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*Review Article*

# Nanosuspension: A novel approch to enhance solubility of poorly water soluble drugs - A review

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## Abstract

Solubility is the crucial factor for drug effectiveness, independence of the route of administration. Large proportions of newly discovered drugs are water insoluble & therefore poorly bioavailable contributing to desert development effort. Nanosuspensions have emerged as a promising strategy for the efficicent delivery of hydrophilic drugs because of their versatile features &unique advantages. The reduction of drug particles into submicron range leads to a significant increase in dissolution rate & therefore enhances bioavailability. Nanosuspension contains submicron colloidal dispersion of the pharmaceutical active ingredient particles in a liquid phase stabilised by surfactant. Nanosuspensions can be delivered by oral & non-oral route of administration. Study is focused on various methods of preparation with advantages & disadvantages, characterization properties, applications.

## 1. Introduction [3,10]

A nanosuspension is a submicron colloidal dispersion of drug particles. A pharmaceutical nanosuspension is defined as a very finely colloid, biphasic, dispersed, solid drug particles in aqueous vehicle, size below 1µm, without any matrix material, stabilised by surfactants & polymers, prepared by suitable methods for drug delivery applications, through various routes of administration like oral, topical, parenteral, ocular & pulmonary routes. A nanosuspension not only solves the problem of poor solubility & bioavailability but also alters the pharmacokinetics of drug & that improves safety & efficacy. Nanosuspension formulation approach is most suitable for the compounds with high log P value, high melting point & dose. Nanosuspension has been reported to enhance adsorption & bioavailability it may help to reduce the dose of the convectional oral dosage forms. Drug particle size reduction leads to an increase in surface area & consequently in the rate of dissolution as described by Nernst-Brunner & Levich modification of the Noyes- Whitney equation. In addition, an increase in saturation solubility is postulated by particle size reduction due to an increase dissolution pressure explained by the Ostwald-Freundlich equation. Depending on the production technique applied changes in crystalline structure of the drug particles may also occur. An increasing amount of amorphous drug fraction could induce higher saturation solubility. Furthermore, a general adhesiveness to tissue has been described for nanoparticles. The aim of present study were to evaluate whether providing drug in the form of a nanosuspensions will enhance drug flux resulting from higher transmembraneous concentration gradients.

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.

**1.1 Advantages of Nanosuspension:**

1) Increase in the dissolution velocity and saturation solubility of the drug
2) Improved biological performance
3) Ease of manufacture and scale-up
4) Long-term physical stability
5) Versatility
6) Increase in the oral absorption
7) Improved dose proportionality**.**
8) Its general applicability to most drugs & simplicity
9) It can be applied for poorly water sluble drugs.
10) It can be given by any route.
11) Reduced tissue irritation in case of subcutaneous/intramuscular administration.
12) Rapid dissolution & tissue targeting can be achieved by IV route of administration.
13) Oral administration of nanosuspension provide rapid onset, reduced fed/fasted ratio & improved bioavailability.
14) The absorption form absorption window can be increased, due to reduction in the particle size.
15) Higher bioavailability & more consistent dosing in case of ocular administration & inhalation delivery.
16) Drug with higher log P value can be formulated as nanaosuspensions to increase the bioavailability of such drugs.
17) Improvement in biological performance due to high dissolution rate & saturation solubility of the drugs.
18) Nanosuspensions can be incorporated in tablets, pellets, hydrogel & suppositories are suitable for various routes of administration.
19) Increasing the amorphous fraction in the particles leading to a potential change in the crystalline structure & higher solubility.
20) Possibility of surface-modification of nanosuspension for site specific delivery.
21) Possibility of large-scale production, the prerequisite for the introduction of delivery system to the market.

**1.2 Disadvantages for Nanosuspension Drug delivery system**

1) Physical stability, sedimentation & compaction can cause problems.
2) It is bulky sufficient care must be taken during handling & transport.
3) Improper dose.
4) Uniform & accurate dose cannot be achieved

## 2. Method of Preparation of Nanosuspensuions:[3-10]

Mainly there are two methods for preparation of Nanosuspensions. The conventional methods of precipitation (Hydrosols) are called 'Bottom up technology'. 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).

1) Bottom-up technology
2) Top-down technology

**2.1 Bottom-up technology [11-12]**

The term "Bottom-up technology" means that one starts from the molecular level, and goes via molecular association to the formation of a solid particle. That means that we are discussing classical precipitation techniques by reducing the solvent quality, for example, by pouring the solvent into a nonsolvent or changing the temperature or a combination of both. Precipitation is a classical technique in pharmaceutical chemistry and technology.

**2.1.1 Advantage**

1) Use of simple and low cost equipment.
2) Higher saturation solubility is the advantage for precipitation compared to other methods of Nanosuspension preparation.

**2.1.2 Disadvantages**

1) The drug needs to be soluble in at least one solvent (thus excluding all new drugs that are simultaneously poorly soluble in aqueous and in organic media).
2) The solvent needs to be miscible with at least one nonsolvent.

3) Solvent residues need to be removed, thus increasing production costs.
4) It is an Iittle bit tricky to preserve the particle character (i.e. size, especially the amorphous fraction). In general, it is recommended that a second consecutive process has to be performed for particle preservation that is spraydrying or lyophilisation.

**2.2 Top-Down Technology**

The top down technologies include

a) Media milling
b) High pressure homogenization

**a) Media Milling[20]**

Nanosuspensions are produced by using high-shear media mills or pearl mills. The mill consists of a milling chamber, milling shaft and a recirculation chamber. An aqueous suspension of the drug is then fed into the mill containing small grinding balls/pearls. As these balls rotate at a very high shear rate under controlled temperature, they fly through the grinding jar interior and impact against the sample on the opposite grinding jar wall. The combined forces of friction and impact produce a high degree of particle size reduction. The milling media or balls are made of ceramic-sintered aluminium oxide or zirconium oxide or highly cross-linked polystyrene resin with high abrasion resistance. A planetary ball mill (PM100 andPM200; Retsch GmbH and Co., KG, Haan, Germany) is one example of equipment that can be used to achieve a grind size below 0.1 μm. A Nanosuspension of Zn-Insulin with a mean particle size of 150 nm was prepared using the wet milling technique.

**Advantages**

1. Simple technology
2. Low-cost process regarding the milling itself
3. Large-scale production possible to some extent (batch process).

**Disadvantages**

1. Potential erosion from the milling material leading to product contamination.
2. Duration of the process not being very production friendly.
3. Potential growth of germs in the water phase when milling for a long time.
4. Time and costs associated with the separation procedure of the milling material from the drug nanoparticle suspension, especially when producing parenteral sterile products.

**b) High Pressure Homogenization**

- **Dissocubes[23-26]**

In this case, the suspension of the drug is made to pass through a small orifice that result in a reduction of the static pressure below the boiling pressure of water, which leads to boiling of water and formation of gas bubbles. When the suspension leaves the gap and normal air pressure is reached again, the bubbles implode and the surrounding part containing the drug particles rushes to the center and in the process colloids, causing a reduction in the particle size. Most of the cases require multiple passes or cycles through the homogenizer, which depends on the hardness of drug, the desired mean particle size and the required homogeneity. To produce a Nanosuspension with a higher Concentration of solids, it is preferred to start homogenization with very fine drug particles, which can be accomplished by pre-milling. The major advantage of high- pressure homogenization over media milling is that it can be used for both diluted as well as concentrated suspensions and also allows aseptic production.

- **Nanopure[27-28]**

Nanopure is suspensions homogenized in water-free media or water mixtures. In the Dissocubes technology,the cavitation is the determining factor of the process.But, in contrast to water, oils and oily fatty acids have very low vapour pressure and a high boiling point. Hence,the drop of static pressure will not be sufficient enough to initiate cavitation. Patents covering disintegration of polymeric material by high- pressure homogenization mention that higher temperatures of about 800C promoted disintegration, which cannot be used for thermolabile compounds. In nanopure technology, the drug suspensions in the non- aqueous media were homogenized at 00C or even below the freezing point and hence are called "deep-freeze" homogenization.

- **Nanoedge[29]**

The basic principles of Nanoedge are the same as that of precipitation and homogenization. A combination of these techniques results in smaller particle size and better stability in a shorter time. The major drawback of the precipitation

technique, such as crystal growth and longterm stability, can be resolved using the Nanoedge technology. In this technique, the precipitated suspensionis further homogenized; leading to reduction in particle size and avoiding crystal growth. Precipitation is performed in water using water-miscible solvents such as methanol, ethanol and isopropanol. It is desirable to remove those solvents completely, although they can be tolerated to a certain extent in the formulation. For an effective production of Nanosuspensions using the Nanoedge technology, an evaporation step can be included to provide a solvent-free modified starting material followed by high-pressure homogenization.

**2.3 Emulsion Diffusion Method [30]**

Apart from the use of emulsion as drug delivering vehicle they can also be used as templates to produce Nanosuspension. The use of emulsions as templates is applicable for those drugs that are soluble in either volatile organic solvent or partially water-miscile solvent.Such solvents can be used as the dispersed phase of the emulsion. An organic solvent or mixture of solvents loaded with the drug is dispersed in the aqueous phase containing suitable surfactants with stirring to form an emulsion. The obtained emulsion was further homogenized by high pressure homogenization. After homogenization cycles the emulsion was diluted with water, homogenized by homogenizer to diffuse the organic solvent and convert the droplets into solid particles. Since one particle is formed in each emulsion droplet, it is possible to control the particle size of the Nanosuspension by controlling the size of the emulsion optimizing the surfactant composition increases the intake of organic phase and ultimately the drug loading in the emulsion. Originally methanol, ethanol, ethyl acetate chloroform are used as a organic solvents.

**Advantages**

- Use of specialized equipment is not necessary.
- Particle size can easily be controlled by controlling the size of the emulsion droplet.
- Ease of scale-up if formulation is optimized properly.

**Disadvantages**

- Drugs that are poorly soluble in both aqueous and organic media cannot be formulated by this technique.
- Safety concerns because of the use of hazardous solvents in the process.
- Need for diultrafiltration for purification of the drug Nanosuspension, which may render the process costly.
- High amount of surfactant/stabilizer is required as compared to the production techniques described earlier.

**2.4 Micro emulsion Template [31]**

This technique follows an organic solvent or mixture solvent loaded with the drug dispersed in an aqueous phase containing suitable surfactants to form an emulsion. The organic phase is then evaporated under reduced pressure to make drug particles precipitate instantaneously to form the Nanosuspension which is stabilized by surfactants. Another method makes use of partially water-miscible solvents such as butyl lactate, benzyl alcohol and triacetin as the dispersed phase instead of hazardous solvents.

**Advantages**

- Use of specialized equipment is not necessary.
- Particle size can easily be controlled by controlling the size of the emulsion droplet.
- Ease of scale-up if formulation is optimized properly.

**Disadvantages**

- Drugs that are poorly soluble in both aqueous and organic media cannot be formulated by this technique.
- Need for diultrafiltration for purification of the drug Nanosuspension, which may render the process costly.
- High amount of surfactant/stabilizer is required as compared to the production techniques described earlier.

**2.5 Supercritical Fluid Method [29-31]**

Supercritical fluid technology can be used to produce nanoparticles from drug solutions. The various methods attempted are rapid expansion of supercritical solution process (RESS), supercritical anti-solvent process and precipitation with compressed anti-solvent process (PCA).The RESS involves expansion of the drug solution in supercritical fluid through a nozzle, which leads to loss of solvent power of the supercritical fluid resulting in precipitation of the drug as fine particles. Young *et al* prepared cyclosporine nanoparticles in the size range of 400-700 nm using this process. In the PCA method, the drug solution is atomized into a chamber containing compressed $CO_2$. As the solvent is removed, the solution gets supersaturated and thus precipitates as fine crystals. The supercritical anti- solvent process uses a supercritical fluid in which a drug is poorly soluble and a solvent for the drug that is also miscible with the supercritical fluid. The drug solution is injected into the supercritical fluid and the solvent gets extracted by the supercritical fluid and the drug solution gets supersaturated. The drug is then precipitated as fine crystals.

**Disadvantages**

- Use of hazardous solvents and use of high proportions of surfactants and stabilizers as compared with other techniques,
- Particle nucleation overgrowth due to transient high super saturation, which may also result in the development of an amorphous form or another undesired polymorph.

**2.6 Melt emulsification method [33-34]**

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. The emulsion was then cooled down either slowly to room temperature or on an icebath.

**Advantage**

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

**Dry Co-Grinding [34]**

Recently, Nanosuspensions can be obtained by dry milling techniques. Successful work in preparing stable Nanosuspensions using dry-grinding of poorly soluble drugs with soluble polymers and copolymers after dispersing in a liquid media has been reported. Many soluble polymers and co-polymers such as PVP, polyethylene glycol (PEG), hydroxypropyl methylcellulose (HPMC) and cyclodextrin derivatives have been used.

## 3. Formulation consideration: [3-10]

**3.1 Stabilizer**

The main function of a stabilizer is to wet the drugparticles thoroughly, and to prevent ostwald's ripening and agglomeration of Nanosuspensions in order to yield a physically stable formulation by providing steric or ionic barrier. The type and amount of stabilize has a pronounced effect on the physical stability and in vivo behavior of Nanosuspension. Stabilizers that have been used so far are poloxomers, polysorbate, cellulosics, povidones, and lecithins.Lecithin is the stabilizer of choice if one intends to develop a parentally acceptable and autoclavable nanosuspension.

**3.2 Organic Solvent**

Organic solvents are used in the formulation of Nanosuspension if emulsions or micro emulsions are used as a template. The pharmaceutically acceptable less hazardous water miscible solvent, such as methanol,ethanol, chloroform, ispropanol, and partially water miscible solvents ethyl acetate, ethyl formate, butyl lactate, triacetin, propylene carbonate, benzyl alcohol,are preferent in the formulation over the conventional hazardous solvents, such as dichloromezthane.

**3.3 Co-Surfactants**

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

**3.4 Other additives**

Nanosuspensions may contain additives such as buffers, salts, polyols, osmogent and cryoprotectant.

## 4. Post-production processing [3-10]

Post-production processing of Nanosuspensions becomes essential when the drug candidate is highly susceptible to hydrolytic cleavage or chemical degradation. Processing may also be required when the best possible stabilizer is not able to stabilize the Nanosuspension for a longer period of time or there are acceptability restrictions with respect to the desired route. Considering these aspects,techniques such as lyophilization or spray drying may be employed to produce a dry powder of nano-sized drug particles. Rational selection has to be made in these unit operations considering the drug properties and economic aspects. Generally, spray drying is more economical and convenient than lyophilization.

**4.1 Characterization of Nanosuspension:[3-10]**

***In-vitro* evaluations**

**Color, Odor, Taste**

These characteristics are especially important in orallyadministered formulation. Variations in taste, especially of active constituents, can offered be attributed to changes in particle size, crystal habit and subsequent particle dissolution.

Changes in color, odor and taste can also indicate chemical instability.

**Particle Size Distribution**

Particle size distribution determines the physiochemical behavior of the formulation, such as saturation solubility, dissolution velocity, physical stability, etc. The particle size distribution can be determined by photon correlation spectroscopy (PCS), laser diffraction (LD) and coulter counter multisizer. The PCS method can measure particles in the size range of 3 nm to 3µm and the LD method has a measuring range of 0.05-80µm. The coulter counter multisizer gives the absolute number of particles, in contrast to the LD method, which gives only a relative size distribution. For IV use, particles should be less than 5µm, considering that the smallest size of the capillaries is 5-6 µm and hence a higher particle size can lead to capillary blockade and embolism.

**Zeta Potential**

Zeta potential is an indication of the stability of the suspension. For a stable suspension stabilized only by electrostatic repulsion, a minimum zeta potential of ±30mV is required whereas in case of a combined electrostatic and steric stabilizer, a zeta potential of ±20 mV would be sufficient.

**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 calorimetry or differential thermal analysis can be utilized. 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.

**Dissolution Velocity and Saturation Solubility**

Nanosuspensions have an important advantage over other techniques, that it can increase the dissolution velocity as well as the saturation solubility. These two parameters should be determined in various physiological solutions. The assessment of saturation solubility and dissolution velocity helps in determining the *in vitro* behavior of the formulation. Böhm *et al.* reported an increase in the dissolution pressure as well as dissolution velocity with a reduction in the particle size to the nanometer range.Size reduction leads to an increase in the dissolution pressure.

**Density**

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

**pH Value**

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

**Droplet Size**

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

**Viscosity Measurement**

The viscosity of lipid based formulations of several compositions can be measured at different shear rates at different temperatures using Brookfield type rotary viscometer. The sample room of the instrument must be maintained at 370C by a thermo bath and the samples, for the measurement are to be immersed in it.

**Stability of Nanosuspension**

The high surface energy of nanosized particles induces agglomeration of the drug crystals. The main function of the stabilizer is to wet the drug particles thoroughly to prevent Ostwald ripening and agglomeration of the Nanosuspension and form a physically stable formulation by providing a steric or an ionic barrier. Typical examples of stabilizers used in Nanosuspensions are cellulosics,poloxamer, polysorbates, lecithin, polyoleate and povidones. Lecithin may be preferred in developing parenteral Nanosuspension.

***In-Vivo* Biological Performance**

The establishment of an in-vitro/in-vivo correlation andthe monitoring of the in-vivo performance of the drug is an essential part of the study, irrespective of the route and the delivery system employed. It is of the utmost importance in the case of intravenously injected

Nanosuspensions since the in-vivo behavior of the drug depends on the organ distribution, which in turn depends on its surface properties, such as surface hydrophobicity and interactions with plasma proteins In fact, the qualitative and

quantitative composition of the protein absorption pattern observed after the intravenousinjection of nanoparticles is recognized as the essential factor for organ distribution. Hence, suitable techniques have to be used in order to evaluate the surface properties and protein interactions to get an idea of in vivo behavior. Techniques such as hydrophobic interaction chromatography can be used to determine surface hydrophobicity, whereas 2-D PAGE can be employed for the quantitative and qualitative measurement of protein adsorption after intravenous injection of drug nanosuspensions in animals.

**Evaluation for surface-modified Nanosuspension**

- Surface hydrophilicity
- Adhesion properties
- Interaction with body proteins

## 5. Applications of nanosuspensions:[3-10]

### 5.1 Oral

Oral drug delivery is the most widely preferred route of administration of drugs. But, some drugs possess the problem of limited bioavailability due to poor solubility and absorption which ultimately reduces its efficacy. In such cases, Nanosuspension can solve the problem as it helps in improving the dissolution rate and absorption due to increased surface area and enhanced adhesiveness. Nanosuspension can lead to increased mucoadhesion which can increase gastrointestinal transit time and lead to increased bioavailability. The enhancement in oral bioavailability can be attributed to increased surface area, saturation solubility and the adhesiveness of the drug Nanosuspension. Taste masking of particulate system is also easily possible.

### 5.2 Parenteral

Nanosuspensions can be used to transform poorly soluble non-injectable drugs into a formulation suitable for intravenous administration. Although the production of Nanosuspension for parenteral use is critical, current developments in this technology have proved its utility as injectable formulations. The methods used for preparation of Nanosuspension are now precisely controlled, and are able to produce uniform particles with better control over maximum particle size. Various research reports are available which emphasize the applicability of Nanosuspensions for parenteral administration.

### 5.3 Ocular delivery

Nanosuspension can prove to be a boon for drugs that exhibit poor solubility in lachrymal fluids.Nanosuspensions represent an ideal approach for ocular delivery of hydrophobic drugs due to their inherent ability to improve saturation solubility of drugs. Kassem et al have developed Nanosuspension delivery system for certain glucocorticoid drugs.

### 5.4 Pulmonary

Nanosuspensions can be advantageous for delivering drugs that exhibit poor solubility in pulmonary secretion.Currently available approaches for pulmonary delivery such as aerosols or dry powder inhalers possess certain disadvantages such as limited diffusion at required site, less residence time etc, which can be overcome by Nanosuspensions. Fluticasone and budesonide have been successfully formulated as Nanosuspension for pulmonary Delivery.

### 5.4 Dermal

The nanocrystalline form possesses increased saturation solubility resulting in enhanced diffusion of the drug into the skin. Nanocrystals also exhibit various properties such as increased penetration into a membrane, enhanced permeation and bioadhesiveness which could be very useful for dermal application.

### 5.5 Targeting

The uptake of drug nanoparticles depends on their particle size. By changing the surface properties of the nanoparticles, their *in vivo* behavior can be altered and can be used as targeted delivery system. The phagocytotic uptake of nanocrystals can be avoided by preparing stealth nanocrystals or by preparing smart crystals i.e. drug particles below particle size of 100nm, which can be used as a targeted drug delivery system. Due to method simplicity, development of nanosuspension is a commercially viable option for targeted delivery. Mucoadhesive nanosuspension was reported for targeting of Cryptosporidium parvum. The surface properties of particles such as surface hydrophobicity, charge, presence and concentration of certain functional groups determine its organ distribution.Thus, Tween 80 coated nanocrystals can be used for brain targeting.

### 5.6 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.

**Marketed products:**

**Table 1: Marketed products of nanosuspension**

| Product | Drug | Indication | Company |
|---|---|---|---|
| Triglide | Fenofibrate | Treatment of hypercholestero lemia | First horizon pharmaceutical |
| Tricor | Fenofibrate | Treatment of hypercholestero lemia | Abbott |
| Megace | Megestrol aceyate | Appetite stimulant | PAR-Pharma ceutical |
| Rapamune | Sirolims | Immunosuppress | Wyeth |

## 6. Conclusion

Nanosuspensions appear to be unique & yet commercially viable approach to combating problems 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. The dissolution problems of poorly water soluble drugs have been largely solved to improve drug absorption & bioavailability. Nanosuspension technology can be combined with traditional dosage forms: tablets, capsules, pellets, & can be used for parenteral products. To take advanateg of nanosuspension drug delivery, simple formulation technologies & variety applications, nanosuspensions will continue to be interest as oral formulations & non-oral administration develop in the future.

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