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Nanosuspensions: A Novel Strategy for Overcoming Drug Solubility Challenges

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ABSTRACT

Nanosuspensions are a promising drug delivery strategy designed to address the challenges of poorly water-soluble drugs by enhancing their bioavailability and solubility. These colloidal dispersions consist of drug nanoparticles stabilized by surfactants, reducing particle size to less than 1 µm, which significantly improves drug dissolution and absorption. Nanosuspensions are versatile in their administration routes, including oral, intravenous, ocular, and pulmonary delivery, making them suitable for a wide range of therapeutic applications. The key preparation methods include techniques such as media milling, high-pressure homogenization, and supercritical fluid technology, which offer flexibility and scalability in formulation development. Nanosuspensions are particularly beneficial for drugs in BCS classes II and IV, which suffer from poor solubility or permeability. Despite certain limitations, such as stability concerns and the complexity of production, nanosuspensions offer numerous advantages like improved drug bioavailability, faster therapeutic onset, and the potential for targeted drug delivery. This review highlights the preparation methods, formulation considerations, and potential applications of nanosuspensions in enhancing the efficacy of poorly soluble drugs, making them an attractive option for modern pharmaceutical development.

KEYWORDS: Nanosuspension, High pressure homogenization, Media milling, Supercritical fluid, Solubility, Particle size.

INTRODUCTION [1,2]

A Pharmaceutical suspension is a coarse dispersion in which internal phase is dispersed uniformly throughout the external phase. The internal phase consisting of insoluble solid particles having a specific range of size which is maintained uniformly throughout the suspending vehicle with aid of single or combination of suspending agent. The external phase (suspending medium) is generally aqueous in some instance, may be an organic or oily liquid for non-oral use. The absorption of drugs from the intestine is mainly dependent on their solubility in the intestinal fluids and their intestinal membrane permeability. Insufficient absorption of poorly soluble drugs is mainly due to slow dissolution and the generation of a small concentration gradient across the intestinal mucosa. To overcome these problems different formulations of nanosized drugs have been developed. Nanosuspensions are colloidal dispersions of solid drug particles in a liquid phase with average particle sizes below 1 µm stabilized by the use of surfactants. Solubility is an essential factor for drug effectiveness, independent of the route of administration. Poorly soluble drugs are often a challenging task for formulators in the industry. Conventional approaches for enhancement of solubility have limited applicability, especially when the drugs are poorly soluble simultaneously in aqueous and in non-aqueous media. Nanosuspension technology can be used to improve the stability as well as the bioavailability of poorly soluble drugs. Nanosuspensions are biphasic systems consisting of pure drug particles dispersed in an aqueous vehicle, stabilized by surfactants. These are simple to prepare and are more advantageous than other approaches. Techniques such as wet milling, high-pressure homogenization, emulsification-solvent evaporation and super critical fluid have been used in the preparation of nanosuspensions. It has the advantage of delivery by various routes, including oral, parenteral, pulmonary and ocular routes. The present article reviews the current methods used to prepare nanosuspensions and their application in drug delivery. Nanosuspensions are colloidal dispersions of nanosized drug particles stabilized by surfactants. They can also be defined as a biphasic system consisting of pure drug particles dispersed in an aqueous vehicle in which the diameter of the suspended particle is less than 1 µm in size. Nanosuspensions can be used to enhance the solubility of drugs that are poorly soluble in aqueous as well as lipid media. As a result, the rate of flooding of the active compound increases and the maximum plasma level is reached faster (e.g., oral or intravenous [IV] administration of the nanosuspension). This is one of the unique advantages that it has over other approaches for enhancing solubility. It is useful for molecules with poor solubility, poor permeability or both, which poses a significant challenge for the formulators. The reduced particle size renders the possibility of intravenous administration of poorly soluble drugs without blockade of the blood capillaries. Nanosuspensions have been prescribed as an all-inclusive delivery approach for orally administered drug particles that fall into BCS class II and class IV category of drugs.

Advantages of Nanosuspension Drug Delivery System[3,4]

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

Disadvantages for Nanosuspension Drug delivery system [5]

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.

FORMULATION CONSIDERATIONS IN NANOSUSPENSION [6]

Table no.1: Formulation Considerations

Excipients	Function	Examples
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.	Buffers, salts, polyols, osmogens, cryoprotectants, etc.

TECHNIQUES FOR NANOSUSPENSION PREPARATION [7-26]

There are primarily two approaches to preparing Nano suspensions. The traditional method, referred to as "bottom-up technology,' involves precipitation to form hydrosols. Conversely, "top-down technologies' are disintegration methods that are preferred over precipitation techniques.

These "top-down technologies' include media milling for nanocrystals, high pressure homogenization in water for dissocubes, high-pressure homogenization in non-aqueous media for nanopures, and a combination of precipitation and high-pressure homogenization known as nano edge.

1. Bottom-up technology:

An approach known as "bottom-up technology" begins at the molecular level and develops through molecular association to produce solid particles. This method uses conventional precipitation approaches, such as changing the temperature or adding a nonsolvent to change the solvent's quality. In pharmaceutical chemistry and technology, precipitation is a well-known process.

Advantages:

• Simple as well as cost-effective equipment can be used.

• Precipitation offers higher saturation solubility when compared with methods used in the preparation of nanosuspension.

Disadvantages:

• The drug must exhibit solubility in at least one solvent, which excludes new drugs with poor solubility in both aqueous and organic media.

• At least one non-solvent must be miscible with the solvent being utilised.

• Removal of residues of solvent increases production costs.

• Preserving the particle characteristics, particularly size and the amorphous fraction, can be challenging. To maintain particle integrity, a subsequent process such as lyophilization or spray drying is often recommended.

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2. Top-down technology:

The top-down technologies encompass two methods:

a) Media milling:

Nanosuspensions can be prepared by utilizing pearl mills. This process involves utilizing a recirculation chamber, a milling shaft, and a milling chamber. Initially, a drug suspension is introduced into the mill, along with an aqueous medium, and combined with pearls or small grinding balls. At a high shear rate balls rotate, leading to friction and impact within the grinding jar, effectively reducing the size of the particles. The milling media, typically made of durable materials such as zirconium oxide, demonstrate excellent resistance to wear and tear. Advanced equipment like planetary ball mills, such as the PM200, PM100 models can achieve particle sizes below 0.1µm. In a specific study, researchers employed a wet milling technique to produce a nanosuspension that consists of Zn-Insulin, resulting in particle size that is about 150 nm. However, it's important to note that media milling has its limitations, including potential contamination from milling material erosion, the risk of thermolabile drug degradation due to heat generation, and the occurrence of particles that are around 5 µm in size.

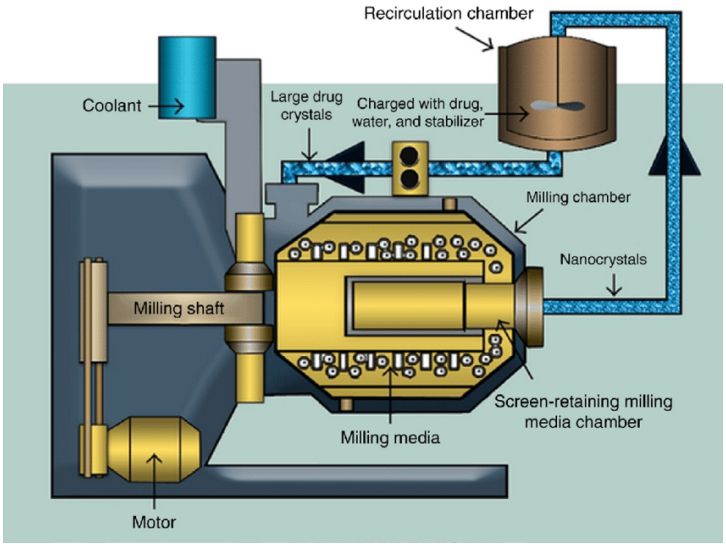

Fig no.1: Media milling

Advantages:

• Straightforward technology

• Milling process is cost-effective

• To a certain extent, achieving extensive manufacturing is possible through the utilization of batch processing.

Disadvantages:

• There is a credible possibility that the erosion of milling material could result in the contamination of the product.

• The process duration may not be optimal for efficient production.

• Potential for microbial growth in the water phase during prolonged milling periods

• The duration and expenses related to the milling material's separation from the nanosuspension pose significant considerations, particularly in the production of sterile parenteral products.

b) High pressure homogenization

It is a technique that involves passing a drug suspension through a narrow valve under pressure. This process utilizes cavitation and implosion of gas bubbles to reduce particle size. Pre-milling of fine drug particles is recommended for higher solid concentrations. High-pressure homogenization provides several benefits, including its applicability to both diluted and concentrated suspensions and the capability for aseptic manufacturing.

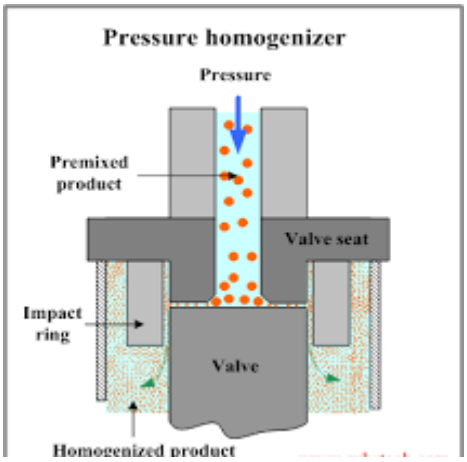

Fig no.2: High Pressure Homogenizer

Nanopure:

Nanopure is a method of homogenization that employs media or mixtures without water. In technology involving Dissocubes cavitation is crucial, but when non-aqueous media are employed, the decrease in static pressure is inadequate to induce cavitation. Nanopure achieves homogenization at lower temperatures, even below the freezing point, making it suitable for thermolabile substances. It provides comparable results to Dissocubes in milder conditions.

NanoedgeTM:

Nanoedge TM combines homogenization and precipitation techniques to achieve smaller particle size that is small an. d effectively enhances the stability. It addresses the limitations commonly associated with precipitation methods, such as long-term stability issues and crystal growth. Initially here suspension that is precipitated undergoes additional homogenization in order to decrease size of particle and inhibit crystal development. Methanol, ethanol, and isopropanol are just a few examples of water miscible solvents that can be used in the precipitation process. These solvents can be tolerated in the formulation to some extent, while it is desirable to totally remove them. An evaporation stage may be added to the NanoedgeTM nanosuspension manufacturing process to provide a modified starting material devoid of solvent, which is subsequently homogenised under high pressure.

Emulsion diffusion method:

In this method, emulsions are used as both a vehicle for delivery of drug and templates for generating Nano suspensions. This technique is suitable only when the drug shows solubility in organic solvents that are volatile in nature or solvents that show partial solubility in water. The dispersed phase of the emulsion contains these solvents, which carry the drug. The mixture of solvent is dispersed within an aqueous phase containing appropriate surfactants, and the resulting emulsion is stirred. Subsequently, high-pressure homogenization is employed to homogenise the emulsion. Through multiple cycles of homogenization, water is used to dilute the emulsion, and it is further homogenised so that organic solvent gets diffused and droplets get converted into solid particles. By controlling the emulsion's size, the nanosuspension's particle size is adjusted accordingly. The optimisation of the composition of surfactant enhances the absorption of the organic phase, hereby increasing the emulsion's drug loading. Initially, solvents like chloroform, ethanol, ethyl acetate, and methanol were used more commonly in this process.

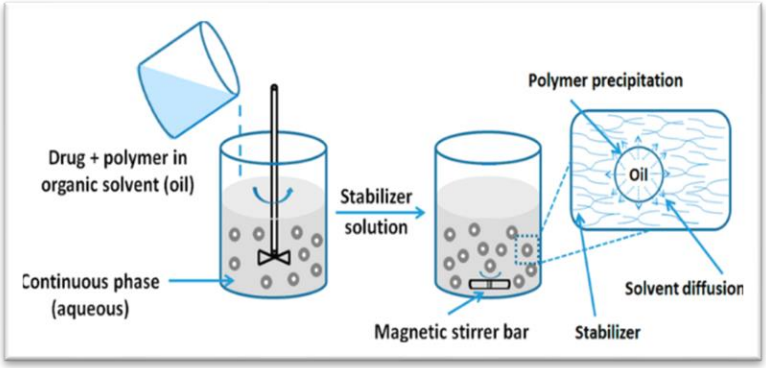

Fig no.3: Emulsion diffusion method

Advantages:

• It doesn't require any specialised equipment.

• By adjusting the emulsion's droplet size, it is easy to regulate the particle size.

• The formulation can be optimised to ensure scalability.

Disadvantages:

• Drugs whose solubility is limited in organic and aqueous media are not suitable for this method.

• Issues associated with safety may arise due to the use of hazardous solvents during the process. Purifying the drug nanosuspension through ultrafiltration may increase overall costs.

• Relatively larger amounts of surfactant/stabilizer are needed compared to other previously mentioned production techniques.

Micro-emulsion template:

This method involves dispersing the drug in a combination of organic or inorganic solvents, which must be coupled with an aqueous phase and an appropriately surfactant-containing aqueous phase to form an emulsion. The drug's particles quickly precipitate at low pressure as the organic phase evaporates, creating nanosuspension. The drug particles quickly precipitate and create the nanosuspension by rapidly evaporating the organic phase at decreased pressure. The stability of the nanosuspension is ensured by the use of surfactants. Triacetin, benzyl alcohol, and butyl lactate are a few examples of solvents that can be used in the dispersion phase as an alternative to employing harmful solvents.

Advantages:

• It doesn't require any specialised equipment.

• By adjusting the emulsion's droplet size, it is simple to regulate the particle size.

• The scalability of the process is achievable with appropriate formulation optimisation.

Disadvantages:

• Drugs that show low solubility in both media, i.e., organic and aqueous, are not suitable for this technique.

• The purification process of nanosuspension through diultrafiltration may lead to increased process costs.

• Compared to the other manufacturing methods previously described, more surfactant or stabiliser is needed.

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Supercritical fluid method:

From drug solutions, it is possible to make drug nanoparticles using supercritical fluid technology. Precipitation using the compressed anti-solvent process (PCA), the rapid expansion of the supercritical solution process (RESS), and the supercritical anti-solvent process are a few of the techniques that have been tested. The RESS technique involves expanding a medicinal solution using a nozzle and a supercritical fluid. As a result of the loss of solvent power, tiny drug particles precipitate. In the PCA technique, compressed CO2 is used to atomize the drug solution, causing super saturation and the drug to precipitate as tiny crystals. In the supercritical anti-solvent method, a drug solvent that is miscible with the supercritical fluid and a supercritical fluid in which the medicine is only weakly soluble are both used. The drug is injected into the supercritical fluid, the solvent is withdrawn, and the drug supersaturates and precipitates as tiny crystals. These methods have been used to produce poorly soluble nanoparticles of numerous medicines.

Disadvantages:

• The use of toxic solvents and a larger quantity of stabilisers and surfactants compared to other procedures.

• Potential particle nucleation overgrowth owing to temporary high super saturation may lead to the creation of unwanted forms or polymorphs.

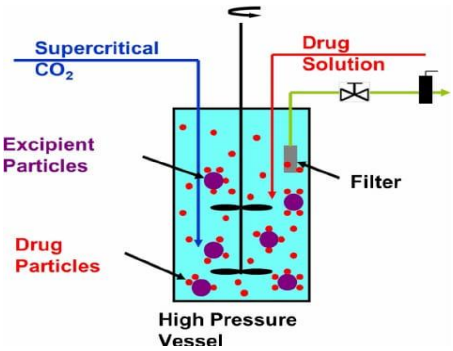

Fig no.4: Supercritical Fluid method

Emulsification melt method:

The drug is heated past its melting point while being dissolved in an aqueous solution of a stabiliser during the melt emulsification process. The mixture is then homogenised to produce an emulsion. The temperature of the emulsion is maintained above the melting point of the medication throughout the operation using a heating tape with a temperature controller. The emulsion is then either slowly cooled to room temperature or immediately chilled in an ice bath.

Advantage:

• When employing the melt emulsification method, no organic solvents are used at all throughout the production process.

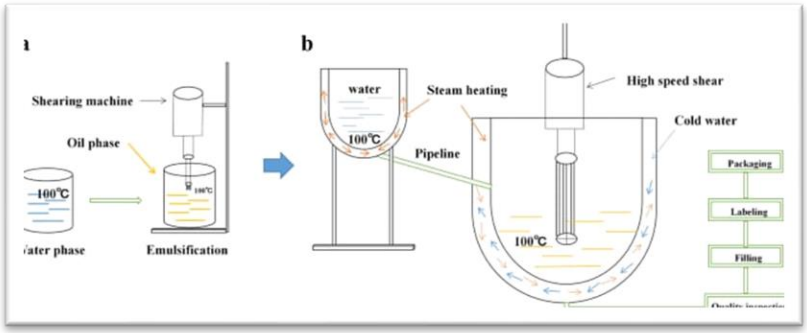

Fig no.5: Emulsification melt method

Dry co-grinding:

Dry milling techniques have lately been used to create nanosuspensions. This approach involves mixing poorly soluble drugs with soluble copolymers and polymers in a liquid environment to produce stable Nanosuspensions. Many soluble polymers and copolymers, such as PVP, polyethylene glycol (PEG), hydroxypropyl methylcellulose (HPMC), and cyclodextrin derivatives, have been subjected to this approach.

CHARACTERIZATION OF NANOSUSPENSION [27-29]

Color, odor and taste: These characteristics are especially important in orally administered 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 multi-sizer. The PCS method can measure particles in the size range of 3 nm to 3µm and the LD method has a measuring range of 0.05-80 µm. The coulter counter multi-sizer 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 ±30 mV 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.

Saturation solubility and dissolution velocity: The determination of the saturation solubility and dissolution velocity is very important as these two parameters together help to anticipate any change in the in-vivo performance (blood profiles, plasma peaks and bioavailability) of the drug. As nanosuspensions are known to improve the saturation solubility of the drug, the determination of the saturation solubility rather than an increase in saturation solubility remains an important investigational parameter. The saturation solubility of the drug in different physiological buffers as well as at different temperatures should be assessed using methods described in the literature. The investigation of the dissolution velocity of nanosuspensions reflects the advantages that can be achieved over conventional formulations, especially when designing the sustained-release dosage forms based on nanoparticulate drugs. The dissolution velocity of drug nanosuspensions in various physiological buffers should be determined according to methods reported in the pharmacopoeia.

In-vivo biological performance: The establishment of an in-vitro/in-vivo correlation and the 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 behaviour 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 27, 28. In fact, the qualitative and quantitative com position of the protein absorption pattern observed after the intravenous injection of nanoparticles is recognized as the essential factor for organ distribution 27, 28, 29. Hence, suitable techniques have to be used in order to evaluate the surface properties and protein interactions to get an idea of in-vivo behaviour. Techniques such as hydrophobic interaction chromatography can be used to determine surface hydrophobicity , whereas 2-D PAGE 27 can be employed for the quantitative and quailtative measurement of protein adsorption after intravenous injection of drug nanosuspensions in animals.

APPLICATIONS [30]

- Oral administration Nanosizing of drugs leads to an increased oral absorption and subsequent bioavailability. Improved bioavailability is due to the adhesiveness of drug nanoparticles to the mucosa and the increased saturation solubility leading to an

increased concentration gradient between gastrointestinal tract lumen and blood. Aqueous nanosuspensions can be used directly in a liquid dosage form and a dry dosage form such as tablet or hard gelatin capsule with pellets. Granulates can also be produced by spray drying of nanosuspensions.

• Ophthalmic drug delivery Nanosuspensions have been providing to be vital for drugs that exhibit poor solubility in lachrymal fluids. Suspensions offer advantages such as prolonged residence time , which is desirable for most ocular diseases for effective treatment and avoidance of high tonicity created by water soluble drugs. Their actual performance depends on the intrinsic solubility of the drug in lachrymal fluids. Thus the intrinsic dissolution rate of the drug in lachrymal fluids governs its release and ocular bioavailability.

• Intravenous administration Parenteral route of administration provides a quick onset of action, rapid targeting and reduced dosage of the drug. It is the preferred route for drugs undergoing first-pass metabolism and those that are not absorbed in the GIT or that get degraded in the GIT. One of the important applications of nanosuspension technology is the formulation of intravenously administered products. IV administration results in several advantages, such as administration of poorly soluble drugs without using a higher concentration of toxic cosolvents, 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.

• Targeted drug delivery Nanosuspensions can also be used for targeted delivery as their surface properties and in vivo behaviour can easily be altered by changing either the stabilizer or the milieu. Their versatility, ease of scale up and commercial product has helped in developing commercial viable nanosuspensions for targeted delivery.

• Pulmonary administration Aqueous nanosuspensions can be nebulized using mechanical or ultrasonic nebulizers for delivery of the drug into lungs. Because of their small size, it is likely that in each aerosol droplet at least one drug particle is contained, leading to a more uniform distribution of the drug in lungs. They also increase adhesiveness and thus cause a prolonged residence time. Budenoside drug nanoparticles were successfully nebulized using an ultrasonic nebulizer.

• 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". Then, the concentrated suspension acts as a reservoir of particles and an adsorption process takes place rapidly. The direct contact of the particles with the intestinal cells through a bioadhesive phase is the first step before particle absorption. The adhesiveness of the nanosuspensions not only helps to improve bioavailability but also improves targeting of the parasites persisting in the GIT.

CONCLUSION:

Nanosuspension technology represents a significant advancement in addressing the challenges associated with poorly soluble drugs. It provides an effective solution to enhance bioavailability, enabling faster drug absorption and improved therapeutic effects. The ability to administer drugs via various routes - oral, intravenous, pulmonary, and ocular adds to the versatility of nanosuspensions. Despite some limitations, such as issues with physical stability and the complexity of production processes, ongoing research and technological advancements continue to address these challenges. The potential of nanosuspensions to deliver next-generation therapeutics, including biologics and site-specific drugs, makes this a promising area for future exploration in pharmaceutical sciences.

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