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# RESEARCH ARTICLE

## REVIEW ON NANOSUSPENSION IN DRUG DELIVERY

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**ABSTRACT**

Solubility is the significant component for medication adequacy, freedom of the course of administration Gigantic proportions of recently discovered medications are water-insoluble, and hence poorly bioavailable adding to forsook improvement efforts. These so-known as Brickellia's competitors can now be conveyed through detailing them into Nanosuspension. Nanosuspension technological know-how solved the drawback of medications that are inadequately watery dissolvable and have less bioavailability. The steadiness and bioavailability of the medications can be expanded using Nanosuspension technology. Coaching of Nanosuspension is simple and relevant to all medicinal drugs which are fluid insoluble. Nanosuspensions are readied through utilizing a wet mill, high strain homogenizer, emulsion-solvent evaporation, melt emulsification approach, and super significant fluid systems. Nanosuspension can be prepared with the aid of using stabilizers, natural and organic solvents, and different components such as buffers, salts, polyols, osmogent, and cry protectants. Nanosuspensions can likewise be delivered with the aid of oral, parenteral, aspiratory, and visual courses. Nanosuspensions can additionally be used for distinct drug supply when included in the ocular inserts and mucoadhesive hydrogels.

## INTRODUCTION

Various method parameters that play a relevant position within the successful formulation of medications are aqueous solubility, steadiness at ambient temperature and dampness, photostability, similarity with dissolvable and excipient. Amongst this watery dissolvability grew to become a hurdle for the system of recent molecular entities. Greater than 40% of the new synthetic substances being produced using medication revelation projects are ineffectively water-soluble or lipophilic mixes. Defining an ineffective water solvent medication has perpetually been a challenging challenge confronted by using pharmaceutical scientists. The formula of Nano-sized particles can be applied to all drug compounds belonging to biopharmaceutical classification system (BCS) courses II and IV to build their dissolvability and henceforth parcel into a gastrointestinal hindrance. Micronization is utilized for class II medicinal drugs of (BCS), i.e. Medicinal drugs having excellent permeability and poor solubility. There are a lot of customary methodologies for growing the solvency of inadequately solvent medicines, which comprise micronization, solubilisation using co-solvents, salt kind, surfactant dispersions, precipitation system, an oily solution. Different approaches are like liposomes, emulsions, microemulsion, strong dispersion, and inclusion complexation using cyclodextrins (1) show intelligent achiever, and however they need in all-inclusive relevance to all medicinal drugs. These methods are now not relevant for those medications which are usually not soluble in aqueous and organic solvents. Nanotechnology can be utilized to remedy the problems associated with these traditional strategies for dissolvability and bioavailability upgrades.

**The average particle size of nanosuspension ranges from 200-600nm:** Nanosized particles, increase 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 resulting 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 state with reduced particle size, leading to an increased dissolution rate and therefore improved bioavailability

**Need of nanosuspension:** To date, More than 40% of drugs are poorly soluble in water, so they show difficulties in formulating them in conventional dosage forms. Also, for class II drugs that are poorly soluble in aqueous and organic media, the problem is more difficult. Preparing nanosuspension is chosen for such compounds that are insoluble in water (but are soluble in oil) with a high log p-value. Various methods to resolve problems of low solubility and low bioavailability micronization, solvency, oily solution, salt formation- some other techniques are liposomes, emulsions, microemulsion,

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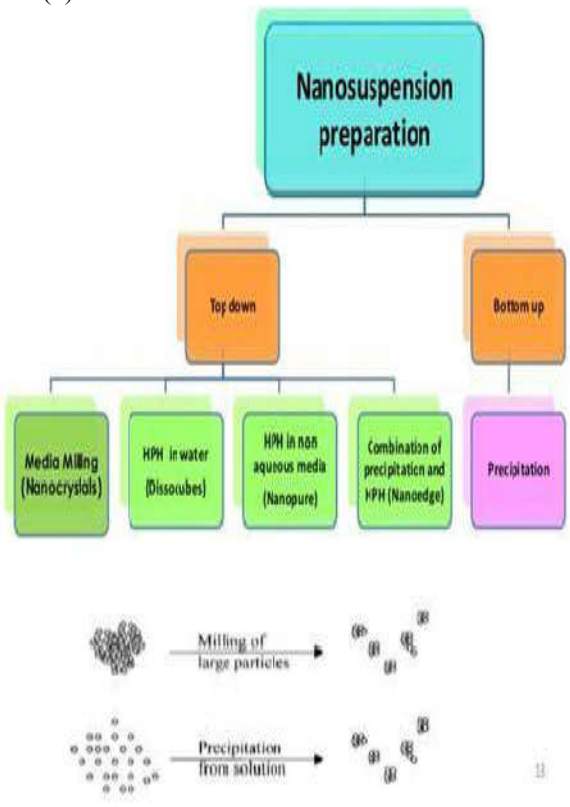
solid dispersion, ß-cyclodextrin inclusion complex, etc. But, many of these techniques are not universally applicable toall drugs.In these cases, nanosuspensions are preferred. In the case of drugs that are insoluble in both water and inorganic media in their place of using lipidic systems, nanosuspensions are used as a formulation method. It is most appropriate for the compounds with a high log P value, high melting point, and high dose. Nanosuspensions can be used to improve the solubility of drugs that are poorly soluble in aqueous as well as lipid media. As a result, the rate of flooding of the active compound rises, and the maximum plasma level is reached faster (e.g., oral or intravenous (IV) administration of the nanosuspension). This is one of the typical advantages that it has over other approaches for increasing solubility. It is useful for molecules with poor solubility, poor permeability, or both, whichposes an important challenge for the formulators. Major issues associated with poorly water-soluble compounds.

**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 the reduced tendency of the crystal to dissolve, regardless of the solvent.
API with a very large dose.

**METHOD OF PREPARATION:** Bottom-Up process-form nanoparticles from precipitation, microemulsion, melt emulsification method Top-down process-nanoparticles obtained by high-pressure homogenization and milling methods (2).




**Bottom-up Technology:** The conventional methods of precipitation (Hydrosols) are called Bottom-Up technology. The precipitation method is a general method used to prepare submicron particles of poorly soluble drugs. In this method, the drug is dissolved in the solvent and then the solution is mixed with a solvent to which the drug is insoluble in the presence of surfactant.

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 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 a nonsolvent**.**

**The bottom-up process is an assembly method that forms nanoparticles from molecules**.

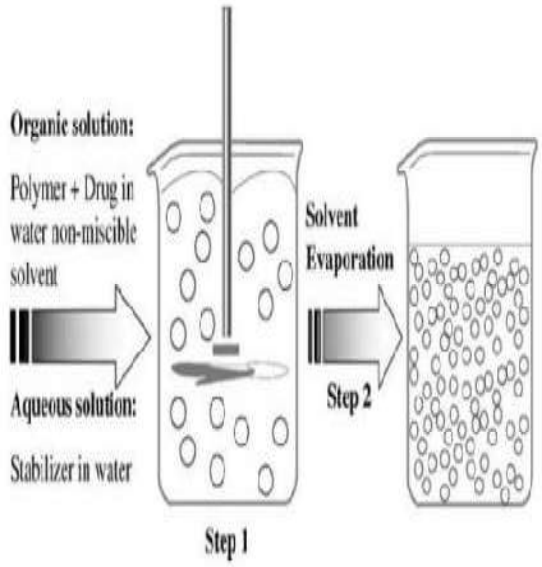
Examples include
Solvent-Antisolvent method
Supercritical fluid process
Emulsification- Solvent evaporation technique
Lipid emulsion/Micro-emulsion template.

**Precipitation (solvent-antisolvent method) method:** Precipitation has been applied to prepare submicron particles, especially for 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 supersaturation of drug and formation of ultrafine crystalline or amorphous drug solids. The 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 a 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: The growing of crystals needs to be limited by surfactant addition. Drugs must be soluble at least in one solvent.

**Supercritical fluid process:** This method utilizes solubilization and nanosizing technologies through the supercritical fluid process for particle size reduction. Supercritical fluids (SCF) are noncondensable dense fluids whose temperature and pressure are greater than their critical temperature (Tc) and critical pressure (Tp).This process allows the micronization of drug particles to the submicron level. Recent advances in the SCF process are to create a nanoparticulate suspension of particle size of 5 to 2000nm indiameter. 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.

**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 were washed with distilled water to remove the additives like

surfactants, and then it was lyophilized. remove the additives like surfactants, and then it was lyophilized.




**Lipidemulsion/microemulsion template:** This method is applicable for drugs that are soluble in either volatile organic solvents or partially water-miscible solvents. Here the drug was dissolved in a suitable organic solvent and it is emulsified in an 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.

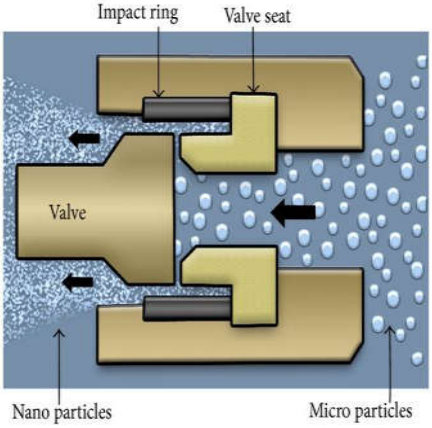
**Melt emulsification method:** In this method, the drug is dispersed in the aqueous solution of stabilizer and heated above the melting point of the drug, and homogenized to give an emulsion. During this process, the sample holder was enwrapped with a heating tape fitted with a temperature controller,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

**Emulsification-solvent evaporation technique:** This technique involves preparing a solution of drug followed by itsemulsification in another liquid that is 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.

**Top-down process:** The top-down process involves the disintegration from large particles, microparticles to nanosized particles. The techniques used are follows:

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

**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.




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

**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:** It does not cause the erosion of processed materials. It is applicable to the drugs that are poorly soluble in both aqueous and organic media.

**Disadvantages:** Pre-processing like micronization of drug is required. High-cost instruments are required that increases the cost of dosage form.

**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.

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

**Principle:** In this technique, the 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 the combination of rapid precipitation and high-pressure homogenization.

**Advantage:** The disadvantage of precipitation techniques such as crystal growth and long-term stability can be overcome by using the Nanoedge technology Particles of smaller size and better stability in a short time can be achieved.

**Nanojet:** It is also called 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 a high velocity of 1000m/s.The high shear forces produced in this process lead to a reduction in particle size.

**Limitation:** High numbers of passes (nearly about 75) are required through the microfluidizer, and the product obtained contains a relatively large fraction of microparticles.

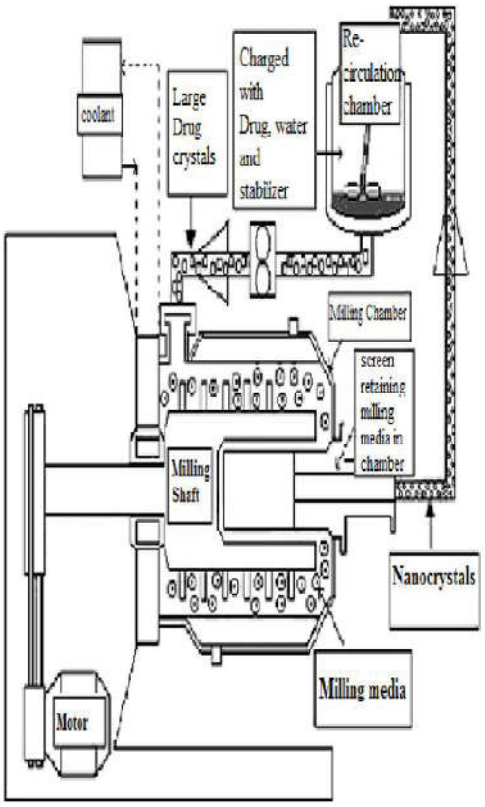
**This process requires a large production time.**

**Milling techniques**

**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 for at least 2-7 days. The high energy shear forces are formed as a result of the impaction of milling media with the drug which results in the breaking of drug microparticles to nanosized particles.

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




Drugs that are poorly soluble in both aqueous and organic media can be easilyformulated into nanosuspensions. Ease of scale-up and little batch-to-batch variation.

**Disadvantages:** Generation of residues of milling media, which may be introduced in the final product as a result of erosion 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 (8).

**Dry-Co-grinding:** The 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:** Easy process and no organic solvent required. Require short grinding time

**Need of Nanosuspension:** The preparing of nanosuspension is preferred for the compound that is insoluble in water with a high log P value, in the case of a drug that is insoluble of both water and organic media instead of lipidic system nanosuspension are used as formulation approach is most suitable for the drug with high log P value, high melting point, and high dose.

**Advantages of nanosuspension:** Drugs that are poorly soluble in both aqueous and organic media can be easily formulated into nanosuspensions. Ease of scale-up and little batch-to-batch variation. Narrow size distribution of the nanoparticulate drug present in the final product. Allows aseptic production of nanosuspensions for parenteral administration.
Flexibility in handling the drug quantity, ranging from 1 to 400 mg mL1, thus enabling the formulation of very dilute as well

as highly concentrated nanosuspensions. It enhances the solubility and bioavailability of compounds. Suitable for hydrophilic compounds. Higher drug loading is possible. Dose reduction is possible. Enhance the physical and chemical stability of drugs. Can be given by any route. Reduced tissue irritation in case of subcutaneous/intramuscular administration. Rapid dissolution & tissue targeting can be achieved by the IV route of administration. Increasing the amorphous fraction in the particles leads to a potential change in the crystalline structure & higher solubility.Enhance the solubility and bioavailability of medications.

Suitable for hydrophilic medications Larger drug loading can also be done

**Disadvantages of Nanosuspension:** Physical stability, sedimentation & compaction cause problems.It is bulky sufficient care must be taken during handling & transport. Improper dose. Uniform & accurate dose cannot be achieved.

**Formulation Consideration:** The following agent is used in the preparation of nanosuspension

- Stabilizer
- Organic solvents
- Surfactant
- Co-surfactant
- Other additives.

**Stabilizer:** 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 functions of a stabilizer are to wet the drug particles thoroughly and to prevent Ostwald's ripening and agglomeration of nanosuspensions to yield a physically stable formulation by providing exterior ionic barriers. The type and amount of stabilizer have a pronounced effect on the physical stability and in-vivo behavior of nanosuspensions. In some cases, a mixture of stabilizers is required to obtain a stable Nanosuspension Commonly used stabilizers are polysorbate (Tween/Span series), povidone, cellulosic, poloxamers, and lecithin.

**Organic Solvents:** The acceptability of the organic solvents in the pharmaceutical area, 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.

**Surfactants:** Surfactants are incorporated in formulation to improve dispersion by reducing the interfacial tension. Surfactants also act as wetting or deflocculating agents. Tweens and Spans - widely used surfactants in nanosuspension.

**Co-surfactants:** The choice of co-surfactant is critical when using microemulsions to formulate nanosuspensions. Since co-surfactant can greatly influence phase behavior, the effect of co-surfactant on uptake of the internal phase for selected microemulsions composition and drug loading should be investigated.Although the literature describes the use of bile salts and dipotassium glycyrrhizinate 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:** 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.

**Evaluation Parameter**

**Mean Particle Size and Particle Size Distribution:** The mean particle size and the span of the particle size distribution (polydispersity index, PI) are two important characteristic parameters because they affect the saturation solubility, dissolution rate, physical stability, even in-vivo behavior of nanosuspensions. The particle size distribution can be determined by 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 Nano suspensions and should be as low as possible for the long-term stability of Nano suspensions. A PI value of 0.1– 0.25 indicates a fairly narrow size distribution whereas a PI value greater than 0.5 indicates a very broad distribution.

**Particle Charge (Zeta Potential):** Zeta potential gives certain information about the surface charge properties and furthers the long-term physical stability of the nanosuspension. Particle charge determines the stability of Nano suspension. For electrostatically stabilized Nano suspension a minimum zeta potential of ±30mV and for combined steric and electrostatic stabilization it should be a minimum of ± 20Mv.

**Crystal Morphology:** To characterize the polymorphic changes due to the impact of high-pressure homogenization in the crystalline structure of the drug, techniques like X-ray diffraction analysis in combination with differential scanning calorimetric or differential thermal analysis can be utilized. The change in the solid-state of the drug particles as well as the extent of the amorphous fraction can be determined by X-ray diffraction analysis and supplemented by differential scanning calorimetry. To get an actual idea of particle morphology, scanning electron microscopy is preferred.

**Saturation Solubility and Dissolution Velocity:** The nanosuspension has an important advantage over the other techniques, that it can increase the saturation solubility as well as dissolution velocity. Saturation solubility is a compound-specific constant depending upon temperature and the properties of the dissolution medium. Kelvin equation and the Ostwald-Freundlich equations can explain the increase in saturation solubility.

**pH:** 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. The electrolyte should not be added to the external phase of the formulation to stabilize the pH. Prepared nanosuspension was taken in 10ml beaker and pH was measured using the pH meter.

**Osmolarity:** The osmolarity of nanosuspension can be measured by using Osmometer. Intravenous dosage form should be iso-osmolar with the blood so the nanosuspension formulation checked for osmolarity. Practically osmolarity was measured using an osmometer and theoretically, it was calculated using the following formula

Osmolarity (mOsmol) =weight in gm/lit. No. of species * 1000molecular weight*100

**Surface Hydrophilicity:** Surface hydrophilicity/hydrophobicity is considered as one of the important parameters affecting the in vivo organ distribution after i.v. injection. The surface hydrophobicity determines the interaction with cells before phagocytosis and; in addition, it is a relevant parameter for the adsorption of plasma proteins the key factor for organ distribution. To avoid artifacts, the surface hydrophobicity needs to be determined in the original environment of the drug nanoparticles, which means in the aqueous dispersion medium. A suitable technique is hydrophobic interaction chromatography (HIC), previously employed to determine the surface hydrophobicity of bacteria, and then transferred to the characterization of nanoparticulate drug carriers.

**Adhesion Properties:** In vivo bioadhesive study is performed where Male Wistar rats can be used. In general, each animal receives a single oral dose of 1ml aqueous suspension containing 10 mg of the nanoparticles loaded with the drug (approximately 45 mg particles/kg Body Weight). The animal is sacrificed by cervical dislocation at 1 and 3 h post-administration. The abdominal cavity is opened and the stomach, small intestine, and cecum are removed, opened lengthwise along the mesentery, and rinsed with phosphate saline buffer (pH 7.4). Further, the stomach, small intestine, and cecum are cut into segments of 2 cm length and digested in suitable alkali for 24 h. Drug extracted from the digested samples by addition 2ml methanol, vortexes for 1 min and centrifuged. An aliquot (1 ml) of the supernatants is assayed for the drug by spectrofluorimetryto estimate the fraction of adhered nanoparticles to the mucosa. For calculations, a standard curve of the drug can also be prepared.

**Interaction with Body Proteins:** In vitro interaction between nanoparticles and mucin can be studied by incubation of mucin and nanoparticles (1:4 weight ratio) either in acidic or in neutral medium. The incubation is carried out under stirring at a temperature of 37°C. The dispersions are then be centrifuged and 150µl of each supernatant is placed in a test plate. Micro BCA Protein Assay Reagent Kit (150µl) is then added to the supernatants and the plate is incubated for 2 hrs at 37°C. According to this procedure, the absorbance of mucin can be measured by colorimeters at $\lambda_{max}$ of the drug. The amount of the mucin adsorbed to the nanoparticles can be determined as a difference between its initial concentration and the concentration found in the dispersion after incubation and centrifugation. The calculations can be made based on mucin standard curves.

**Pharmaceutical applications of Nanosuspension in Drug Delivery**

- Oral Drug Delivery
- Parental Drug Delivery
- Ophthalmic Delivery
- Pulmonary Drug Delivery
- Targeted Drug Deliver
- Topical
- Mucoadhesion of The Nanoparticles
- Bioavailability Enhancement.

**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 buparvaquone reflect this problem very well. Nanosizing of such drugs can lead to a dramatic increase in their oral absorption and subsequently bioavailability. The oral administration of naproxen nanoparticles leads to an area under the curve (AUC) (0-24 h) of 97.5 mg-h/l compared with just 44.7 mg-h/l for Naprosyn suspensions and 32.7 mg-h/l for Anaprox tablets. Oral administration of the gonadotropin inhibitor Danazol as a nanosuspension leads to an absolute bioavailability of 82.3 and the conventional dispersion (Danocrine) only to 5.2%. A nanosuspension of Amphotericin B developed by a significant improvement in its oral absorption in comparison with the conventional commercial formulation.

**Parental Drug Delivery:** Nanosuspensions are administered through various parental routes such as intraarticular, intraperitoneal, intravenous, etc. Additionally, Nano suspensions increase the efficacy of parenterally administered drugs. Paclitaxel nanosuspension was reported to have superiority in reducing the median tumor burden. Clofazimine nanosuspension showed an improvement in instability as well as efficacy above the liposomal clofazimine in Mycobacterium avium-infected female mice.

**Ophthalmic Delivery:** Certain drugs have poor solubility in the lachrymal fluid. If it is formulated as nanoparticles its saturation solubility and bioavailability will increase. Mainly applied for hydrophobic drugs. It increases the residence time in the cul-de-sac. The best example of nanosuspension is ibuprofen. The anti-inflammatory activity of ibuprofen increased compared with the aqueous preparation.

**Pulmonary Drug Delivery:** Nanosuspensions may prove to be an ideal approach for delivering drugs that exhibit poor solubility in pulmonary secretions. Aqueous Nano suspensions can be nebulized using mechanical or ultrasonic nebulizers for lung delivery. Because of their small size, it is likely that in each aerosol droplet at least one drug particle is contained, leading to a more uniform distribution of the drug in the lungs**.** The nanoparticulate nature of the drug allows the rapid diffusion and dissolution of the drug at the site of action.

**Targeted Drug Delivery:** Targeted drug delivery can be used for the anti-mycobacterial, fungal, or leishmanial drugs to macrophages if the infectious pathogen is persisting intracellular. The further plan of action for targeted drug delivery system is by using various surface coatings for active or passive targeting., atovaquone nanosuspension concentration in brain, lungs, sera, liver is high and has improved therapeutic efficacy against toxoplasma encephalitis in murine mold infected with toxoplasma gonidii.

**Topical Drug Delivery:**
Drug nanoparticles can be incorporated into creams & water-free ointments. The nanocrystalline forms lead to an increased

saturation solubility of the drug in the topical dosage form, thus enhancing the diffusion of the drug into the skin.

**Mucoadhesion of the Nanoparticles:** Nanosuspension containing drug nanoparticles orally diffuses into the liquid media and rapidly encounters the mucosal surface. The particles are immobilized at the intestinal surface by an adhesion mechanism referred to as "bioadhesion." From this moment on, the 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 Nano suspensions not only helps to improve bioavailability but also improves targeting of the parasites persisting in the GIT.

**Bioavailability Enhancement:** Nanosuspensions resolve the problem of poor bioavailability by solving the twin problems of poor solubility and poor permeability across the membrane. The bioavailability of poorly soluble oleanolic acid, a hepatoprotective agent, was improved using a nanosuspension formulation. The therapeutic effect was significantly enhanced, which indicated higher bioavailability.

**Properties of Nanosuspension:**

**Following are the properties of nanosuspensions**

- Physical long-term stability.
- The internal structure of nanosuspension.
- Adhesiveness.
- Crystalline State and Particle Morphology.
- Increase in Saturation Solubility and Dissolution Velocity of Drug.
- Nano Suspension Provide Passive Targeting

**Physical Long-term Stability:** Dispersed systems show physical instability due to Ostwald ripening which is responsible for crystal growth to form microparticles. Ostwald ripening is caused due to the difference in dissolution velocity/ saturation solubility of small and large particles. In nanosuspensions all particles are of uniform size hence there is little difference between saturation solubility of drug particles because of that Ostwald ripening is absent.

**Internal Structure of Nanosuspensions:** The high-energy input during the disintegration process causes structural changes inside the drug particles. When the drug are exposed to high-pressure homogenization, particles are transformed from crystalline state to amorphous states. The change in state depends upon the hardness of drug, number of homogenization cycles chemical nature of drug and power density applied by homogenizer.

**Adhesiveness:** Increase in adhesiveness of ultra-fine powders compared to coarse powders. This adhesiveness of small drug nanoparticles can be exploited for improved oral delivery of poorly soluble drugs.

**Crystalline State and Particle Morphology:** The assessment of the crystalline state and particle morphology together helps in understanding the polymorphic or morphological changes that a drug might undergo when subjected to nanosizing. Nanosuspensions 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. The changes in the solid state of the drug particles as well as the extent of the amorphous fraction can be determined by X-ray diffraction analysis and supplemented by differential scanning calorimetry.In order to get an actual idea of particle morphology, scanning electron microscopy is preferred.

**Increases in Saturation Solubility and Dissolution Velocity of Drug:** Dissolution of drug is increased due to increase in the surface area of the drug particles from micrometers to the nanometer size. According to Noyes-Whitney equation dissolution velocity increases due to increase in the surface area from micron size to particles of nanometer size.

$$dx/dt = \left[ (D \times A)/h \right] \left[ Cs - X/V \right]$$

Where; D is diffusion coefficient,
A is surface area of particle,
dx/dt is the dissolution velocity,
V is volume of dissolution medium and
h is the thickness of the diffusion layer and X is the concentration in surrounding liquid.

**Nano Suspension Provide Passive Targeting:** Most of drugs have failed to achieve favorable outcomes because they do not have the ability to reach the target site of action. A significant amount of the administrated drug is distributed over the normal tissues or organs that are not involved in the pathological process, often leading to severe side effects.

An effective approach to overcome this critical issue to development of targeted drug delivery systems. Versatility the flexibility offered in the modification of surface properties and particle size, and ease of post-production processing of nanosuspensions enables them to be incorporated in various dosage forms, such as tablets, pellets, suppositories, and hydrogels, for various routes of administration, thus proving their versatility.

**Conclusion**

Nanosuspensions appear to be a unique and yet commercially viable approach to combating such as poor bioavailability that are associated with the delivery of hydrophobic drugs, including those that are poorly soluble in aqueous as well as organic media. Production techniques such as media milling and high-pressure homogenization have been successfully for large-scale production of Nano suspensions. Attractive features, such as increased dissolution velocity, increased saturation solubility, improved bioadhesivity, versatility in surface modification and ease of post-production processing, have widened the applications of Nano suspensions for various routes.

The applications of Nano suspensions in parenteral and oral routes have been very well investigated and applications in pulmonary and ocular delivery have been realized. Poor aqueous solubility is rapidly becoming the leading hurdle for formulation scientists working on oral delivery of drug compounds and leads to employment of novel formulation technologies. The use of drug nanocrystals is a universal formulation approach to increase the therapeutic performance of these drugs in any route of administration.

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