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A Comprehensive Review on Nanosuspension as a Promising Drug Delivery System

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ABSTRACT:

Although a large number of new drug molecules with varied therapeutic potentials have been discovered in the recent decade, most of them are still in developmental process. Nanotechnology has emerged as a tremendous field in the medicine. Nano refers to particles size range of 1-1000nm. Nano suspensions are part of nanotechnology. Rapid advancement in drug discovery process is leading to a number of potential new drug candidates having excellent drug efficacy but limited aqueous solubility. One of the major problems associated with poorly soluble drugs is very low bioavailability. The problem is even more complex for drugs like which are poorly soluble in both aqueous and non-aqueous media, belonging to BCS class II as classified by biopharmaceutical classification system. Formulation as Nano suspension is an attractive and promising alternative to solve these problems. A pharmaceutical Nano suspension is defined as very finely colloid, biphasic, dispersed solid drug particles in an aqueous vehicle, size below 1 μ m stabilized by surfactants and polymers prepared by suitable methods for drug delivery applications. It provides efficient delivery of hydrophobic drugs and increases the bioavailability. Nano suspension is an attractive and promising technology to improve poor solubility and bioavailability of the drugs. This review article describes the methods of preparation, and applications of Nano suspensions in the field of pharmaceutical sciences .

Keywords: Bioavailability, Nanotechnology, Nano suspension, poorly soluble drugs, Drug delivery system

1. INTRODUCTION:

Nano suspensions are colloidal dispersions and biphasic systems made up of drug particles dispersed in an aqueous medium with a diameter of less than one micrometre. Because of their increased surface area and saturated solubility, medication particles reduced to nanometre size accelerate the rate of dissolution. (2)





Drug molecules with low water solubility have emerged as the most problematic problem in the pharmaceutical industry and research in recent years (6). It appears that medications with low water solubility have numerous issues when it comes to formulation, including poor dissolution and limited bioavailability for BCS-II medications. Traditional strategies to improve the solubility of poorly soluble pharmaceuticals include micronization, the use

of fatty solutions, the use of penetration enhancers or co-solvents, the process of surfactant diffusion, salt formation, precipitation, etc. However, the usefulness of these procedures is limited.

They have the potential to improve the solubility of medications that have low solubility in lipid and aqueous media (7). Among the primary obstacles are the potential decline in the dose- response linearity of medications with low water solubility and the possibility of an unexpected drug collapse upon delivery, which could result in lower patient compliance and lower bioavailability. The most significant of them is the creation of Nano scale drug delivery devices, which is one of the many encouraging advancements in the research conducted over the past century to address these issues (6). Drug delivery techniques such liposomes [4], nanoparticles [5], solid lipid nanoparticles [6], polymeric micelles [7], dendrimers [8], quantum dots [9], Nano-emulsions [10], and Nanosuspensions [11, 12] are the most often utilized since they enhance solubility and consequently the bioavailability.

Since Müller et al. initially reported on Nanosuspensions in 1994 [13] (6), numerous research involving poorly soluble medicines have been carried out with this technique. The use of Nanosuspension can help to increase or improve characteristics including bioavailability and absorption, as well as potentially lower the dosage of conventional oral dosage forms (7). The administration of poorly water-soluble and poorly water-and lipid-soluble medications can be addressed by Nanosuspensions, which are special due to their ease of usage and the benefits they offer over alternative approaches.

The several facets of Nanosuspensions and their potential as a viable medication delivery technique were the primary focus of this review. The engineering and research done at the nanoscale, or 10^{-9} m², is known as nanotechnology (2, 9). Since the majority of biological qualities exhibiting NCEs are weakly water-soluble, the pharmaceutical industry are always searching for novel ways to achieve an appropriate oral bioavailability (2). These systems' primary feature is their quick rate of dissolution, which improves bioavailability following oral administration (2, 9).



Figure 2: Schematic representation of method of preparation, dosage forms, components and applications of Nanosuspensions in drug delivery systems

Criteria for Selection Of Drug For Nanosuspensions:

Any of the following features of an API can lead to the production of Nanosuspension:

- API are insoluble in both water and oils, or they should be soluble in oil (high logP).
- Medicines with a decreased propensity for crystals to dissolve in any kind of solvent.
- API at extremely high dosages (4, 1)

ADVANTAGES:

- 1. An increase in the drug's saturation solubility and dissolution velocity.
- 2. Better biological output.
- 3. Simplicity in production and expansion.
- 4. Extended bodily stability.
- 5. Flexibility.
- 6. A rise in absorption by the mouth.
- 7. A better proportionality of dose.

- 8. Its simplicity and broad applicability to the majority of medications.
- 9. It works with medications that aren't very soluble in water.
- 10. Any method can be used to deliver it.
- 11. Lessened tissue irritation whether administered subcutaneously or intramuscularly.
- 12. The intravenous method of delivery allows for rapid breakdown and tissue targeting.
- 13. Oral administration of Nanosuspension results in enhanced bioavailability, a decreased fed/fasted ratio, and a faster onset.
- 14. A decrease in particle size can lead to an increase in the absorption form absorption window.
- 15. Better bioavailability and more reliable dosage when applied topically and inhaled.
- 16. To improve a medicine's bioavailability, Nanosuspensions of that drug with a higher log P value can be created.
- 17. An increase in biological performance as a result of the medications' high saturation solubility and dissolution rate.
- 18. Tablets, pellets, hydrogel, and suppositories can all be made with Nanosuspensions, making them appropriate for a variety of delivery methods.
- 19. Raising the percentage of amorphous particles in the particles, which may cause a change in the crystalline structure and increase solubility.
- 20. The potential for Nanosuspension surface modification for site-specific delivery.
- 21. The ability to produce on a large scale, which is a requirement for releasing a delivery system onto the market. (13)

2. FORMULATION CONSIDERATION: (7)

2.1 Stabilizer:

In order to provide a physically stable formulation, a stabilizer is employed to moisten the drug particles systematically and to provide an ionic or stearic barrier that inhibits the maturation and agglomeration of Nanosuspension. Lecithin, poloxamers, polysorbate, cellulose, and povidones are a few of the stabilizers. Drug particles distributed in a liquid continuous medium are stabilized by electrostatic, steric, or a mixture of both mechanisms with the use of surfactants and/or polymers. Nonionic polymers and nonionic surfactants, such as cellulose derivatives, poloxamers (sometimes referred to as polymeric surfactants), polysorbates, and povidones, are typically responsible for steric stabilization by keeping particles out of the reach of attractive Vander Waals forces. Ionic surfactants, such as sodium dodecyl sulfate (SDS), dioctyl sulfosuccinate sodium salt (DOSS), and benzethonium chloride (BKC), which mutually repress comparable charged particles, are typically responsible for electrostatic stabilization.

2.2 Organic Solvents:

The two key factors that determine the suitability of organic solvents in the pharmaceutical industry when forming Nanosuspensions utilizing emulsion or microemulsion as templates are their potential for toxicity and how simple it is to remove them after formulation. While ethyl acetate, ethyl formate, butyl lactate, triacetin, propylene carbonate, and benzyl alcohol are less dangerous and appropriate for use in pharmaceuticals, ethanol and isopropanol are solvents that are somewhat water-miscible.

2.3 Surfactants:

It is mixed with a formulation surfactant, which acts as a wetting agent or deflocculant to lighten the dispersion by lowering the tension at the interfaces. Lecithin, povidone, cellulosics, poloxomers, and polysorbate (Tween/Span series) are examples of surfactants that are frequently utilized.

2.4 Co-Surfactants:

This explains additional co-surfactants for particular stabilizers that are safe to use in the formulation of microemulsions. Salts, or dipotassium glycyrrhizinate, are examples of co- surfactants that are safe to use with stabilizers like glycerol, ethanol, and isopropanol.

2.5 Other Additives:

Osmogene, cryo-protectant, polyols, buffers, and salts are examples of Nanosuspensions whose composition is dependent on either the product moiety's characteristics or the mode of administration.

3. METHODS OF PREPARATION OF NANOSUSPENSIONS:

As seen in Figure 1, there are primarily two approaches utilized to manufacture Nanosuspensions: "Bottom up technology" and "Top down technology."[1, 16] Top down technology involves breaking down bigger particles into nanoparticles; examples of this process include high-pressure homogenization and milling techniques. Bottom up technology involves an assembly method to generate nanoparticles, such as precipitation, micro-emulsion, and melt emulsification method. (1) The methodologies' guiding principles are discussed in detail, and Table 1 displays their advantages and disadvantages. [14, 15]



Figure 3: Approaches for preparation of Nanosuspension

3.1 Precipitation Technique (Solvent-Antisolvent Method):

For many years, the precipitation process was employed to prepare submicron particles. It is mostly useful for medications that dissolve poorly. The first medication is fully dissolved in an appropriate solvent. Following that, this solution is combined with a miscible anti-solvent system that contains surfactants. Drug-containing solution is quickly added to the anti-solvent, causing the drug to suddenly become super-saturated in the mixed solution and form ultrafine drug solids. The two main stages of the precipitation method are the production of crystal nuclei and crystal development. A strong nucleation rate combined with a low growth rate is required to prepare a stable form of suspension with the smallest possible particle size. The temperature affects both rates. The drug must be miscible with non-solvent and soluble in at least one solvent in order to be used in this approach [4, 17].



Figure 4: Precipitation method

3.2 Lipid Emulsion/Microemulsion Template:

Simply diluting the emulsion, which is created by employing a somewhat water-miscible solvent as the dispersed phase, yields Nanosuspensions as well. Drugs that are soluble in volatile organic solvents or partially miscible in water are treated using the emulsion approach. Furthermore, Nanosuspensions are also produced using micro-emulsion templates. Dispersions known as micro-emulsions are made up of two immiscible liquids, such as water and oil, and are thermodynamically stabilized by a surfactant or co-surfactant. Drugs can be intimately mixed to achieve saturation, and the medication can be poured into either the internal phase or the prepared phase of the microemulsion.[1] Sodium taurodeoxycholate, water, butyl lactate, lecithin, and the microemulsion process are used to create grenaflour Nanosuspension.[1]



Figure 5: Micro-emulsion Method

3.3 Melt Emulsification Method:

The most popular technique for producing solid lipid nanoparticles is melt emulsification. Kipp and colleagues originally used the melt emulsification process to manufacture ibuprofen Nanosuspensions. There are four steps in this process. First, the drug is added to the aqueous solution containing the stabilizer. To create an emulsion, the solution is heated to a temperature greater than the drug's melting point and then homogenized using a high-speed homogenizer. Throughout the entire procedure, the temperature must be kept above the drug's melting point. In order to cause the particles to precipitate, the emulsion is finally cooled. The key factors influencing the size of the Nanosuspension particles are the drug concentration, the kind and concentration of stabilizers used, the cooling temperature, and the homogenization procedure. (1)

3.4 Supercritical Fluid Method:

To create nanoparticles, a variety of techniques are employed, including the rapid expansion of supercritical solution (RESS) process, the supercritical anti-solvent process, and the precipitation with compressed anti-solvent (PCA) process. The RESS technique involves expanding a drug solution through a nozzle into a supercritical fluid, which causes the drug to precipitate as small particles due to the supercritical fluid's lack of solvent power. Young et al. produced 400–700 nm diameter cyclosporine nanoparticles using this technique. The drug- containing solution is atomized and introduced into the CO2 compressed chamber using the PCA method. The solution becomes supersaturated as the solvent is removed, and precipitation eventually takes place. The medication solution is introduced into the supercritical fluid during the supercritical anti-solvent procedure, and the solvent is also removed as well as the drug solution becomes supersaturated. (18, 1)



Figure 6: Schematic representation of the critical parameters of bottom-up technology by the fishbone diagram. (6)

3.5 Homogenization:

(a) High Pressure Homogenization (Disso-cubes):

Using a pressure plunger pump and high pressure, this approach forces the suspension through a tiny valve [4]. Water boils and gas bubbles arise as a result of the static pressure dropping below the boiling point of water due to the passage of suspension through the orifice. Bubbles will burst and the pressure will return to normal after it exits the orifice. As a result, nearby particles are able to surge to the surface, which reduces size. The apvgaulin micron lab 40 homogenizer works on this theory.





(b)Homogenization in (Nano-pure) non-aqueous media:

In a water-free or water-mixture medium, it is homogenized. At freezing point, the temperature will be zero degrees or even. This is why deep freeze homogenization is the term used. For the thermolabile compounds, it is the most effective and popular technique [4].



Figure 8: Schematic representation of the critical parameters of the high-pressure homogenization method by the fishbone diagram. (6)

3.6 Media Milling:

Both media mills and high shear pearl mills can be used to create Nanosuspensions. The milling chamber, recirculation chamber, and milling shaft are the components of these mills. Grinding media consisting of ceramic sintered zirconium oxide or aluminium oxide pearls or balls. Water, milling material, stabilizer, and medication are all loaded into the milling chamber. The balls have an effect on the sample when they are rotated at a high shear rate at a controlled temperature. Particle size reduction and the production of nanoscale particles are caused by the combined effects of friction force and impact mechanism.



Figure 9: Schematic Representation of Media milling method



Figure 10: Schematic representation of the critical parameters of the wet milling method by the fishbone diagram. (6)



Figure 11. Schematic representation of the Nanosuspension preparation methods (6)

3.7 Combination Technology:

Together with these technologies—bottom-up and top-down—it is also feasible to combine many approaches to prepare NSs and, with minor adjustments, produce NSs with the necessary characteristics [19, 20]. The studies in the literature address using multiple methods in combination as shown in Table 2, and they also offer an assessment of the benefits of the

aforementioned methods. Through the use of mixed techniques, NSs can be prepared for the obtained formulation by first employing top-down technology and then bottom-up technology, or vice versa.

3.8 Microprecipitation - High-Pressure Homogenization (Nanoedge):

The fusion of high-pressure homogenization with micro-precipitation processes is known as Nano edge. This process involves precipitating the friable materials and then breaking them apart using a lot of heat or shear force. [1] Figure 8 illustrates the nano edge preparation techniques.



Figure 12: Preparation method of Nanoedge

4. CHARACTERIZATION OF NANOSUSPENSION:

4.1 Particle size distribution:

The mean particle size and width of the particle size distribution, which define the physicochemical features including saturation solubility, dissolving velocity, physical stability, and even biological performance, are the most appropriate parameters for characterizing the Nanosuspension. The change in saturation solubility and dissolving velocity is caused by a change in particle size. Reduced particle size increases the solubility and dissolution of the saturated state. [5]

4.2 Zeta Potential (Particle Charge):

One distinguishing feature that establishes the physical stability of a Nanosuspension is its zeta potential. The indirect measurement of the diffusion layer thickness that can be utilized to forecast long-term stability is known as zeta potential. In order to get a well- stabilized Nanosuspension, an electrostatically stabilized Nanosuspension must have a minimum zeta potential of \pm 30 mV, whereas a combined electrostatic and steric stabilization would benefit from a minimum zeta potential of \pm 20 mV. [5]

4.3 Crystal Morphology:

X-ray diffraction analysis is used with differential scanning calorimetry and scanning electron microscopy to identify polymorphic variations in the drug's crystalline structure caused by the effects of high-pressure homogenization. Due to high-pressure homogenization, Nanosuspension changes in crystalline structure, perhaps taking on an amorphous shape or other polymorphic forms. It is possible to get greater saturation solubility by increasing the proportion of amorphous drug fraction.

4.4 Saturation Solubility and Dissolution Velocity:

The dissolving velocity and saturation solubility are improved by Nanosuspension. Size reduction is the cause of the increase in dissolving pressure, while increased solubility is the cause of the relatively small particle size. The primary cause of size decrease is a rise in saturation solubility brought on by a change in surface tension.

5. APPLICATIONS OF NANOSUSPENSION:(7)

5.1 Oral Drug Delivery:

The conventional dosing approach, which involves administering drugs orally, has several issues that lead to poor solubility, insufficient absorption, and insufficient effectiveness. So, oral Nanosuspension has been developed as a solution to the issue. Oral Nanosuspension contributes to the oral bioavailability and solubility of poorly soluble medicines (BCS class- II) because of its vast surface area and tiny particle size (Fig. 8). Some of the drugs like Gliczaide, silymarin, cyclosporine are formulated into nanosuspension.

5.2 Parenteral Drug Delivery:

Drugs that are not injectable and are poorly soluble can be changed into a form that can be administered intravenously using Nanosuspensions. While creating Nanosuspensions for parenteral administration is essential, recent advancements in this field have demonstrated its applicability as an injectable formulation.

5.3 Pulmonary Drug Delivery:

Mechanical or ultrasonic nebulizers can be used to nebulize Nanosuspensions for pulmonary administration. All aerosol droplets include drug nanoparticles because of the abundance of tiny particles. Due to their small particle size, aqueous medication solutions are easily nebulized and administered via the pulmonary route. A few medications that have been effectively administered by pulmonary route include itraconazole, budesonide, ketotifen, ibuprofen, indomethacin, and nifedipine.

5.4 Ocular Drug Delivery:

Because they naturally increase the saturation solubility of medications, Nanosuspensions are employed in ocular delivery for prolonged release, making them the perfect method for ocular delivery of hydrophobic pharmaceuticals.

5.5 Dermal:

Increased saturation solubility in the nanocrystalline form leads to improved drug diffusion into the skin, including improved penetration, permeation, and bioadhesion, all of which can be highly advantageous for dermal administration. Products like Rapamune, Emend, TriCor, Megase, and Silver are a few that are advertised.

5.6 Transdermal Drug Delivery:

The process of "nanonization" involves shrinking the drug particle to a nanoscale. The primary drawback of the transdermal method is the sluggish penetration of many medications through the skin layer. These methods, which include topical formulations with penetration enhancers, allow substances to pass through the epidermal barrier.

5.7 Drug Targeting:

Targeting their surface characteristics and changing the stabilizer's behavior in vivo are also possible with nano suspension. For localized drug administration, the medication must be absorbed by the mono nuclear phagocytic system. If the infectious pathogen continues to live inside cells, this might be utilized to target macrophages with anti-microbial and anti- leishmanial medications.

5.8 Bioavailability Enhancement:

The issue of low bioavailability can be resolved by using Nanosuspensions to address the dual challenges of low solubility and low membrane permeability. The faster dissolving (90% in 20 min) and consequently higher bioavailability of the Lyophilized Nanosuspensions powder compared to a coarse powder (15% in 20 min) greatly increased the therapeutic impact.

5.9 Mucoadhesion Of The Nanoparticles:

When taken orally, nanoparticles in suspension dissolve into the liquid medium and quickly come into contact with the mucosal surface. A method of adherence known as bio adhesion, illustrated in FIG. 1, immobilizes the particles at the intestinal surface. Prior to particle absorption, the initial stage is for the particles to make direct contact with the intestinal cells through a bio adhesive phase, which enhances bioavailability and targets the parasites that are still present in the gastrointestinal tract.



Figure 13: Applications of Nanosuspensions (7)

5.10 Dry Eye Disease: (21)

Kerato-conjunctivitis sicca, another name for dry eye disease (DED), is a multifactorial disorder that can cause pain to the eyes, visual abnormalities, and possible damage to the ocular surface due to insufficient tear production, poor tear quality, or excessive tear evaporation. The ocular surface inflammation, aberrant neurosensory function, and disturbed tear film dynamics are all part of the pathogenesis of dry eye illness.



Figure 14: Dry Eye Disease

Here's an overview of the key components of dry eye disease pathophysiology:

Tear Film Instability: The lipid, aqueous, and mucin layers that make up the tear film work together to keep the ocular surface hydrated, lubricate, and guard against microbial infection. Any of these layers' composition or function can be disrupted, which can cause instability in the tear film and increase dryness and tear evaporation.

Decreased Tear Production: Aqueous deficit, or decreased tear production, can be brought on by a number of conditions, including aging, autoimmune illnesses like Sjögren's syndrome, hormonal changes like menopause, prescription drugs like antihistamines, and environmental variables like low humidity. The ocular surface is not sufficiently hydrated and lubricated as a result of insufficient aqueous tear production.

Increased Tear Evaporation: Meibomian gland dysfunction (MGD), a common cause of evaporative dry eye, can result in excessive tear evaporation. Increased evaporation and instability of the tear film are caused by anomalies in the lipid layer of the tear film caused by MGD.

Ocular Surface Inflammation: A key factor in the etiology of dry eye illness is persistent inflammation of the ocular surface. Damage to the ocular surface and environmental stresses cause an upregulation of inflammatory mediators, including chemokines, cytokines, and matrix metalloproteinases (MMPs). Goblet cell loss, epithelial cell injury, and compromised corneal and conjunctival barrier function are all influenced by inflammation.

Neurosensory Dysfunction: Neurosensory abnormalities are brought on by changes in the density and function of the corneal nerves in cases of dry eye illness. Symptoms including burning, itching, and a feeling of a foreign body are caused by aberrant neural transmission and reduced corneal sensitivity.

Corneal and Conjunctival Damage: Long-term exposure to inflammatory mediators and desiccating stimuli can cause punctate epithelial erosions, squamous metaplasia, corneal conjunctivalization, and damage to epithelial cells. These alterations worsen the symptoms of dry eyes and jeopardize the integrity of the ocular surface.

Tear Film Hyper-osmolarity: One of the main characteristics of dry eye disease is increased tear film osmolarity, which can be caused by either greater tear evaporation or decreased tear volume. Ocular surface injury, inflammation, and neurosensory dysfunction are all exacerbated by hyperosmolarity.

The complex pathophysiology of dry eye illness is attributed to the interplay of various components such as ocular surface integrity, neurosensory function, inflammation, and tear film dynamics. It is imperative to comprehend these fundamental principles in order to devise efficacious diagnostic and therapeutic approaches for the management of dry eye disease.



Figure 15: Pathophysiology of Dry Eye Disease

5.11 Nanosuspensions In Treating Dry Eye Disease: (21)

As Nanosuspensions may effectively carry medications to the ocular surface, they have showed promise in the treatment of dry eye disease. The multifactorial illness known as dry eye disease (DED) is characterized by either excessive or insufficient tear evaporation, which can cause discomfort in the eyes and can harm the ocular surface.

Here's how Nanosuspensions can be beneficial in treating DED:



Figure 16: Developing Nanosuspension for DED

Increased Drug Bioavailability: As Nanosuspensions increase the solubility and dissolution rate of medications, they can improve the bioavailability of certain pharmaceuticals. This is especially crucial for medications that are frequently used to treat DED and are poorly soluble in water.

Improved Ocular Penetration: Compared to traditional eye drops, nanoparticles in Nanosuspensions are more effective at penetrating the cornea and getting to the target tissues. Better therapeutic effects may result from this increased penetration.

Extended Drug Release: With less frequent dosage, sustained drug release can be achieved with Nanosuspensions, guaranteeing long-lasting therapeutic effects. Convenience and patient compliance may both benefit from this.

Reduced Irritation: By reducing contact with the ocular surface and enhancing drug dispersion within the eye, nanoparticles can help lessen ocular discomfort brought on by some drugs.

Combination Therapy: When several medications are combined into one formulation using Nanosuspensions, therapeutic results are enhanced and synergistic effects are possible when compared to when pharmaceuticals are administered separately.

Stabilization of Tear Film: In order to maintain the tear film and lessen tear evaporation, certain Nanosuspensions can imitate the lipid layer of the tear film. This is advantageous for treating evaporative dry eye.

Targeted Delivery: Functionalization of nanoparticles can facilitate targeted delivery of drugs to specific ocular tissues, minimizing systemic side effects and enhancing therapeutic efficacy.

Numerous intriguing formulations are being investigated in the ongoing research on Nanosuspensions as a potential treatment for dry eye illness. Before being widely used in clinical settings, more research is necessary to determine the best formulation characteristics, test clinical efficacy, and determine long-term safety.



Figure 17: Nanosuspensions: A Promising Drug Delivery Technology

6. CONCLUSION:

Nanosuspensions seem to be a novel and yet commercially feasible way to address issues like low bioavailability that come with hydrophobic drug delivery. Large-scale production of Nanosuspensions, particularly those that are poorly soluble in both organic and aqueous media, is accomplished through the use of fabrication techniques such media milling and high-pressure homogenizers. There are several ways to administer Nanosuspensions, including parenteral, topical, ophthalmic, oral, and pulmonary. As a result, more clinical trials are required, the pharmacokinetic data obtained from the administration of different NSs must be improved, and theoretical models must be established in order to pinpoint the steps involved in the formulation creation and optimization of NSs. Furthermore, a few technologies and supporting devices that also offer great stability and simple scaling up will become increasingly crucial in the future. The number of products in clinical trials and on the market, as well as the products' dates of release, can be used to evaluate the technology and concept of NS formulations. Thus both the research potential in the field of pharmacy and the patients can profit greatly from Nanosuspension technology.

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