oleanolic acid, a hepatoprotective agent, was improved using a Nanosuspensions formulation. The therapeutic effect was significantly enhanced due to the faster dissolution (90% in 20 min) of the Lyophilized Nanosuspensions powder when compared with the dissolution from a coarse powder (15% in 20 min) and thus bioavailability [16].

6. Topical formulations:

Incorporating the nanocrystalline form of drug into creams and water-free ointments leads to an increased saturation solubility of the drug in the topical dosage form, thus enhancing the diffusion of the drug into the skin [17].

7. **Mucoadhesion of the nanoparticles:**

Nanoparticles orally administered in the form of a suspension diffuse into the liquid media and rapidly encounter the mucosal surface. The particles are immobilized at the intestinal surface by an adhesion

mechanism referred to as bioadhesion. Afterthis, concentrated suspension acts as a reservoir of particles and an adsorption process takes place very rapidly. 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 helps to improve bioavailability and targeting of the parasites persisting in the GIT [18].

Table 2. Current marketed formulations using Nanosuspensions technology [19, 20]

Product	Drug	Use	Company/ Individual
RAPAMUNE®	Sirolimus	Immunosuppressant	Wyeth
EMEND®	Aprepitant	Antiemetic	Merck
TriCor®	Fenofibrate	Treatment of hypercholesterolemia	Abbott
MEGACE® ES	Megestrol Acetate	Appetite stimulant	PAR Pharmaceutical
Triglide™	Fenofibrate	Treatment of Hypercholesterolemia	First Horizon Pharmaceutical
LA.Zanaflex CapsulesTM	Tizanidine Hydrochloride	To treat spasticity	Acorda
Ritalin®	Methylphenidate Hydrochloride	Treatment of Attention Deficit Hyperactivity Disorder.	Novartis
Avinza®	Morphine Sulphate	To treat moderate to severe pain that lasts for more than a few days.	King Pharmaceutical
Focalin®XR	Dexmethylphenidate Hydrochloride	Treatment of Attention Deficit Hyperactivity Disorder.	Novartis

CONCLUSION:

Nanosuspension formulation appear to be solve the solubility as well as dissolution problems of hydrophobic drugs, thus improving drug absorption and bioavailability.Increased dissolution velocity, increased saturation solubility, improved bioadhesivity, versatility in surface modification and ease of post-production processing makes the nanosuspensions technology, a unique and commercially feasible method. Production techniques such as media milling and high pressure homogenization have been widely used for large scale production. Applications of nanosuspensions in parentral, oral routes, pulmonary and ocular delivery have been realized. However, their applications in buccal, nasal and topical delivery are still awaiting exploration.

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