



A Comprehensive Review of Nanosuspension: Formulation, Evaluations and Pharmacokinetics Aspects.

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ABSTRACT

This review focuses on drug delivery that uses particle delivery techniques to transport both larger and smaller molecules. Nanosuspension formulations offer an acceptable alternative to these issues. Nanosuspension technique improved drug bioavailability and aqueous solubility properties. Drug stability and bioavailability can be increased using nanosuspension technology. Nanosuspensions are interesting options for improving the dissolution of medications which are poorly water-soluble. Nanosuspensions can be developed via either a top-down or bottom-up strategy. The former involves reducing the size of big particles through milling or high-pressure homogenization. The latter focuses on the mechanisms of nucleation and particle growth. Particulate systems—like nanoparticles—have been employed as a physical method to modify and enhance the pharmacokinetic and pharmacodynamic characteristics of different medicinal compounds. Nanosuspension will be simple for manufacturing and works with any active ingredient that is insoluble in water. Nanosuspension is potentially viable formulation for the future that enhances therapeutic efficiency and safety.

Keywords: Nanosuspension, Pharmacokinetics, Nanoparticle, Solubility.

INTRODUCTION

In the 21st century, nanotechnology emerged as an innovation in science. Nanoparticles have numerous applications, including the environment, agriculture, food, biotechnology, medicinal, and pharmaceutical industries.¹ Nanomedicine is one of the most well-known applications of nanotechnology research. Nanotechnology enables the development of customized pharmacological solutions for illness diagnosis, prophylaxis, and treatment. Nanoparticles range in size from 1 to 100 nm. The active pharmaceutical ingredient (API) is entrapped, encapsulated, dissolved, or connected with the nanoparticle matrix.² Poor solubility and permeability of lead compounds is a major barrier to developing novel medication formulations. Drug development programs create roughly 40% of new chemical entities that are either weakly water-soluble or lipophilic. Creating a medication with low water solubility is a difficult task for pharmaceutical industry.³ Micronization, solubilization with cosolvents, salt form, surfactant dispersions, precipitation process, and oily solution are some of the standard techniques for making poorly soluble medications more soluble. Although other methods including liposomes, emulsions, microemulsions, solid dispersions, and inclusion complexation with cyclodextrins can significantly improve drug solubility, they are not universally applicable to all medications. Nevertheless, these techniques have drawbacks, such as the high concentration of chemicals that could cause toxicity and stability problems. They are usually not the best option for clinical treatment as a result. Nanosuspension has gained increased interest as a forming solution for poorly soluble pharmaceuticals since it was initially proposed as a drug delivery system in 1994.⁴

Nanosuspensions are pure drug nanoparticles with an average diameter of less than 1 μ (200-500nm).⁵ A Pharmaceutical Nanosuspension is a biphasic liquid system that distributes unable to dissolve solid medication particles uniformly in a water-based medium. Dosage forms are colloidal and stabilized using surfactants and polymers.³ All medication compounds in Classes II and IV of the Biopharmaceutical Classification System can benefit from the formation of nanosized particles, which will boost their solubility and allow them to pass through the gastrointestinal barrier.⁶ Following figure describe all classes in Fig. 1.

According to the Noyes-Whitney and Ostwald-Freundlich principles, a nanometer-sized particle can improve a nanosuspension's dissolving velocity and saturated solubility, which is typically accompanied by an improvement in bioavailability.⁷ Because nanotechnology has so many applications in oral, parenteral, transdermal, transmucosal, ophthalmic, and pulmonary drug delivery routes, it is becoming more and more popular in the pharmaceutical industry. Nanoparticle engineering has been created and documented for use in medicinal applications throughout the past ten years. Numerous benefits of nanosuspension include a higher rate of absorption, greater oral bioavailability, a quicker onset of action, a lower required dose, less fed/fasted variability, a high drug loading capacity, suitability for hydrophilic drugs, the ability to reduce dosage, and improved chemical and physical stability of medications.⁸ Nanosuspensions can be prepared using two methods: "bottom-up technology" and "top-down technology". Bottom-up technique involves creating nanoparticles using procedures such as



precipitation, microemulsion, and melt emulsification. Top-down technology.

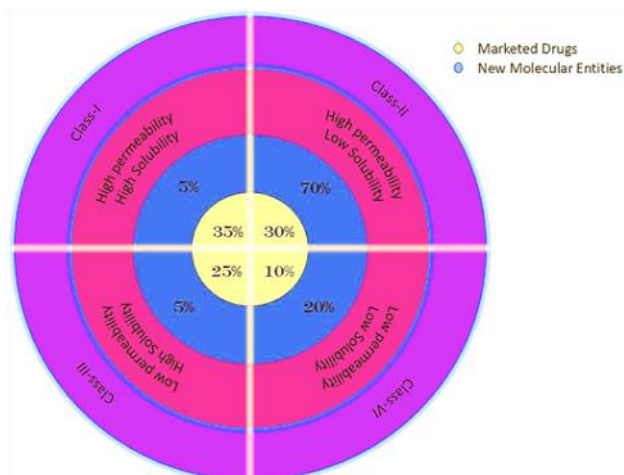


Figure 1: Biopharmaceutical Classification of New Molecular Entity (NME) and Marketed drugs.

disintegrates bigger particles into nanoparticles, such as through high-pressure homogenization or milling.⁷ Nanosuspension is a dispersion of a poorly water-soluble medication, with no matrix material. Nanosuspension preparation is straightforward and can be used for any water-insoluble medication. Nanosuspension increases drug safety and efficacy by addressing poor solubility and bioavailability issues, as well as altering pharmacokinetics.

Application of nanosuspension:

Because of the size-dependent deviation of their properties from those of corresponding bulk materials, nanocrystalline materials offer highly intriguing materials for material science. Manufactured NPs exhibit physicochemical traits that result in distinct electrical, mechanical, optical, and imaging qualities that are highly desired in certain applications in the commercial, ecological, and medical domains.⁹

Routes of administration:

The route of delivery determines how the body cells will perceive the nanoparticles and the path they will take after administration.¹⁰ Through surface modification, nanosuspensions may be able to be investigated as a tailored drug delivery mechanism to avoid macrophage phagocytosis.¹¹

A) Oral administration:

Oral suspension provides chemical stability and allows for liquid medication, which is recommended in seniors and pediatric populations. Other benefits include concealing medicinal bitterness, increasing duration of action, boosting aqueous solubility for weakly water-soluble medicines, and improving dissolution and bioavailability.¹²

Due of its many well-established benefits, the oral route is typically used. Some antibiotics taken orally, include atovaquone and Buparvaquone does a great job at reflecting this issue. When such medications are nanosized,

their oral absorption and, thus, bioavailability can be dramatically increased.¹³ Because of its wide surface area and small particle size, oral nanosuspension aids in improving the oral bioavailability and solubility of poorly soluble medications (BCS class-II).¹⁴ In prevalent market the most preferred suspension are pharmaceutical nanosuspension DDS(Drug Delivery System).

B) Ophthalmic preparation:

Drug solutions applied topically as eye drops are used to treat the majority of ocular conditions.¹⁵ The main anatomical, physiological, and physicochemical barriers of the eye are mostly to blame for the low ocular bioavailability of many medications from traditional ophthalmic drug delivery systems.¹¹ But the properties of nano-sized medication particles may be most advantageous for ocular drug delivery than for any other route of administration.¹⁵

C) Parenteral administration:

Parenteral delivery of nanocrystals addresses two primary concerns: lowering the toxicity of the current non-aqueous formulation and achieving a desired effect.¹⁰ The development of injectable nanosuspensions for the poorly water-soluble medications has led to a more palatable formulation. Several parenteral methods, including intravenous, intraperitoneal, and intraarticular injections, can be used to give nanosuspensions.¹⁵

D) Topical Pulmonary:

One non-invasive alternative for lung treatment is the local and systemic administration of pulmonary medications. Aerosols produced by nebulizers and inhalers can be given directly to a person's lungs. The most common method of treating a variety of respiratory conditions is the local administration of therapeutic medications to the lungs. When compared to alternative routes of administration, it provides the benefits of increased local drug concentrations and selectivity.¹⁸

Approaches for preparation of nanosuspension:

Bottom-up method:

The process of bottom-up nanoprecipitation has been used for decades to create micronized particles. The manufacture of nanocrystals using this method began in the late 1980s.¹⁰ The precipitation of supersaturated solutions is the foundation of the bottom-up methodology. Both single drops and bulk solutions of nanosuspensions are commonly produced using it. The bottom-up method has several benefits, including the ability to produce monodisperse particles, which have a restricted size distribution range, the use of low energy and low processing temperatures for thermolabile medications, the absence of sophisticated equipment, and an overall cost-effective process.¹⁹ Hence following figure describe process of preparation of nanosuspension in Fig no. 2

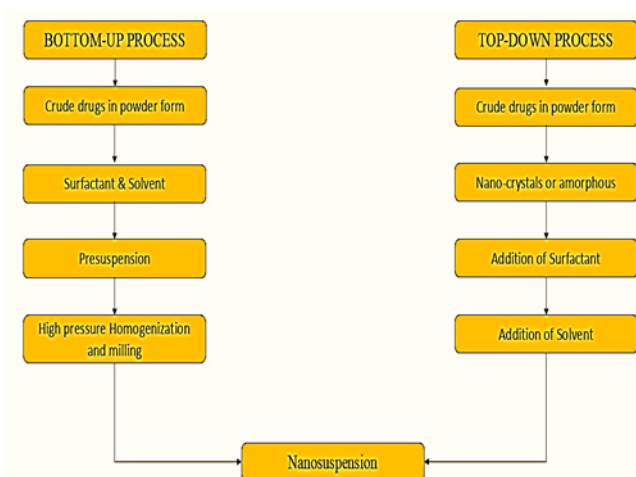


Figure 2: Bottom-up and Top-down approaches for formulation of Nanosuspension.

One efficient method for creating medication particles that are micro- or nano-sized is antisolvent precipitation. The medication is first dissolved in the solvent in this precipitation process, and afterward, the drug-containing fluid is promptly incorporated in antisolvent. Precipitation of crystals happens when there is a drug concentration and excessive saturation. To provide improved stability of the Nanosuspension; sufficient amounts of the stabilizer should be employed possessing a high diffusivity and a strong affinity for the particle surface which can cover the created surface in a short amount of time. In addition, the amount of stabilizer ought to be able to entirely encase the particle surface, precipitation is used to create Trans retinoic acid nanosuspensions. The advantage of the precipitation process over other ways of nanosuspension creation is the use of straightforward, inexpensive equipment and the benefit of enhanced saturation solubility. For medications that are poorly soluble in both aqueous and non-aqueous environments, the precipitation approach is not suitable. For this method to work, the medication must dissolve in at least one solvent that is miscible with non-solvent.⁴

Top-down method:

Top-down methods rely on the reduction of size and disintegration of massive materials into nanometer-sized particles through the use of pulsed laser fragmentation, high pressure homogenization, and milling.²⁰ These methods don't employ toxic solvents. All media milling methods, however, are extremely inefficient and need a large amount of energy. These processes produce a significant quantity of heat, which makes processing thermolabile materials challenging.²¹

Milling method:

Developed by Liversidge et al., this patent-protected technology has been divided out into three steps: first, the drug and surfactants were combined to create a homogenous mixture and then put into the milling chamber; second, the milling pearls or ball were placed inside, and either a certain amount of water was added or

not; and third, the miller was turned on for a few to dozens of hours to prepare the nanosuspensions.¹⁵

The components of a mill are a recirculation chamber, a milling chamber, and a milling shaft. A mill with tiny grinding balls or pearls is then fed an aqueous suspension of the medication. These balls fly through the inside of the grinding jar and strike the sample on the other grinding jar wall during a controlled temperature rotation at a very high shear rate.⁽²²⁾ Preparing drug nanosuspensions using media milling with stabilizers is a highly effective procedure. The key to processing drug nanosuspensions is compensating for the additional free energy of freshly exposed surfaces. The degree of compensation in media milling depends on drug-stabilizer interactions. Maintaining crystallinity in drug particles during processing improves their stability.⁵

Dry co-grinding:

Dry-co grinding is a simple, cost-effective process that doesn't require organic solvents. Co-grinding improves the surface polarity and changes a crystalline drug into an amorphous one, which improves the physicochemical characteristics and dissolving of poorly water-soluble medicines.²² Dry co-grinding of a variety of polymers and copolymers, including polyvinyl pyrrolidone, hydroxypropyl methylcellulose (HPMC), polyethylene glycol, sodium dodecyl sulphate, and derivatives of cyclodextrin, produced a stable nanosuspension.¹¹

High Pressure Homogenization:

Nanosuspensions morphology and stability are impacted by manufacturing methods and operation conditions. The high-pressure homogenization technique can produce short needle-shaped nanosuspensions, which can then be lengthened during storage through Ostwald ripening. Furthermore, the high-pressure homogenization operation did not promote the crystal shape transition. Media milling can cause particle crystallinity to decrease, leading to sphericity nanocrystals compared to high pressure homogenization. The bottom-up technique, like media milling, can promote crystal form transition. However, it produces needle-shaped nanosuspensions. Furthermore, the bottom-up technique resulted in increased Ostwald ripening and particle size. HPH-prepared drug nanosuspensions demonstrated superior chemical stability compared to drug solutions. This technique can be used to create drug nanosuspensions formulations that prevent degradation of chemically sensitive medications.⁵

Melt emulsification method:

This method involves dispersing the drug in a water or aqueous stabilizer solution, heating it above the drug's melting point, and homogenizing the resulting emulsion. The sample holder was covered with a heating tape that had a temperature controller attached, ensuring that the emulsion's temperature remained above the drug's melting point. The emulsion is then cooled either gradually to room temperature or on an ice bath.²³

Emulsion diffusion method:

The dispersed phase in this approach is made up of somewhat water-miscible and volatile organic solvents such as butyl lactate, benzyl alcohol, triacetin, and ethyl acetate. The emulsion is made by dispersing the medication in a solvent mixture or an organic solvent before producing an emulsion with water using high pressure homogenization or other procedures. When droplets change into solid particles, dilution causes the internal phase to diffuse into the external phase, resulting in the production of nanosuspensions.

The size of the emulsion droplets determines particle size. The use of organic solvents such as ethyl acetate, ethanol, methanol, and chloroform, as well as the existence of residual solvents in the end products, are significant downsides of this method in terms of both environmental dangers and human safety concerns.²⁴

Homogenization in Nonaqueous Media:

A suspension homogenized in a water-free media is called nanopure. This type of homogenization, known as "deep-freeze homogenization," involves homogenizing drug suspensions in nonaqueous media at 0°C or occasionally lower. Since water, oils, and fatty acids have relatively high boiling points and low vapor pressures, cavitation in nanopure technology cannot be initiated with a static pressure drop alone. Additional homogenization technology and patents pertaining to the homogenization procedures.²⁵

Pharmacokinetics advancement of nanosuspension:

Pharmacokinetics is the study of how quickly and how much a chemical or medicine is absorbed, distributed, metabolized, and eliminated in the body using mathematical modeling and experimental methods. Before drugs or ingredients are used for medical purposes, pharmacokinetic examinations are frequently carried out.²⁶ And this parameter characterized the particular drug activity are:-

Table 1: Parameters of Pharmacokinetics used for determination of drug activity.²⁶

Pharmacokinetic Parameter	Definition of parameters
Clearance (Cl)	Cl is an evaluation of the extent to which a substance can be eliminated from the body.
Half-time($t_{1/2}$)	$T_{1/2}$ is the amount of time required to complete 50% of a process, such as absorption and elimination. Generally, this parameter is calculated by: $T_{1/2} = 0.693 \times V_d/Cl$
Volume of distribution (V_d)	The administered dose and the measured blood concentration are determined by the proportionality constant V_d . It is an important indicator of the effectiveness of drug distribution into the tissues and fluids of the body. It is usually denoted by ($V_d = \text{dose}/\text{concentration}$).
Mean Residence Time (MRT)	The average amount of time a molecule remains in the body is symbolized by MRT.
Bioavailability (F)	F indicates the proportion of a dose that is absorbed by the body and is available for systemic circulation.

The majority of potential medications are rejected during the research and development of new pharmaceuticals because of their poor solubility and bioavailability. These factors also restrict the range of uses for many medicinal medications. Nanodrug delivery systems (NDDS) such as liposomes, noisome, solid lipid nanoparticles, and nano emulsions have been employed extensively to get around all of these problems. In recent years, a novel dosage form for insoluble medications has been developed: nano-suspensions (NS), which have the qualities of rapid manufacturing and high repeatability. The drug particle size can be regulated at the nanometer level by employing a little quantity of polymeric or surfactant material as a stabilizer. In order to lower the drug dosage and prevent adverse drug reactions caused on by an overdose, this greatly improves the drug's surface area, solubility, dissolving rate, and bioavailability. The feasibility of nanosuspensions has always been restricted because of their physical stability.²⁷ During the past a decade, the percentage of medication candidates in the discovery stage that contain poorly water-soluble compounds has grown.

Nanosuspension technologies have recently been developed to boost the bioavailability of poorly water-soluble pharmaceutical products.²⁸ In an earlier investigation, we have studied using a rotation/revolution mixer to optimize a method of preparing nanosuspensions for oral administration, and we demonstrated that this method enhanced exposure in rats. However, in preclinical toxicological and pharmacological investigations, the solubility limits of substances preclude administration techniques like intravenous (IV) injection. Even though a lot of additives can make poorly water-soluble medications partially soluble, chemicals cannot dissolve at extremely high concentrations for toxicity testing. Due to their high surfactant sensitivity, dogs are especially vulnerable to the issue of additive toxicity. Dogs exposed to certain surfactants exhibited a hypotensive response and histamine release. Due to its ability to be made without a lot of additives and allow for the administration of doses higher than the saturation solubility of compounds, nanosuspension is a promising solution to these issues; in fact, reports of nanosuspensions for intravenous use have



been made, and a number of medications have been marketed in this form.²⁹ Designing new drug delivery systems, nanosuspensions continue to be the most effective option to deliver the medication to the target location at the ideal moment to provide the intended therapeutic effect. The potential of nano-carriers to treat a variety of infectious diseases with fewer adverse effects is currently being investigated to a greater extent. Because of their greater surface area to volume ratio, nanocarriers (50–1,000 nm) enhance the pattern of biodistribution and pharmacokinetics. They enable surface modification for delivering fast release, longer release, or targeted characteristics.³⁰ There are several reasons for the drug's increased bioavailability. The first is the decrease in particle size brought about by nanosizing, which results in an increase in surface area. The second is a decrease in the thickness of the diffusion barrier and a rise in the surface area of adhesion to the intestinal epithelium of villi and nanoparticles, which allows for direct surface contact. Third, the drug's instant release increases its availability at the absorption site.³¹

Recent advancements in nanotechnology have demonstrated its effectiveness in medicine delivery

applications and in getting around a number of standard therapies' issues. The carrier/vehicle made conceivable by nanoengineering can efficiently transport the medications into the infection site and get rid of the parasites, viruses, protozoa, etc. from the host organisms that are affected. The nanoparticles typically reside nanosized and have distinct physico-chemical and biological characteristics that might assist in future developments in drug delivery applications. They can be created utilizing materials at the atomic or molecular level.³²

With increasing saturation solubility and surface area available for dissolution, the nanosuspensions platform has emerged as a sophisticated and effective drug delivery method for water-insoluble medications. Water-insoluble medications prepared as nanosuspensions generally offer biopharmaceutical benefits such as enhanced formulation performance, including high drug loading, reproducible oral absorption, improved dose-bioavailability proportionality, decreased toxicity and undesirable effects, and improved patient compliance by necessitate fewer oral units to be taken.⁵ Following table gives wide range example of flourishing of Nanosuspension and its formulation available in market.

Table 2: List of patents on nanosuspension. ¹⁷

Nanocrystal	Name of investigator Company	Patent no.
Hydrosol	Novartis (prev. Sandoz)	GB22695336
Nanocrystal™	Elan nanosystem	US5145684
Dissocubes ^R	SkyePharma	US5858410
Nanoedge™	Baxter	US6884436

Evaluation of Nanosuspension:

1) Drug Content Uniformity:

After dissolving 10 ml of each formulation in 10 ml of isotonic solution, the mixture was left overnight. 10 mg of the medication (as in the formulation) was ingested, and it was diluted to 10µg/ml. UV was used to filter the dilutions and assess the homogeneity of their contents. The compositions absorbance was measured in a UV-Vis spectrophotometer using a single cm cell. At a particular maximum absorption (λ_{max}) nm, the instrument was set. Each formulation's drug content was determined using the absorbance values of established standard solutions.³

2) Stability of Nanosuspension:

Because there are more unstable surface atoms and molecules when particle size is reduced, surface energy rises. Any alteration in the drug's in vivo performance (blood profiles, plasma peaks, and bioavailability) can be investigated with the aid of the saturation solubility estimation. Stabilizers are used to prevent particle clustering and lower the likelihood of Ostwald ripening. The combination of polymers and surfactants helps to stabilize nanosuspensions over a prolonged period.¹⁴ The

nanosuspensions may be tested for stability at 4°C in a refrigerator. Particle size measurements were conducted on small aliquots of suspensions stored for 2 weeks, 1 month, and 3 months.²⁴

3) pH:

pH values were measured at 25°C using a digital meter at 20±1°C. The formulation was equilibrated for 1 minute by contacting the pH meter electrode. The process was repeated three times, and the mean and standard deviation were calculated.³

4) Viscosity:

A Brookfield-type rotating viscometer can measure the viscosity of lipid-based formulations at varied shear rates and temperatures, regardless of composition. However, not all nanosuspensions contain lipids. Nanosuspensions can contain a variety of stabilizers and carriers, such as polymers, surfactants, and non-lipid-based compounds. Lipid-based nanosuspensions are one method for producing stable and effective nanosized medication particles. To conduct this measurement, samples must be immersed in a thermal bath at 37°C in the instrument's sample chamber.¹⁸



Marketed Preparation:

Itraconazole and other poorly soluble medications can be easily prepared and lyophilized for long-term storage as nanocrystalline solutions, which also offer a promising novel therapeutic formulation for oral drug administration to treat fungal infections. A dissolution investigation in 0.1N HCl demonstrates that the nanosuspension formulation releases more drug than the commercial formulation.³³

The release of diclofenac sodium solid in oil nanosuspension, the use of nanosuspension technology for

topical medicinal formulations saw a major advancement. The delivery of medications with low solubility was addressed by this invention. This strategy was demonstrated with ibuprofen, a non-steroidal anti-inflammatory (NSAID) medication used to treat both acute and chronic arthritic diseases. Because ibuprofen is not very soluble, it was thought that skin permeability may be increased by using nanosuspension gel formulations.¹⁸ Following table give examples Nanosuspension/Nanoparticle incorporated with API in their respective formulation available in markets.

Table 3 : Examples of Nanosuspension/Nanoparticles in the market.²⁸

Trade Name	Active ingredient	Dosage form	Marketed and manufactured by	Month and year of launching
Rapamune	Sirolimus	Oral Suspension: 1-2 mg	Wyeth	Marketed in 2000
Tricor	Fenofibrate	Oral tablet: 48-145 mg	Abbott	Marketed in 2004
Emend	Antiemetics	Oral Capsule: 80-125 mg	Merck	Marketed in 2003

Future Perspectives and Challenges:

Because nanosuspension can be a useful for product development experts to tackle numerous formulation and medication delivery issues, especially with intractable pharmaceuticals, the future prospects of this technology are bright. The crucial stability issues related to nanosuspension remain unresolved despite the numerous published studies in the field. The key elements that require more research are the electrostatic and steric stabilizers' stabilizing capabilities and their relationship to API characteristics, the achievable maximum particle size, and the consequent physical stability. The development of biotechnology and modification tools such antibody-drug conjugates and nanobodies is likely to result in the production of high concentration monoclonal and biosimilar products that are administered subcutaneously and have improved biopharmaceutical and safety properties.³⁴

CONCLUSION

Based on the studies and reviews mentioned above, it can be said that NS resolved the issue of the medications' poor solubility. Large-scale NS production is commonly achieved by the use of media milling, and high-pressure homogenizer production techniques. In order to improve the bioavailability and, consequently, the therapeutic efficacy of poorly water-soluble pharmacological compounds, nanosuspensions are highly helpful. Supersaturated liquids are precipitated for the creation of nanoparticles in the bottom-up method. For the nanosuspension to remain stable, a number of parameters in the particle, dispersion medium, and formulation/storage conditions are crucial. Similar mechanisms underlie both nucleation and particle growth and instability; that is, the same principles that lead to nucleation and particle creation can also lead to inappropriate growth and agglomeration. Therefore, the use of excipients like stabilizers necessitates appropriate type and concentration optimization, which means that

every formulation needs a unique optimization procedure. If a drying process is used, one should take into account the effects of additional variables to guarantee the appropriate particle size and behavior as well as the stability and therapeutic efficacy of the formulation. When designing a formulation, significant factors to consider are drug loading, chemical stability, scale-up capabilities, and permeability. Nano- and micro-particles differently depending on their size.

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