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Review Article

# Nanosuspension: A Novel Approach

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**ABSTRACT**

Nanosuspension is an attractive and promising alternative to solve these problems. Nanosuspension consists of the poorly water-soluble drug without any matrix material suspended in dispersion. Preparation of Nanosuspension is simple and applicable to all drugs which are water insoluble. A Nanosuspension not only solves the problems of poor solubility and bioavailability, but also alters the pharmacokinetics of drug and thus improves drug safety and therapeutic efficacy. Solubility is the crucial factor for drug effectiveness, independence of the route of administration. Large proportions of newly discovered drugs are water insoluble, and therefore poorly bioavailable contributing to deserted development effort. Preparation of Nanosuspension is simple and applicable to all drugs which are aqueous insoluble. Nanosuspensions are prepared by using wet mill, high pressure homogenizer, emulsion solvent evaporation, melt emulsification method and super critical fluid techniques. Nanosuspension can be prepared by using stabilizers, organic solvents and other additives such as buffers, salts, polyols, and cryoprotectant. Nanosuspensions can be delivered by oral, parenteral, pulmonary and ocular routes. Nanosuspensions can also be used for targeted drug delivery when incorporated in the ocular inserts and mucoadhesive hydrogels.

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## INTRODUCTION

A range of parameters like solubility, stability at room temperature, compatibility with solvent, excipient, and photo stability play a critical role in the successful formulation of drugs. Till date, more than 40% of the new chemical entities being generated through drug discovery programs are lipophilic or poorly water-soluble compounds [1, 2]. Many formulation approaches are available to solve the problems of low solubility and low bioavailability of drugs which are conventional approaches and some additional approaches. Over the last decades, nanoparticle engineering has been developed and reported for pharmaceutical applications [3, 4].

A pharmaceutical nanosuspension is defined as very finely dispersed solid drug particles in an aqueous vehicle for either oral and topical use or parenteral and pulmonary administration. The particle size distribution of the solid particles in nanosuspensions is between 200 and 600nm.

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Nanosuspensions differ from nanoparticles. Nanoparticles are commonly polymeric colloidal carriers of drugs whereas solid lipid nanoparticles are lipidic carriers of drugs. Nanosuspensions differ from nanoparticles. Nanoparticles are commonly polymeric colloidal carrier of drugs whereas solid lipid nanoparticles are lipidic carriers of drugs. In nanosuspension technology, the drug is maintained in the crystalline state with reduced particle size, leading to increase dissolution rate & therefore improved bioavailability. Drugs encapsulated within nanosuspensions exist in pharmaceutically accepted crystalline or amorphous state. Nanaosuspensions can successfully formulate the brick dust molecules for improved dissolution & good absorption [5].

Nano sized particles can increase solution velocity and saturation solubility because of the vapor pressure effect. In addition, the diffusional distance on the surface of drug nanoparticles is decreased, thus leading to an increased concentration gradient. The increases in surface area and concentration gradient lead to a much more pronounced increase in the dissolution velocity as compared to a micronized product.

Another possible explanation for the increased saturation solubility is the creation of high energy surfaces when disrupting the more or less ideal drug microcrystals to nanoparticles. The absence of particles with large differences in their size in nanosuspensions prevents the existence of different saturation solubilities and concentration gradients, consequently preventing the Oswald ripening effect. Ostwald ripening is responsible for crystal growth and subsequently formation of microparticles. It is caused by a difference in dissolution pressure/saturation solubility between small and large particles. Molecules diffuse from the higher concentration area around small particles which have higher saturation solubility to an area around larger particles possessing a lower drug concentration. This leads to the formation of a supersaturated solution around the large particles and consequently to drug crystallization and growth of the large particles [6].

Nanosuspension is favoured for compounds that are insoluble in water (but are soluble in oil) with high log P value, high melting point and high doses. Nanosuspension technology can also be used for drugs which are insoluble in both water and organic solvents. Hydrophobic drugs such as naproxen, clofazomine, bupravaquone, nimesulide, mitotane, amphotericin B, omeprazole. Nanosuspensions contain a pure poorly water soluble drug of nano size range (1-1000 nm) in dispersion. Nanosuspension is submicron colloidal dispersion of pure particles of drug stabilized by surfactants. Nanosuspension consists of pure poorly water soluble drug without any matrix material suspended in dispersion [7].

**Potential Benefits of Nanosuspension [8]**

1. Reduced particle size, increased drug dissolution rate, increased rate and extent of absorption, increased bioavailability of drug, area under plasma time curve, onset time, peak drug level, reduced variability, reduced fed/fasted effects.
2. Nanosuspensions can be used for compounds that are water insoluble but which are soluble in oil. On the other hand, Nanosuspensions can be used in contrast with lipid systems, successfully formulate compounds that are insoluble in both water and oils.
3. Nanoparticles can adhere to the gastrointestinal mucosa, prolonging the contact time of the drug and thereby enhancing its absorption.
4. A pronounced advantage of Nanosuspension is that there are many administration routes for Nanosuspensions, such as oral, parenteral, pulmonary, dermal and ocular.
5. Nanosuspension of nanoparticles (NPs) offers various advantages over conventional ocular dosage forms, including reduction in the amount of dose, maintenance of drug release over a prolonged period of time, reduction in systemic toxicity of drug, enhanced drug absorption due to longer residence time of nanoparticles on the corneal surface, higher drug concentrations in the infected tissue, suitability for poorly water-soluble drugs and smaller particles are better tolerated by patients than larger particles, therefore nanoparticles may represent auspicious drug carriers for ophthalmic applications.
6. Nanosuspension has low incidence of side effects by the excipients.
7. Nanosuspensions overcome delivery issues for the compounds by obviating the need to dissolve them, and by maintaining the drug in a preferred crystalline state of size sufficiently small for pharmaceutical acceptability
8. Increased resistance to hydrolysis and oxidation, increased physical stability to settling.
9. Reduced administration volumes; essential for intramuscular, subcutaneous, ophthalmic use.

**Methods of Preparation of Nanosuspension**

Mainly there are two methods for preparation of Nanosuspensions. The conventional methods of precipitation (Hydrosols) are called 'Bottom uptechnology'. The 'Top Down Technologies' are the disintegration methods and are preferred over the precipitation methods. The 'Top Down Technologies' include Media Milling (Nanocrystals), High Pressure Homogenization in water (Dissocubes), High Pressure Homogenization in non aqueous media (Nanopure) and combination of Precipitation and High-Pressure Homogenization (Nanoedege) [7].

**1. Bottom Up Technology**

The time period of "Bottom up technology" way that one begins from the molecular degree, and goes by way of molecular organization to the arrangement of a strong molecule.

**Table 1:** Marketed Formulated Nanosuspension

| Product | Drug compound | Indication | Company |
|---|---|---|---|
| Emend | Aprepitant | Antiemetic | Merck |
| TriCor | Fenofibrate | Antiemetic | Merck |
| Megace | Fenofibrate | Hypochole steremic | Abbott |
| Triglide | Fenofibrate | Hypochole steremic | First Horizon Pharma |
| Azitral | Azitromycin | Anti bacterial | Sun Pharma |
| Cesamet | Nabilone | Antiemetic | lilly |
| Rapamune | Sirolimus | Immuno suppressant | Wyeth |

That we are talking about established precipitation approaches by lowering the solvent excellent, for illustration, by means of pouring the solvent right into a nonsolvent or altering the temperature or a combo of each. Precipitation is a classical process in pharmaceutical chemistry and technology [8].

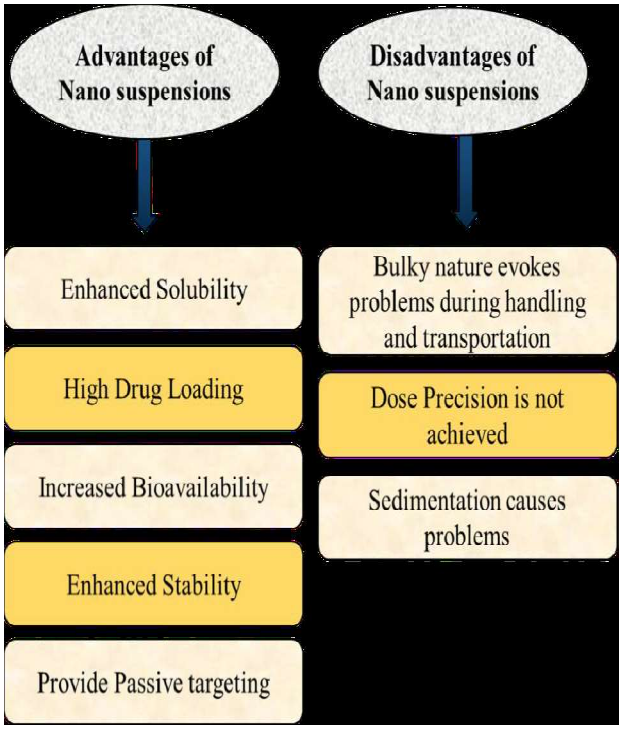


**Figure 1 :** Advantages and disadvantages of Nanosuspension

**Advantages**

1. Use of easy and low cost apparatus and,
2. Bigger saturation solubility is the advantage for precipitation manner in comparison to different methods of Nanosuspension guidance.

**Disadvantages**

1. Precipitation system is no more material to medications which are inadequately solvent in fluid and non-watery media. In this system, the medication goals to be dissolvable in at least one dissolvable which is miscible with non-solvent.
2. Prevent crystal progress due to Ostwald ripening being brought about via unique saturation solubilities in the vicinity of otherwise sized particles.

**2. Top Down Technology**

The top down technologies include:

(a) Media milling
(b) High pressure homogenization
(c) Emulsion diffusion method
(d) Melt emulsification method

**Media Milling**

Liversidge et al. had a patent on Nano crystal technological know-how. On this technique, medicines are subjected to media processing for nanoparticle generation. Impact of impaction between the processing media and medications gives fundamental vigour for disintegration of the microparticulate method into nanoparticles. On this system, the council of processing is accused of the processing media including medication, stabilizer, and water compatible buffer, which is turned around at an awfully high shear cost to produce suspension. Deposits deserted in the completed item are a principal situation of this approach [9].

**High Pressure Homogenization**

This method involve the next three steps: First, tranquilize powders are scattered in a stabilizer solution to kind pre suspension; after that, pre suspension is homogenized with the aid of high strain homogenizer at a low stress in many instances for pre milling; and subsequently homogenized at an excessive pressure for 10 to 25 cycles unless the Nanosuspensions are formed with preferred measurement.

**Emulsion Diffusion Method**

Apart from the usage of emulsion as drug offering auto they can likewise be utilized as

formats to provide Nanosuspension. The utilization of emulsions as layouts is material for those medications which might be dissolvable in both volatile natural solvent and incompletely water-miscible dissolvable. Such solvents can be utilized in light of the fact that the scattered period of the emulsion. A natural dissolvable or mix of solvents stacked with the medication is scattered in the watery fragment containing reasonable surfactants with blending to type an emulsion.

**Melt Emulsification Method**

In this procedure medication is scattered in the watery arrangement of stabilizer and warmed over the liquefying variable of the medication and homogenized to give an emulsion. During this strategy, the example holder was enwrapped with a warming tape outfitted with temperature controller and the temperature of emulsion used to be kept up over the dissolving component of the medicationThe emulsion was then chilled off either gradually to room temperature or on an ice-tub [10].

**Pharmaceutical Application of Nanosuspension**

**1. Bioavailability Enhancement**

The poor oral bioavailability of the drug may be due to poor solubility, poor permeability or poor stability in the gastrointestinal tract (GIT). Nanosuspensions resolve the problem of poor bioavailability by solving the twin problems of poor solubility and poor permeability across the membrane. The oral administration of naproxen nanoparticles lead 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 an aprox tablets [11]. Oral administration of the gonadotroph ininhibitor Danazol as a nanosuspension leads to an absolute bioavailability of 82.3 and the conventional dispersion (Danocrine) only to 5.2% [12]. A nanosuspension of Amphotericin B developed by Kayser*et al.* showed a significant improvement in its oral absorption in comparison with the conventional commercial formulation [13]. 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. This was due to the faster dissolution (90% in 20 min) of the lyophilized nanosuspension powder when compared with the dissolution from a coarse powder (15% in 20 min).[13]showed a significant improvement in the dissolution rate (65% in 10 min) of Ibuprofen made as a lyophilized nanosuspension powder as compared with (<15 in 10 min) that of the micronized drug [14]. The ocular anti-inflammatory activity of Ibuprofen-Eudragit RS100 nanosuspensions was greatly improved when compared with an aqueous solution of Ibuprofen lysinate. Further, the aqueous humor drug concentration was significantly higher in groups treated with Ibuprofen-Eudragit RS when compared with the Ibuprofen- treated group. Langutth*et al.* showed a nearly 5.7- fold increase in the AUC for spiranolactone, a low solubility drug made as a solid lipid nanoparticle. Dissocubes type showed about 3.3-fold increase in the AUC [15]. They observed that the improvement in drug solubility in the intestine as well as in the dissolution rate of spiranolactone is the most likely mechanism for the increase in the AUC.

**2. Intravenous Administration**

The parenteral route of administration provides a quick onset of action, rapid targeting, and reduced dosage of the drug, it is the preferred route for drugs undergoing first-pass metabolism and those that are not absorbed in the GIT or degraded in the GIT. One of the important applications of nanosuspension technology is the formulation of intravenously administered products. IV administration results in several advantages, such as administration of poorly soluble drugs without using a higher concentration of toxic co-solvents, improving the therapeutic effect of the drug available as conventional oral formulations and targeting the drug to macrophages and the pathogenic microorganisms residing in the macrophages. Peters *et al.* prepared clofazimine nanosuspensions for IV use and showed that the drug concentrations in the liver, spleen, and lungs reached a comparably higher level, well in excess of the minimum inhibitory concentration for most *Mycobacteriumavium* strains [16]. Further, the study also indicates that the nanoparticle formulation accumulated more in the liver than the liposomal formulation, indicating a better targeting potential of the nanoparticle formulation. Injectable nanosuspensions of poorly soluble drug tarazepide have been prepared to overcome the limited success achieved using conventional solubilization techniques, such as use of surfactants, cyclodextrins, etc., to improve bioavailability [17]. A stable intravenously

injectable formulation of omeprazole has been prepared to prevent the degradation of orally administered omeprazole [18].

### 3. Pulmonary Administration

Aqueous nanosuspensions 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 lungs. They also increase adhesiveness and thus cause a prolonged residence time. Budenoside drug nanoparticles were successfully nebulized using an ultrasonic nebulizer [19]. The pharmacokinetics of the nebulized nanocrystal budenoside suspension showed comparable AUC, higher $C_{max}$ and lower $T_{max}$ as that of the pulmicort respules. Other applications include ocular delivery of the drugs as nanosuspensions to provide a sustained release of drug. Pignatello *et al.* prepared Eudragit retard nanosuspensions of cloricromene for ocular delivery [20]. They observed that the drug showed a higher availability in rabbit aqueous humor and the formulation appeared to offer a promising means of improving the shelf-life and the bioavailability of this drug after ophthalmic application.

### 4. Drug targeting

Nanosuspensions can also be used for targeting as their surface properties and changing of the stabilizer can easily alter the *in vivo* behavior. The drug will be up taken by the mononuclear phagocytic system to allow regional-specific delivery. This can be used for targeting anti-mycobacterial, fungal or leishmanial drugs to the macrophages if the infectious pathogen is persisting intra-cellularly [21]. Kayser formulated a nanosuspension of Aphidicolin to improve drug targeting against leishmania-infected macrophages. He stated that the drug in the conventional form had an effective concentration (EC 50) of 0.16 mcg/ml whereas the nanosuspension formulation had an enhanced activity with an EC (50) of 0.003 mcg/ml. Scholar [22] showed an improved drug targeting to the brain in the treatment of toxoplasmic encephalitis in a new murine model infected with *Toxoplasmagondii* using a nanosuspension formulation of Atovaquone [12].

### 5. 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." 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 [23]. The adhesiveness of the nanosuspensions not only helps to improve bioavailability but also improves targeting of the parasites persisting in the GIT, e.g., *Cryptosporidium parvum*. Bupravaquone nanosuspensions have been reported demonstrate an advantage in TRC-alpha-deficient mice infected with *Cryptosporidiumparvum* oocytes. The bioadhesion can also be improved by including a mucoadhesive polymer in the formulation.

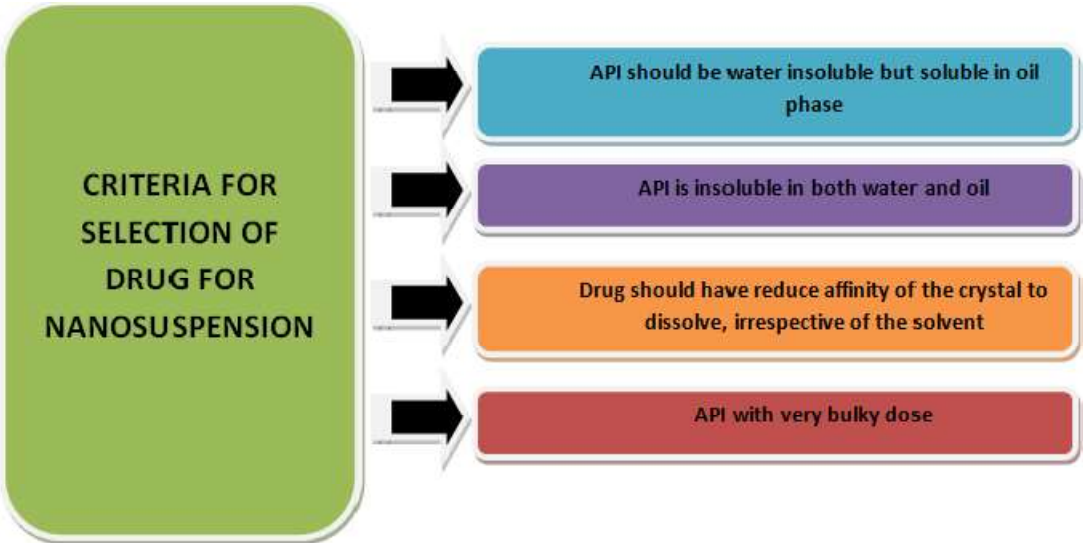


**Figure 2:** Criteria for selection of drug for nanosuspension

**Table 2:** Some marketed formulation with different polymer

| Sr. No. | Approach | Drug | Polymer | Outcome | Reference |
|---|---|---|---|---|---|
| 1 | Nanosuspension | Moxifloxacin Hydrochloride | PLA | Improve precorneal residence time and ocular bioavailability | 24 |
| 2 | Nanosuspension | KetotifenFumarate | PLGA | Increase drug release and Permeability through bovine cornea | 25 |
| 3 | Nanosuspension | Sulfacetamide | Eudragit @RL100 | Enhanced Encapsulation efficiency (40%) with good stability | 26 |
| 4 | Nanosuspension | Terbutalin sulphate | Poloxame r 188 | The effective cumulative drug release until 8 hours compared to the other formulations | 27 |
| 5 | Nanosuspension | Rosuvastatin calcium | PVP k90 | It approach in the delivery of poorly water soluble drug by oral route in a simple and effective way | 28 |

## CONCLUSION

Nanosuspension solved poor bioavailability problem of hydrophobic drugs and drugs which are poorly soluble in aqueous and organic solutions. Productions techniques such as media milling and high pressure homogenizer are used for large scale production of Nanosuspensions. Nanosuspensions can be administered through oral, parenteral, pulmonary, ocular and topical routes. Since nanotechnique is simple, less requirements of excipients, increased dissolution velocity and saturation solubility many poor bioavailability drugs are formulated in Nanosuspension form [23].

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