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# A Review on Nanosuspension: A Promising Alternative Novel Approach of Biphasic Liquid Dosage Form for The Delivery of Hydrophobic Drugs

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**ABSTRACT**

Nanotechnology is the science that deals with the process that occurs at the molecular level and of nano-length scale size. Nanosuspensions are coming under nanotechnology. They are important carriers to develop novel drug formulations. Nanoscales for drug delivery have gained much interest as they ensure safety, therapeutic efficiency, technical simplicity, and cost-effectiveness. The major problem faced in oral drug formulation is the erratic bioavailability and poor aqueous solubility, mainly drugs coming under the BCS class 2 category, which exhibits dissolution rate-limited bioavailability, the uptake of these drugs cannot complete within the time from the absorption site. So, this problem is overcome by reducing the drug particle into the submicron range leading to increased bioavailability. Nanosuspensions have proven to be a better alternative and attractive novel approach compared to other conventional formulations. They have emerged as a promising strategy for the efficient delivery of hydrophobic drugs because of their versatile features and unique advantages.

## INTRODUCTION

The oral route is the most convenient and commonly employed route for drug delivery due to its ease of administration, high patient compliance, cost-effectiveness, least sterility constraints, and flexibility in the design of dosage form. About 50% of the drug compounds are facing the major challenge with the design of oral dosage forms that lies with their poor bioavailability. In recent years, much attention has been focused on nanotechnology for delivering formulations, which is being applied to enhance the solubility & bioavailability of hydrophobic drugs [(1)]. The nano sizing of the drug has the potential to increase surface area, therefore, enhance solubility, rate of dissolution, oral bioavailability, more rapid onset of therapeutic action. Nanotechnology is one of the most important research and development areas in modern science, an emerging field in all areas of science, engineering, and technology. It is a novel interdisciplinary area of comprehensive research that combines medicine and other life sciences[(2)].

The formulation of poorly water-soluble drugs has always been a challenging problem. They show many problems while formulated in conventional dosage forms. One of the critical problems associated with poorly soluble drugs is too low bioavailability and erratic absorption[(3)]. There are several formulation approaches to resolve the problems of low solubility and low bioavailability which include micronization, solubilization using co-solvents, use of permeation enhancers, oily solutions, surfactant dispersions, salt formation, and precipitation techniques. But these techniques show limitations to the drugs which are not soluble in both aqueous and organic solvents, hence there is a need for some different and simple approach to tackle the formulation problems to improve their efficacy and to optimize the therapy concerning pharmacoeconomics[(4)]. Nanosuspension technology can be used to solve the problems associated with various approaches described earlier and the delivery of poorly water-soluble and poorly water and lipid-soluble drugs.

A pharmaceutical nanosuspension is defined as very finely colloid, biphasic, dispersed solid drug particles in an aqueous vehicle, a size below 1 μm stabilized by surfactants and polymers prepared by suitable methods for drug delivery applications[(5,6)]. The particle size distribution of the solid particles in nanosuspensions is usually less than one micron with an average particle size ranging between 200 and 600 nm [(5,6)]. It enhances absorption and bioavailability and helps to reduce the dose of conventional oral dosage forms. Drug particle size reduction leads to an increase in the surface area and consequently the rate of dissolution

as described by the Noyes Whitney equation[4]. In nanosuspension technology, the drug is maintained in the required crystalline state with reduced particle size, leading to an increased dissolution rate. Nanosuspension not only solves the problem of poor solubility and poor bioavailability but also alters the pharmacokinetics of the drug and improves the drug's safety and efficacy [2].

**ADVANTAGES[6,7,8]**

a) The most cost-effective and useful for poorly soluble drugs.

b) Physically more stable than liposome.

c) Provide ease of manufacture and scale-up for large-scale production.

d) Rapid dissolution and tissue targeting.

e) Higher bioavailability especially in ocular and inhalational drug delivery.

f) Improved dose proportionality.

**TABLE NO. 1: ADVANTAGES OF NANOSUSPENSIONS OVER CONVENTIONAL FORMULATIONS**

| **Route of administration** | **Disadvantage of conventional formulations** | **Advantage of nanosuspensions** |
|---|---|---|
| Oral | Slow onset of action/ poor absorption | Rapid onset of action/ improved solubility & bioavailability |
| Ocular | Low bioavailability/ lachrymal wash off | Higher bioavailability & dose consistency |
| Intravenous | Poor dissolution/ nonspecific action | Rapid dissolution/ tissue targeting |
| Intramuscular | Low patient compliance due to pain | Rapid tissue irritation |
| Inhalations | Low bioavailability due to low solubility | High bioavailability/ Rapid dissolution |

## SELECTION OF DRUG FOR NANOSUSPENSION[9]

- Water-insoluble but which are soluble in oil.
- High log P or API that is insoluble in both water and oils.
- Drugs with a reduced tendency of the crystal to dissolve, regardless of the solvent.
- API with a very large dose.

## PROPERTIES OF NANOSUSPENSIONS[9,10,11]

### a) 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. Molecules diffuse from the higher concentrated area around small particles (higher saturation solubility) to areas 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. The diffusion process of the drug from the small particles to the large particles leaves an area around the small particles that are not saturated anymore, consequently leading to the dissolution of the drug from the small particles and finally completes the disappearance of the small particles.

### b) Increase in Saturation Solubility and Dissolution Velocity of the drug:

Dissolution of the drug is increased due to an increase in the surface area of the drug particles from micrometers to the nanometer size. According to the Noyes-Whitney equation, dissolution velocity increases due to an increase in the surface area from micron size to particles of nanometer size.

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

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

**c) Internal Structure of Nanosuspensions:**

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

**d) Adhesiveness:**

As the particle size decreases the adhesive properties of the particles will be improved and thus improves oral delivery of the poorly soluble drug. There is a distinct increase in adhesiveness of ultra-fine powders compared to coarse powders.

**e) Crystalline state and morphology:**

The application of high pressures during the production of nanosuspensions was found to promote the amorphous state.

**FORMULATION CONSIDERATIONS IN NANOSUSPENSION[12,13,24]**

**TABLE NO. 2: FORMULATION CONSIDERATIONS**

| Excipients | Function | Example |
|---|---|---|
| Stabilizers | Wet the drug particles thoroughly, prevent Ostwald's ripening and agglomeration of nanosuspensions, providing a steric or ionic barrier. | Lecithins, Poloxamers, SLS, Povidone |
| Surfactants | To improve the dispersion by reducing the interfacial tension. They act as wetting or foaming agent | Tween 80 or span |
| Co surfactants | Influence phase behavior when microemulsions are used to formulate nanosuspension. | Bile salts, Dipotassium glycyrrhizinate, Transcutol, Ethanol, Isopropanol |
| Organic Solvent | Pharmaceutically acceptable, less hazardous solvent for the formulation of formulations. | Methanol, Ethanol, Chloroform, Isopropanol, Ethyl acetate, etc. |
| Other Additives | According to the requirement of the route of administration or the properties of drug moiety.6. | Buffers, salts, polyols, osmogens, cryoprotectants, etc. |

## PREPARATION TECHNIQUES

Two approaches are there used in the preparation of nanosuspension:-

- Bottom-up technology
- Top-down technology

In the bottom-up technique, molecules are dissolved in a solvent and precipitated by different methods such as solvent addition, spray freezing, evaporative precipitation, and liquid solvent change process. Top-down processes are mechanical processes that include milling and homogenization. Top-down processes are widely used. The mechanical processes have some drawbacks such as time consumption, more energy used, chances of impurities, inadequate control of particle size[14].

### 1. Bottom-up technology

**Nanoprecipitation method (solvent-antisolvent method)[15]:**

It is mainly used for poorly soluble drugs. First drug is dissolved in a suitable solvent. This solution is then mixed with a miscible antisolvent system in the presence of surfactants. Rapid addition of drug solution into the antisolvent leads to the sudden supersaturation of drug in the mixed solution forms ultrafine drug solids. The precipitation method involves two phases – nuclei formation and 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 a nonsolvent.

### 2. Top-down technology

**a. Media milling technique[16] :**

Nanosuspensions are formulated by high shear media mills or pearl mills. It consists of a milling chamber, recirculation chamber, and milling shaft. Milling media consists of balls or pearls which are made up of ceramic sintered aluminum oxide or zirconium oxide. Milling chamber charged with milling media, water, drug, and stabilizer. Balls rotated at a high shear rate under controlled temperature the balls have an impact on the sample. Due to both forces of friction and impact particle size reduction occurs and nanosized particles will be obtained.

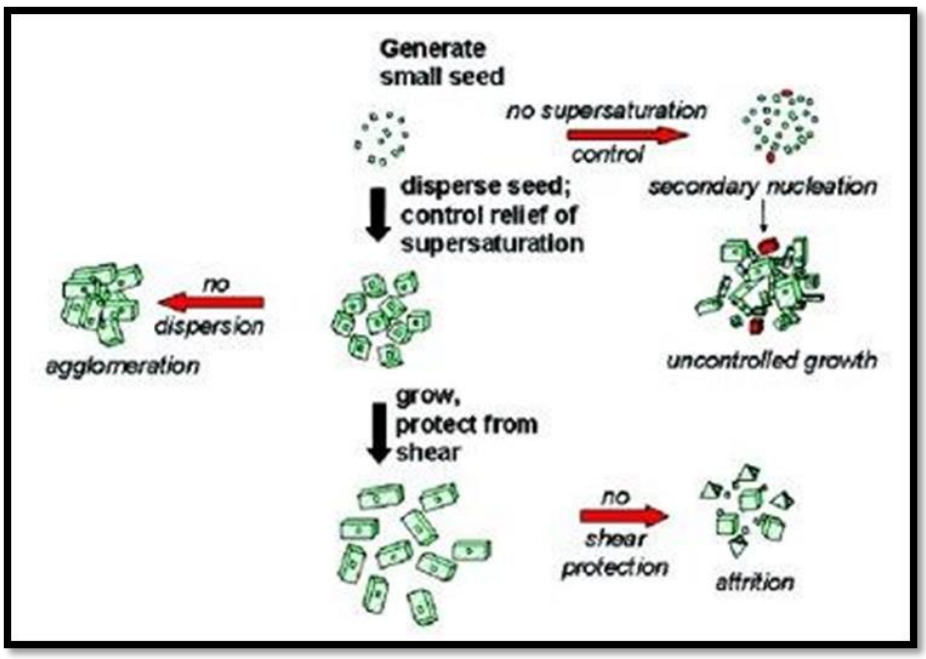


**Figure No. 1: Media Milling Technique**

**b. High pressure homogenization[17] :**

Homogenization involves the forcing of the suspension under pressure through the valve having a narrow aperture. In this method, the surfactant and drug are focused under pressure, and it is through nanosized aperture value of high-pressure homogenization. The principal is based on cavitations in the aqueous phase. The particle cavitation force is sufficiently high to convert the drug microparticles into nanoparticles. Before subjecting the drug to the homogenization process, it is essential to form a presuspension of the micronized drug in a surfactant solution using high-speed stirrers.

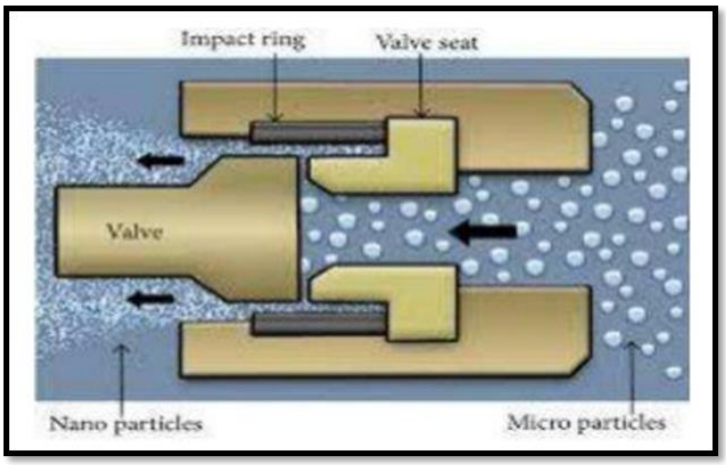


**Figure No. 2: High-Pressure Homogenization Process**

- **Nanopure (Homogenization in nonaqueous media)**: It is homogenized in a water-free media or water mixture. The temperature will be $0^0$C or even at freezing point. So it is known as deep freeze homogenization. It is the best method for the Thermo labile substances.

- **Dissocubes (Homogenization in aqueous media):** In this technique, the suspension is forced by a pressure plunger pump through a narrow valve under high pressure. When the suspension is allowed to as through the orifice the static pressure will be reduced below the boiling pressure of water which results in the boiling of water and formation of gas bubbles. When it leaves the orifice pressure will be normal and bubbles will implode. So surrounding particles will rush into the surface which causes the size reduction.

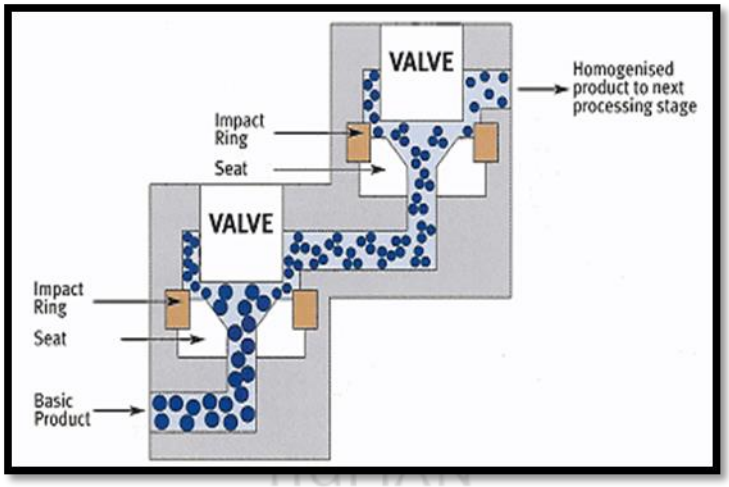


**Figure No. 3: Dissocube**

- **Nanoedge (Combined precipitation and homogenization)**: This technique will be similar to the homogenization method or precipitation method. It is considered as the combination of these two methods which leads to better stability and bioavailability. The suspension obtained by this method will be again homogenized to reduce the particle size and prevent crystal growth. An evaporation technique is also included in the nano edge technology for the better production of nanosuspension which will result in the solvent-free modified starting material.

- **Nanojet:** Nanojet has mostly used technology, in which high pressure of force is applied to passes the suspension which is separated into at least two sections and that are impacted with each other due to high shear forces produced all through the process it marks to reduce of particle size.

**c) Emulsification solvent evaporation technique[18]:**

This technique involves preparing a solution of the drug followed by its emulsification in another liquid that is a non-solvent 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.

**Solvent evaporation:** In the solvent evaporation method, the solutions of the 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. The particle size was influenced by the concentration of polymer, stabilizer, and the speed of homogenizer. These methods require high-speed homogenization or ultrasonication, followed by evaporation of the solvent, either by continuous magnetic stirring at room temperature or under reduced pressure.

**d) 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 heating tape fitted with a temperature controller, and the temperature of the emulsion was maintained above the melting point of the drug. The emulsion was then cooled down either slowly to room temperature or on an ice bath. The main advantage of this method is the total avoidance of organic solvents during the production process.

**e) Supercritical fluid process:**

Particle size reduces via a supercritical fluid process using dense noncondensable fluid. This fluid is whose temperature and pressure are greater than its critical temperature and critical pressure. Its processes allow micronization of drug particles within a narrow range of particle size, often submicron level. This process has demonstrated the ability to create nanoparticulate. Nanosuspension occurs particle size between 5 to 2000 nm in diameter. Poorly soluble drug and surfactant in supercritical $CO_2$ and high pressure requires for these processes, restrict the utility of technology in the industry.

**f) Dry co-grinding [19] :**

Nanosuspension using dry grinding of poorly soluble drug with soluble polymer and co-polymer such as PVP, PEG, HPMC used, after dispersing in liquid media. Physicochemical properties and dissolution of the poorly soluble drug were improved by co-grinding because of an enhancement in surface polarity and transformation from crystalline to an amorphous drug. Dry co-grinding can be carried out easily without organic solvent. It reduces the particle size.

**Table No. 3: Advantage and Disadvantage of Preparation Techniques of Nanosuspensions**

| TECHNIQUES | ADVANTAGE | DISADVANTAGE |
|---|---|---|
| Precipitation | -Simple process<br>-Low-cost equipment<br>-Ease of scale-up | -Drug has to soluble at least in one solvent and that this solvent needs to be miscible with a non-solvent.<br>-Growing of drug crystals needs to be limit by surfactant addition. |
| High-pressure Homogenization | - General applicability to most drugs<br>-Useful for the formation of very dilute as well as highly concentrate nanosuspension<br>-Simple technique<br>-Aseptic production possible<br>-Low risk of product contamination | -High number of homogenization cycles<br>-Prerequisite for a drug to be in micronized state and suspension formation before homogenization<br>-Possible contamination of product could occur from metal ions coming off from the wall of the homogenizer. |
| Emulsion/Microemulsion template | -High drug solubilization<br>-Long shelf life<br>-Ease of manufacture | -Use of hazardous solvent<br>-Use of high amount of surfactant and stabilizers |
| Media milling | -Ease of scale-up<br>-Little batch to batch variation -High flexibility in handling large quantities of drugs | - Generation of the residue of milling media<br>-Require milling process for hours to days<br>-Prolonged milling may induce the formation of amorphous lead to instability |
| Dry Co-grinding | -Easy process<br>-No organic solvent<br>-Require short grinding time | -Generation of the residue of milling media. |

## CHARACTERIZATION OF NANOSUSPENSIONS[4,20,21,23]

Nanosuspension is evaluated as same as conventional suspensions such as appearance, colour, odor, assay (drug content), related impurities, stability studies, etc. Along with that particle size, zeta potential, morphology, dissolution study, *in-vivo* studies are also performed.

### i. Particle size:

Particle size and particle size distribution are two important parameters since they will affect the saturation solubility, dissolution rate, stability, and *in-vivo* behavior of nanosuspensions. Any change in the particle size will lead to a change in solubility and dissolution. Particle size determines the physiochemical behavior of the drug. Particle size can be determined by photon correlation spectroscopy (pcs) or laser diffraction (ld). Particle size distribution will be expressed in the polydispersity index (pi). pi value of 0.1-0.25 indicates fairly nanosize distribution whereas its value greater than 0.5 indicates a very broad distribution.

### ii. Morphology:

Morphological examination of nanosuspension is determined using Scanning electron microscopy (SEM).

### iii. Surface charge (zeta potential):

Zeta potential will determine the stability of nanosuspension. A minimum zeta potential of 30 mV is required whereas, in the case of combined electrostatic or steric stabilizer, a zeta potential of 20 mV would be sufficient.

### iv. Crystalline state and particle morphology:

When the drug undergoes nanosizing the crystalline nature and particle morphology will change. X-ray diffraction analysis is mainly used for the determination of the solid-state of the particle and is supplemented by scanning electron microscopy.

### v. Saturation solubility and dissolution velocity:

Nanosuspension will increase the solution solubility and dissolution velocity. It also helps for the *in-vitro* behavior of the formulation. When the particle size is reduced to the nanometric

range, dissolution velocity and dissolution pressure will increase which leads to the solution solubility due to the change in the surface tension.

**vi. pH:**

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

**vii. Osmolarity:**

Osmolarity was measured using Osmometer

Characterization for surface-modified nanosuspensions can be done by Surface hydrophilicity, Adhesion properties, and Interaction with body proteins.

**APPLICATIONS[8,19,22,23]**

- **Oral Drug Delivery**

Because of the numerous advantages, the oral route is the most preferable route for many of the drugs. By making it in nano size, its solubility and bioavailability will increase. Improved bioavailability can be explained by the adhesiveness of drug nanoparticles to the mucosa, the increased saturation solubility leading to an increased concentration gradient between gastrointestinal tract lumen and blood, and the increased dissolution velocity of the drug.

Aqueous nanosuspension can be used directly in a liquid dosage form and dry dosage forms such as a tablet or hard gelatin capsules.

- **Parenteral drug delivery**

Intravenous administration results in several advantages, such as administration of poorly soluble drugs without using a higher concentration of toxic co-solvent, 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. Injectable nanosuspensions of poorly soluble drug tarazepide have been prepared to overcome the limited success achieved using conventional solubilization techniques, such as the use of surfactants and cyclodextrins to improve bioavailability.

- **Ocular drug delivery**

The ocular bioavailability of nanosuspensions depends on the dissolution rate of the drug in the lacrymal fluid. However, the inflow and outflow of the lacrymal fluid cause variation in the dissolution rate of the drug. Nanosuspensions attain saturation solubility in the lachrymal fluid, representing an ideal approach for the ocular delivery of hydrophobic drugs. The nanosized drug particles had shown a prolonged residual time in the cul-de-sac, giving sustained release of the drug.

- **Pulmonary drug delivery**

Nanosuspensions may prove to be an ideal approach for delivering drugs that exhibit poor solubility in pulmonary secretions. Currently, such drugs are delivered as suspension aerosols or as dry powders using dry powder inhalers. For pulmonary delivery, nanosuspensions can be nebulized through mechanical or ultrasonic nebulizers. Due to the presence of many small particles, all aerosol droplets contain drug nanoparticles.

- **Targeted drug delivery**

Nanosuspensions are suitable for targeting particular organs because of their surface properties. Along with this, it is easy to alter *in-vivo* behavior by changing the stabilizers. The drug will be taken up by the mononuclear phagocytic system which allows region-specific delivery. This can be used for targeting antimycobacterial, fungal, or leishmanial drugs to the macrophages if the infectious pathogen is persisting intracellularly. The further plan of action for targeted drug delivery systems is by using various surface coatings for active or passive targeting.

- **Mucoadhesion of the nanoparticles**

A nanoparticle can adhere to the mucosa surface due to small particles. The adhesion of the nanoparticles is the first step before particle absorption. To further increase the adhesive time nanosuspensions are formulated hydrogels made from mucoadhesive polymers. The adhesiveness of the nanosuspensions not only helps to improve bioavailability but also improves the targeting of the parasites persisting in the GIT.

- **Bioavailability enhancement**

A drug with poor solubility and permeability in the gastrointestinal tract leads to poor oral bioavailability. Nanosuspension resolves the problem of poor bioavailability by solving the problem of poor solubility, and poor permeability across the membranes.

- **Topical formulations**

Drug nanoparticles can be incorporated into creams and water-free ointments. The nanocrystalline form leads to an increased saturation solubility of the drug in the topical dosage form, thus enhancing the diffusion of the drug into the skin.

## CONCLUSION

Nanosuspension is a commercially possible approach for solving the poor solubility as well as poor bioavailability problems of hydrophobic drugs and drugs which are poorly soluble in aqueous and organic solvents. Nanosuspensions can be administered through oral, parenteral, pulmonary, ocular, and topical routes. A nanosuspension not only improves the solubility and bioavailability and drug absorption but also modifies the pharmacokinetics of the drug and thus improves drug safety and efficacy. It has therapeutic advantages, such as a simple method of preparation, less requirement of excipients, increased saturation solubility, and dissolution velocity of the drug. To take advantage of nanosuspension drug delivery, simple formation technologies, and various applications, nanosuspensions will continue to be of interest as oral formulations and non-oral administration develop in the future.

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