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# A Comprehensive Review On Nanosuspension

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## Abstract

The crucial factor that determines the acceptability of a medication and also the flexibility of its administration is its solubility. Significant portions of recently invented drugs are water insoluble, which makes them poorly bioavailable and limits continuous improvement. By combining these acknowledged rivals into Nanosuspension, they can now be conveyed. Nanosuspension invention addressed the issue of medications with poor water solubility and inadequate bioavailability. Using the Nanosuspension technology, The drugs' bioavailability and stabilization can be improved. All medications that are liquids insoluble can benefit from Nanosuspension treatment, which is inexpensive and effective. To create nanosuspensions, a wet mill, high strain homogenizer, melt emulsification method, emulsion solvent evaporation, and super significant fluid systems are utilised. It is possible to create nanosuspension using preservatives, both natural and organic solvents, and other substances such buffers, salts, polyols, osmogent, and cry protectant. Additionally possible methods for administering nanosuspensions include oral, parenteral, aspiratory, and ocular. Nanosuspensions can be employed for mucoadhesive hydrogels and targeted drug administration when used as ocular inserts. The main considerations for better use and scaling up of nanosuspensions include maintaining stability in solution and in the solid state and resuspendability without coalescence. The use of nanosuspensions in a variety of drug delivery methods, including transdermal, buccal, nasal, ocular, and oral is now also the topic of ongoing investigation. Oral drug delivery system of nanosuspension with a receptor mediated endocytosis, which is a desirable capability, can resolve the majority of permeability limiting absorption and associated challenges that adversely affect bioavailability. There are a number of formulation obstacles that protein- and peptide-based medications currently encounter that can be handled well with development of current digital era like Nanosuspension.

**Key Words: Water insoluble, Nanosuspension, Bioavailability, Mucoadhesive and Resuspendability**

## 1.Introduction

Solubility in water, stabilization at room temperature, excessive moisture, inertness, and affinity to mix with additives are only a few variables that are critical for the formulation of drugs. Aqueous dissolvability among them developed into a barrier for the system of modern molecular entities. And over 40 percent of the total of the numerous innovative medications developed by drug research studies are mixes that are inadequately soluble in water or that are lipophilic. Drug industry researchers have always encountered an extreme difficulty formulating water - dissolvable drug that is worthless. Those pharmacological substances categorized as Classes II and IV of the Biopharmaceutical Classification System (BCS) can use the technique of nanosized particles to augment their solubilization and thereafter packaged into the gastric obstruction. Class II medicinal drugs (BCS), or

pharmaceuticals with good permeability with poor solubility, are now using micronization. There are numerous popular methods for improving the solventity of drugs which aren't sufficiently dissolvable, which would include micronization, cosolvent solubilization, salt type, surfactant dispersions, precipitation system, and oily solutions. Alternative techniques typically involve inclusion complexation employing cyclodextrins, liposomes, emulsions, microemulsions, and strong dispersion. Meanwhile, they must be beneficial to all prescription drugs. These procedures are no longer relevant to drugs that are frequently insoluble in both organic and aqueous media. Nanotechnology can address the gaps of these conventional methodologies to strengthening bioavailability and dissolvability. For concentration with significant log P values, undesirable softening points, and high doses that have been not water soluble although dissolvable in oil, nanosuspension is best suited. Along Other drugs including that are insoluble in both water and common solvents would be handled with nanosuspension innovation. Despite it having poor water solubility, few drug candidates can be dissolved using appropriate standard formula methods that include co-solvents, milling techniques, super principal processing, and stable scatterings, including chronic condition and precipitation approaches. Currently, atorvastatin is taken as a calcium salt to acknowledge hypercholesterolemia. It is insoluble in watery solutions with pH values of 4 and below, but it is markedly soluble in water at pH 7. At the physiologically important intestinal pH, atorvastatin has a significant intestinal penetrability for phosphate buffer. The upper duodenum and adjacent small intestine regions are where the medicament is absorbed most extensively. However, it is said that at an oral dose of 40 mg of atorvastatin, its bioavailability (F) is 12%). The dissolvability and absorption parameters of the drug atorvastatin calcium (AC), an ineffectively solvent model, were assessed in the reimbursement study using nanosuspension technology.

## 2. Benefits of using nanosuspensions

The liquid solubility and bio - availability of drug combinations are promoted by nanosuspension, also making it excellent for hydrophilic drugs. Dose reduction can also be used to enable larger drug loading. Parenteral, oral, pulmonary, and topical nanosuspensions have received extensive research and evaluation for both in vitro and in vivo usage via a number of delivery systems. They have furthermore been used to target drug usage.

## 3. Techniques for development of Nanosuspension

Nanosuspensions are made primarily using two ways. The "Bottom up technology" is the term used to describe the conventional precipitation methods (Hydrosols). In bottom-up technology, the medication is dissolved in a suitable solvent, which is then added to non-solvent to precipitate the crystals. In order to stop the creation of microscopic particles and restrict the growth of the drug crystals, this method involves adding surfactant to the precipitation process. Precipitation methods are preferred to disintegration processes, often known as "Top down Technologies." Examples of "Top Down Technologies" (Nanoedege) include media milling (Nanocrystals), high pressure homogenization in non-aqueous media (Nanocrystal), high pressure homogenization in water (Dissocubes), and a combination of precipitation and high-pressure homogenization.

### 3.1.1 Homogenization under high pressure (Disso cubes)

It is the method that is most routinely used to prepare nanosuspensions for drugs with very low aqueous solubility. Disso cubes are created using high-pressure piston-gap homogenizers. A well-liked model of homogenizer is the APV Micron LAB 40. However, you can also make use of additional piston-gap homogenizers from Stansted Gap and Avestin. A high-pressure homogenizer is made composed of a relief valve and a high-pressure plunger pump (homogenizing valve). The energy required for the relief is provided by the plunger pump. The relief valve is composed of an adjustable valve and a fixed valve seat. Together, they create a gap with radial precision that appears to be unrestricted. The force on the valve causes a change in the homogenization pressure because of the gap conditions, resistance, and force operating on the valve.

**Principle**

In piston gap homogenizers, particle size reduction is supported by the cavitation principle. Particles are also reduced as a result of high shear forces and particle collisions. A 25 m-wide hole allows the dispersion to abruptly flow through a 3 cm-diameter cylinder. According to Bernoulli's Theorem, the flow volume of liquid in a closed system per cross section is constant. The static pressure can drop below the boiling point of water at ambient temperature while the dynamic pressure rises due to the reduction in diameter from 3 cm to 25 m. As a result, when cavitations or the suspension exiting the gap, and normal air pressure are established, water begins to boil at room temperature and generates gas bubbles that ascend. The dimensions that are most important to the size of the drug nanocrystals that can develop are temperature, the number of homogenization cycles, the power density of the homogenizer, and homogenization pressure.

**Advantages**

1. It prevents treated materials from eroding.
2. It is possible to generate nanosuspensions that are both extremely diluted and highly concentrated by working with drug concentrations ranging from 1 mg/ml to 400 mg/ml.
3. It applies to medications that have a hardest time dissolving in both aqueous and organic solutions.

**Drawbacks**

1. Pre-processing is required, such as the micronization of medications.
2. Costly machinery is required, which drives up the cost of the dosage form.

**3.1.2 Methods for milling**

**i) Media milling:-** Liversidge is credited with creating and first disclosing the media milling technique (1992) [(14)]. In this method, the nanosuspensions are made in high shear media mills. The milling chamber revolved at a very high shear rate for at least 2 to 7 days at a fixed temperature while being fed with milling media, water, drug, and stabilizing agent.[(15)]. The milling media could be made of glass, zirconium oxide, or a polystyrene resin with a high degree of bonding. The drug's microparticles disintegrate into nanosized fragments when the milling media comes into contact with them, generating high energy shear forces.

**Advantages**

1. Using drug concentrations between 1 mg/ml and 400 mg/ml, one can make nanosuspensions that are both very diluted and highly concentrated.
2. Distribution of the finished product at the nanoscale.

**Disadvantages**

1. The media milling method takes a significant amount of time.
2. Particle fractions that are in the micrometre range exist.
3. Due to mill size and weight, scaling up is challenging.

**3.1.3 Dry-Co-grinding:**

Dry-co-grinding is an easy, inexpensive method that doesn't use organic solvents. Co-grinding enhances the physicochemical properties and dissolving of poorly water soluble medications due to an improvement in surface polarity and a transformation from a crystalline to an amorphous substance.

**Advantages**

1. Simple procedure; no need for an organic solvent.
2. Require minimal time for grinding. Limitations formation of milling media residue.

### 3.1.4 Emulsification-solvent evaporation technique

Making a drug solution and emulsifying it in a separate liquid that isn't the medication's solvent are both necessary steps in this procedure. The drug precipitates as a result of the solvent evaporating. A high-speed stirrer's high shear forces can be employed to regulate particle aggregation and crystal growth.

### 3.1.5 Precipitation

In the past ten years, precipitation has been utilized to produce micro and nano particles, particularly for difficult-to-dissolve pharmaceuticals [18]. The drug is first dissolved in a solvent, and this solution is then mixed with a miscible anti-solvent using surfactants. A drug solution is immediately super-saturated whenever it is added to an anti-solvent, resulting in the formation of nanoscale crystalline or amorphous drug solids.

**Advantages**
It is an inexpensive, simple process that is also simple to scale up.

**Disadvantages**
The addition of surfactants must be used to control crystal growth, and the medication must be soluble in at least one solvent.

### 3.1.6 Process using supercritical fluid

The ultra critical fluid method used solubilization and nanosizing technologies that were more effective in reducing particle size. Drug particles can be micronized to submicron levels with this method. Super critical fluids (SCF) are non-condensable dense fluids whose critical temperature (Tc) and critical pressure (Cp) are higher (Tp). Recent advancements in SCF enable the production of nanoparticulate suspensions with particles as small as 5 nm and as large as 2000 nm.[20]. Due to the limited solubility of drugs and surfactants in supercritical CO2 and the high pressure required for these procedures, the pharmaceutical industry is unable to utilize this technology.

### 3.1.7 Method of melting emulsification

In this process, the drug is combined with the aqueous solution of the stabilizing agent, heated above the drug, and homogenised to produce an emulsion. Throughout this process, the sample holder was covered in heating tape with a thermostat to maintain the emulsion's temperature above the drug's melting point. The emulsion was then either placed in an ice bath or slowly cooled to room temperature.

**Advantages**
In contrast to the solvent evaporation method, the melt emulsification approach completely omits the use of organic solvents during manufacture.

**Disadvantages**
Larger particles can develop, and it is less trustworthy than solvent evaporation.

### 3.1.8 Lipid emulsion/micro emulsion template

Most drugs can be dissolved using this technique if they can be dissolved in solvents that are slightly water miscible or volatile organic solvents. Under this approach, the drug is first dissolved in an adequate organic solvent before being emulsified in an adequate aqueous phase with a surfactant. The drug particles precipitated in the aqueous phase and formed the requisite particle size for the aqueous suspension as a result of the gradual evaporation of the organic solvent under reduced pressure. To make nanosuspensions, the resulting suspension can subsequently be properly diluted. Microemulsions can also be used as templates to make nanosuspensions. Microemulsions, which are held together by an interfacial coating of surfactant and co-surfactant, are isotropically transparent

dispersions of two immiscible liquids, such as oil and water, that are thermodynamically stable. Either the medicine is put into the internal phase or it is thoroughly mixed into the pre-formed microemulsion. The microemulsion is properly diluted to create the drug nanosuspension. When employed as templates to create nanosuspension, lipid emulsions have the benefit of being simple to expand and simple to manufacture. However, using organic solvents has an effect on the environment, requiring the usage of significant amounts of surfactant or stabilizer.

**Advantages**

This method is simple to make, has a high drug solubilization rate, and a long shelf life.

**Disadvantages**

Hazardous solvent usage and heavy surfactant use

### 3.1.9 Solvent evaporation:

For the solvent evaporation process, the polymer solutions are prepared in emulsions and volatile solvents. However, since ethyl acetate has a greater toxicological profile, it has replaced the formerly used dichloromethane and chloroform. The emulsion converts into a suspension of nanoparticles upon the evaporation of the polymer's solvent, which is then let to seep into the continuous phase of the emulsion. The two primary methods for producing emulsions in conventional techniques are the production of single-emulsions, such as oil-in-water (o/w), or double-emulsions, such as (water-in-oil)-in-water (w/o)/w One of these methods requires high-speed homogenization or ultrasonication before the solvent may be evaporated. Then, this solvent must be continually magnetically stirred at room temperature or at low pressure. After being distilled water rinsed to remove any additives like surfactants, the resultant solidified nanoparticles were lyophilized. The particle size was modified by the polymer concentration, stabiliser concentration, and homogenizer speed.

## 4. FORMULATION OF NANOSUSPENSIONS

Stabilizer or surfactant, the appropriate solvent system, and other chemicals are necessary for the development of nanosuspension formulation.

### 4.1 Stabilizers

Stabilizers are used to wet the surface of solute or drug particles and postpone Ostwald ripening and agglomeration in order to give the particle a high level of physical stability, which further impacts its performance. Stabilisers that are frequently used include polysorbate (Tween/Span series), povidone, cellulosics, poloxomers, and lecithin.

### 4.2 Organic solvent

Organic solvents are commonly used while creating nanosuspension using emulsion or microemulsion technologies as a template. These hazardous solvents can be replaced with less hazardous water-soluble solvents like methanol, ethanol, chloroform, and isopropanol as well as partially water-soluble solvents like ethyl acetate, ethyl formate, butyl lactate, triacetine, propylene carbonate, and benzyl alcohol to avoid harming the environment or human health (reported as a conventional hazardous solvent)

### 4.3 Other additives

Other components' uses depend on the physicochemical structure or administration method of the potential medicine, however some additives, such buffers, salts, polyols, osmogent, and cryoprotectants, are widely used.

## 5. PHARMACEUTICAL APPLICATION OF NANOSUSPENSION

Nanosuspensions are organised into several dose kinds by using postproduction processing. Because of the smaller particle size and greater surface field, nanosuspension increases medication absorption and dissolving rates. Nanosuspensions are all put into different dose forms through the use of postproduction processing. Because of the smaller particle size and bigger floor subject, nanosuspension increases the cost of drug absorption and breakdown.

### 5.1 Oral Drug Delivery

Oral drugs' low solubility, incomplete solvency, poor breakdown, and insufficient adequacy are the main obstacles to their formation. Due to its smaller particle size and noticeably greater floor to volume ratio, oral nanosuspensions are widely used to enhance the absorption rate and bioavailability of poorly soluble drugs. It has been demonstrated that, in the case of azithromycin nanosuspensions, more than 65percent of total of the antibiotic would be broken down in 5 hours as opposed to only 20% of micronized drugs. The Nanosuspension's main focus areas include enhanced oral assimilation, proportional measurements, and low intersubject variability. By using standard production procedures, drug nanosuspensions can also be conveniently added to a range of dosage forms, such as pills, medications, and rapid melts. The nanosuspension of ketoprofen was successfully mixed into pellets for the drug's sustained release over a 24-hour period.

### 5.2 Parental Drug Delivery

Among the incentive systems for parental administration are micellar selections, salt, solubilization with cosolvents, cyclodextrin complexation, and more recently vesicular programmes like liposomes and niosomes. The solubilization potential, parental approval, high manufacturing costs, and other issues are problems that these methods must overcome. To solve the aforementioned issues, the Nanosuspension science is used. Nanosuspensions are managed using a variety of parental courses, including intraarticular, intraperitoneal, intravenous, and many more. Nanosuspensions improve the efficiency of parenterally delivered medications. Paclitaxel nanosuspension is reportedly regularly utilised to lessen the typical tumour burden. Clofazimine Nanosuspension outperformed liposomal clofazimine in terms of both effectiveness and balance in female mice infected with Mycobacterium avium. revealed that intravenous administration of itraconazole nanosuspension to rats increased the viability of antifungal activity compared to formulation.

### 5.3 Pulmonary Drug Supply

For pulmonary administration, nanosuspensions can also be nebulized utilising mechanical or ultrasonic nebulizers. Due to the close closeness of several tiny particles, all vaporised beads contain drug nanoparticles. Budesonide corticosteroid has been effectively produced as a nanosuspension for pulmonary administration. Aqueous solutions of the drug can also be easily nebulized and delivered via the pulmonary route because the particle size may be very small. Nebulizers can be used to give liquid solutions and have amazing designs. Some medications that have been successfully administered via the pulmonary route include budesonide, ketotifen, ibuprofen, indomethacin, nifedipine, itraconazole, interleukin-2, p53 gene, leuprolide, doxorubicin, etc.

### 5.4 Ocular Drug Supply

In order to visually deliver the drugs for supported release, nanosuspensions are used. Using Eudragit, Liang and colleagues set up cloricromene nanosuspension for visual supply. A check confirmed that medications are more easily accessible in rabbit ocular fluid humour. In light of this, nanosuspension components present a possible way to enhance the drug's bioavailability and shelf-life following ophthalmic application.

### 5.5 Distinct Drug Delivery

Because of the surface structures that nanosuspensions have, they are suitable for targeting certain organs. Furthermore, by changing the stabiliser, in vivo behaviour can be easily modified. The medicine will likely be

ingested by the area-specific mononuclear phagocytic technique. If pathogens remain intracellular, this can be used to concentrate on administering antifungal, antimycobacterial, or antileishmanial medications to macrophages. Aphidicolin Nanosuspension, created by Kayser, broadened the drug's focus to macrophages infected with Leishmania. He admitted that the drug's EC50 in its Nanosuspension form was zero.003 g/ml as opposed to 0.16 g/ml in its conventional form. Scholer et al. Described an superior drug concentrating on to brain within the treatment of toxoplasmic encephalitis making use of an atovaquone Nanosuspension.

## 6. RECENT TREND OF NANOSUSPENSION

In recent years, the formulation problems of poorly soluble medications have been successfully addressed by using nanosuspension technology. Most recently, oral administration of poorly soluble medicines has been improved by using nanopowders as a delivery mechanism. Loviride, a hydrophobic antiviral drug, was created on a lab scale using media milling, and sucrose cofreeze-dried nanopowders were produced as a result. Tween 80/poloxamer 188 stabilised the nanosuspension. Practically speaking, pulmonary products are possible. Commercial nebulizers can be used to aerosolize nanosuspensions, although no products have been developed to date. The cause might not be technological but rather business. Simply though pulmonary deposition could be preferable, it makes little sense to switch out a popular product for a nanosuspension. The price of entering the market is too high. An established routine delivery method is preferred even with novel molecules. Additionally, the discipline of injecting poorly water-soluble nanosuspension pharmaceuticals is emerging and rapidly expanding, and it is gaining popularity due to its advantages in lowering toxicity and raising therapeutic efficacy by doing away with cosolvent in the formulation. Present-day methods for parenteral distribution include complexation with cyclodextrin, micellar solutions, solubilization utilising cosolvents, salt creation, and, more recently, liposomes. The solubilization capacity and parenteral acceptability constraints of these techniques, however, place restrictions on their utilisation. Liposomes are far more palatable and flexible in terms of parenteral distribution in this aspect. However, they frequently have issues like physical instability, high production costs, and scaling-up challenges. The aforementioned challenges could be resolved by nanosuspensions. Recent research on stability have shown that quercetin's chemical and optical stability can be greatly improved by nanosuspension when compared to the solution stored in the same conditions. Recently, efforts have been made to generate stable nanosuspensions using a novel flocculent structure known as "open flocs," which would be an effective way to improve the stabilisation of chemically labile pharmaceuticals. The production of BSA nanorods with a 24 aspect ratio used thin film freezing. When mixed with a hydrofluoroalkane (HFA) propellant, these BSA nanorods were discovered to be extremely stable, with no visible sedimentation being noticed for a whole year. Due to the BSA nanorods' high aspect ratio and the van der Waals (vdW) forces' relative strength and attractiveness.

## 7. CONCLUSION

Nanosuspensions are an excellent and economically practical way to address the problems with hydrophobic medicines. The science of high-weight homogenization and media processing were successfully used to the enormous-scale building of Nanosuspensions. Placing characteristics including increased saturation solubility, faster bioadhesivity, flexibility in surface modification, and ease of postproduction preparation have broadened the uses of nanosuspensions for a wide range of organisational disciplines. Despite the need to evaluate their uses for pneumonic and visual delivery, nanosuspensions have been used in oral and parental courses with excellent results. However, their distribution via buccal, nasal, and topical methods still has to be completed.

## 8. CONFLICT OF INTEREST:

I have no conflicts of interest regarding this investigation.

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