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NANOSUSPENSION: AN ENCOURAGING DRUG DELIVERY SYSTEM

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ABSTRACT
Independent of the administration route, solubility is a critical component of drug effectiveness. Since many recently discovered drugs are water insoluble and thus poorly bioavailable, development efforts have been abandoned in large numbers. Now that they have been made into a nanosuspension, these so-called "Brickellia" candidates can be administered. Drugs with low bioavailability and poor aqueous solubility were solved by nanosuspension technology. Drug stability and bioavailability can be increased through the use of nanosuspension technology. All medications that are aqueous insoluble can be prepared as nanosuspension, which is a straight forward process. Wet mill, high pressure homogenizer, melt emulsification method, emulsion solvent evaporation, and super critical fluid techniques are used to create nanosuspensions. Stabilizers, organic solvents, and other additives like buffers, salts, polyols, osmogent, and cryoprotectants can be used to prepare nanosuspension. Delivery methods for nanosuspensions include oral, parenteral, pulmonary, and ocular. By including nanosuspensions in mucoadhesive hydrogels and ocular inserts, targeted drug delivery is also possible.

KEYWORDS: Dissolution, Nanosuspension, Saturation, Solubility, Solubility enhancement.

INTRODUCTION
Nanosuspension is a compound word made up of the words nano and suspension. Nano stands for nanometer, or one billionth of a part in 10-9, and suspension refers to a heterogeneous mixture in which the solute particles are suspended in the solvent and float freely in the medium. Biphasic in nature, nanosuspension is the dispersion of colloidal solid fine particles in an aqueous medium stabilised by surfactants.[1,2] Solubility and bioavailability are the two main factors that are crucial in the development of new pharmaceutical products.[3] Researchers are searching for novel drug delivery strategies to improve the solubility and bioavailability of medications in an effort to address these issues. All drug particles falling under classes II and IV of the Biopharmaceutical Classification System can be made into nanosized particle formulations (BCS).

Drugs can be made more soluble using a variety of techniques, including microionization, precipitation methods, surfactant dispersion, emulsion, microemulsion, and liposomes.[4] While the nanosuspension technique can be used for drugs that are insoluble in both water and organic solvents, these approaches are only appropriate for drugs that are soluble in aqueous and organic solvents. Nanosuspension technology changes the pharmacokinetic properties of the drug, increasing its solubility and bioavailability as well as its effectiveness and safety profile.[5]

Defination
"Very finely dispersed solid drug particles in an aqueous vehicle, stabilised by surfactants, for either oral and topical use or parenteral and pulmonary administration, with reduced particle size, leading to an increased dissolution rate and therefore improved bioavailability," is the definition of a pharmaceutical nanosuspension. The suspended particle has a diameter of less than 1 m. (i.e. 0.1nm-1000 nm).[6,7] The solid particles in nanosuspensions typically have a particle size distribution that is less than one micron, with an average particle size between 200 and 600 nm.[8] An increase in surface area and, consequently, dissolution velocity are related to an increase in the dissolution rate of micronized particles (particle size 10 m). The vapour pressure effect on nanosized particles can accelerate dissolution and increase saturation solubility.[9]

Need of nanosuspention
More than 40% of medications have trouble being formulated into conventional dosage forms because they are not water soluble. The issue is more complicated for class II drugs because they have poor solubility in both aqueous and organic media.[10] For such compounds with high log P values that are soluble in oil but insoluble in water, nanosuspension preparation is preferred. Different strategies to address the issues of low solubility and low bioavailability Other techniques include liposomes, emulsions, microemulsions, solid dispersion, ß-

cyclodextrin inclusion complex, and co-solvency, oily solution, salt formation, among others. Many of these methods, however, do not work with all drugs equally.[10] Nanosuspensions are preferred in these circumstances. In place of lipidic systems, nanosuspensions are used as a formulation strategy for medications that are insoluble in both water and inorganic media. The compounds with a high log P value, high melting point, and high dose are the best candidates. Drugs that are poorly soluble in aqueous and lipid media may be made more soluble using nanosuspensions. When the nanosuspension is administered orally or intravenously (IV), the rate of flooding of the active compound increases and the maximum plasma level is reached sooner. This is one of its distinctive advantages over other methods of improving solubility. For formulators, it is helpful for molecules with poor solubility, poor permeability, or both, which presents a big challenge. Significant problems with poorly water-soluble substances.[11]

- Poor bioavailability.
- Inability to optimize lead compound selection based on efficacy and safety
- Fed/fasted variation in bioavailability
- Lack of dose-response proportionality
- Suboptimal dosing
- Use of harsh excipients, i.e., excessive use of co-solvents and other excipients
- Use of extreme basic or acidic conditions to enhance solubilization

Although all commercially available products are currently made using so-called "top-down techniques," in which the nanoparticles are created by shrinking the product's size to the submicron range, bottom-up techniques, particularly the controlled precipitation method, are interesting for the nanozation of poorly soluble drugs. With this technique, the particle size could be decreased to a few hundred nanometers range without the use of any harsh conditions or complicated equipment. The careful assessment of the type and concentration of the stabiliser is thus a crucial step for the successful production of nanosuspension, regardless of the method used. Stabilizers made of polymers and surfactants can both be used for this. Nanosuspensions are distinct from both solid-lipid nanoparticles (SLN), which are lipidic drug carriers, and nanoparticles, which are polymeric colloidal carriers of drugs (Nanospheres and nanocapsules). The main distinction between nanosuspensions and conventional suspension formulations is that the particle size distribution of the solid particles in nanosuspensions is typically less than 1 m (i.e., 0.1nm–1000nm), with an average particle size range between 200–600 nm. On the other hand, most effective pharmaceutical suspensions call for particle diameters between 1 and 50 m. Increased surface area and reduced particle size in nanosuspensions increase saturation solubility and boost overall bioavailability. The conventional milling techniques are not capable of producing this system.[6]

NANOSUSPENSIONS FORMULATIONS APPROACH

- Preparing nano suspensions is preferred for compounds with a high log P value that are insoluble in water but soluble in oil.
- Drugs that are traditionally formulated in liposome or emulsion systems are those that are soluble in oil phase systems but insoluble in water. However, not all drugs can benefit from these lipidic formulation techniques. Nano suspensions are preferred in these circumstances.
- Instead of lipidic systems, nanosuspensions are used as a formulation strategy for medications that are insoluble in both organic and water-based media.
- The formulation method using nanosuspension is best suited for compounds with high log P values, high melting points, and high doses.[12,13]

DRUG SELECTION CRIETRIA

1) Water insoluble but which are soluble in oil
2) Insoluble in both water and oils
3) Drugs with reduced tendency of the crystal to dissolve, regardless of the solvent
4) API with very large dose.[14]

ADVANTAGES OF NANOSUSPENSION

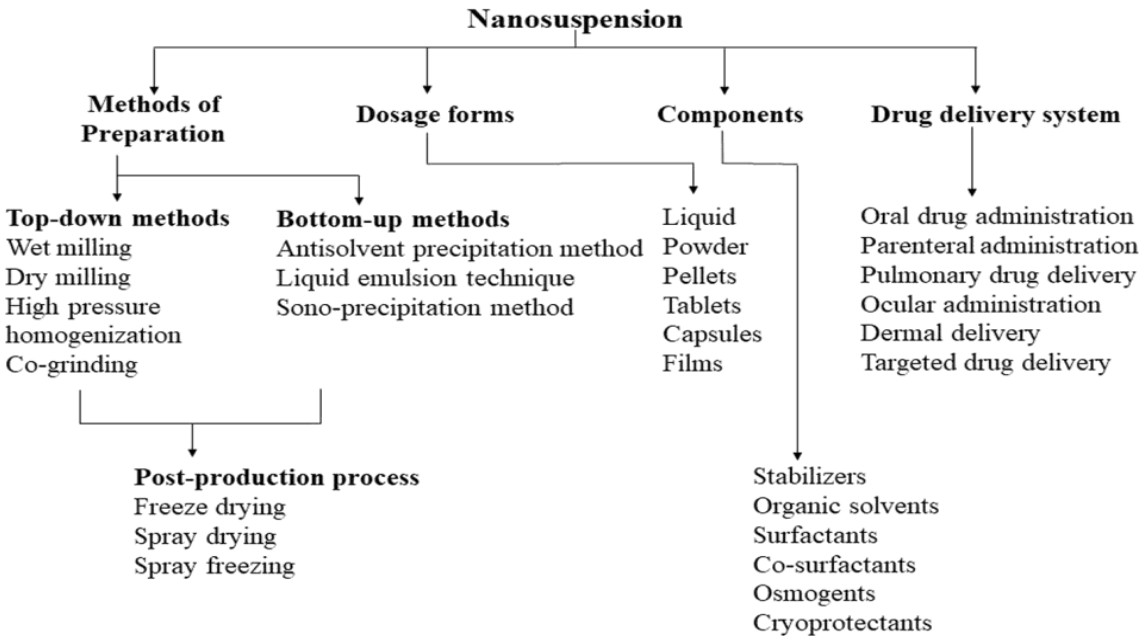
1) Increase in the dissolution velocity and saturation solubility of the drug
2) Improved biological performance
3) Ease of manufacture and scale-up
4) Long-term physical stability
5) Versatility
6) Increase in the oral absorption
7) Improved dose proportionality.
8) Its general applicability to most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

structure & higher solubility.
20) Possibility of surface-modification of nanosuspension for site specific delivery.
21) Possibility of large-scale production, the prerequisite for the introduction of delivery system to the market.

Disadvantages for Nanosuspension Drug delivery system

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

TECHNIQUES FOR PREPARING NANOSUSPENSION[15]



Methods of preparation of nanosuspension

Nanosuspensions are primarily prepared using two methods. The traditional precipitation techniques (Hydrosols) are referred to as "Bottom up technology." Disintegration methods, or "Top Down Technologies," are preferred to precipitation methods. Media milling (Nanocrystals), high pressure homogenization in water (Dissocubes), high pressure homogenization in non-aqueous media (Nanopure), and a combination of precipitation and high-pressure homogenization are among the "Top Down Technologies" (Nanoedege).[16,23]

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

1. Bottom-Up Technology

Bottom-up technology refers to the process of creating solid particles from the molecular level up through molecular association. That indicates that we are talking about traditional precipitation methods that involve lowering the solvent quality, such as by adding a nonsolvent to a solvent or by adjusting the temperature, or both. In pharmaceutical chemistry and technology, precipitation is a traditional technique.[24,28]

Advantage

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

Disadvantages

1) The drug needs to be soluble in at least one solvent (thus excluding all new drugs that are simultaneously poorly soluble in aqueous and in organic media).
2) The solvent needs to be miscible with at least one non- solvent.
3) Solvent residues need to be removed, thus increasing production costs.
4) It is an Iittle bit tricky to preserve the particle character (i.e. size, especially the amorphous fraction). In general, it is recommended that a second consecutive process has to be performed for particle preservation that is spray drying or lyophilization[29,31]

2. Top-Down technology

The top down technologies include

a) Media milling
b) High pressure homogenization

2.1 Media milling

Pearl mills or high-shear media mills are used to make nanosuspensions. The mill is made up of a recirculation

chamber, a milling chamber, and a milling shaft. The drug is then fed into a mill containing tiny grinding balls or pearls in an aqueous suspension. These balls fly through the grinding jar interior and strike the sample on the opposite grinding jar wall as they rotate at a very high shear rate and controlled temperature. A significant amount of particle size reduction results from the combined forces of friction and impact. Aluminium oxide, zirconium oxide, or highly cross-linked, highly abrasion-resistant polystyrene resin are used as the milling media or balls.One piece of machinery that can be used to achieve a grind size below 0.1 m is a planetary ball mill (PM100 and PM200; Retsch GmbH and Co., KG, Haan, Germany). Wet milling was used to create a nanosuspension of zinc-insulin with a mean particle size of 150 nm.The main shortcomings of this technology include the presence of relatively high percentages of particles smaller than five microns and the erosion of balls/pearls that may leave residues as contaminants in the finished product.[32,35]

Advantages

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

Disadvantages

- Potential erosion from the milling material leading to product contamination.
- Duration of the process not being very production friendly.
- Potential growth of germs in the water phase when milling for a long time.
- Time and costs associated with the separation procedure of the milling material from the drug nanoparticle suspension, especially when producing parenteral sterile products.[32-35]

2.2 High pressure homogenization

Dissocubes

When homogenising, the suspension is forced through a valve with a small aperture while under pressure. Muller et al. created Dissocubes in 1999. In this instance, the drug suspension is made to pass through a small orifice, which lowers the static pressure below the boiling point of water, causing the water to boil and create gas bubbles. When the suspension exits the gap and atmospheric pressure returns to normal, the bubbles explode, causing the drug particles to rush to the centre where they collide and reduce the particle size. Depending on the difficulty of the drug, the preferred mean particle size, and the required homogeneity, the majority of cases necessitate multiple passes or cycles through the homogenizer. The APV Gaulin Micron LAB 40 Homogenizer (APV Homogenizer, Lbeck, Germany) and the NS 1001L-Panda 2K high-pressure homogenizer both use this principle (Nirosuavi. S.P.A., Parma, Italy).

Pre-milling can be used to start homogenising with very small drug particles in order to create a Nanosuspension with a higher concentration of solids. The ability to use high-pressure homogenization for both diluted and concentrated suspensions as well as aseptic production is its main advantage over media milling.[36-39]

Nanopure

Homogenized suspensions in water-free or water-mixed media are considered nanopure. The cavitation is what controls the process in the Dissocubes technology. Oils and oily fatty acids, however, have a very low vapour pressure and a high boiling point in comparison to water. Therefore, the static pressure drop won't be enough to start cavitation. Patents on the high-pressure homogenization method of disintegrating polymeric materials mention that higher temperatures, around 80^0C, promoted disintegration but not thermolabile compounds. The drug suspensions in non-aqueous media were homogenised in nanopure technology at ^{0}C or even below the freezing point, hence the term "deep-freeze" homogenization. . The results obtained were comparable to Dissocubes and hence can be used effectively for thermolabile substancesat milder conditions.[40,41]

Nanoedge™

Precipitation and homogenization share the same fundamental principles as Nanoedge. These methods work best when combined because it produces smaller particles with better stability faster. The Nanoedge technology can address the main issues with the precipitation method, such as crystal growth and long-term stability. This method involves further homogenising the precipitated suspension to reduce particle size and prevent crystal growth. Solvents that are water-miscible, such as methanol, ethanol, and isopropanol, are used to precipitate in water. Although they can be tolerated to some extent in the formulation, it is preferable to completely eliminate those solvents. An evaporation step to provide a modified starting material free of solvent can be added for effective production of nanosuspensions using the Nanoedge technology, which is then followed by high-pressure homogenization.[42]

Emulsion diffusion method

They can be used as templates to create nanosuspension in addition to being used as a drug delivery system. For drugs that are soluble in either volatile organic solvent or partially water-miscible solvent, emulsions can be used as templates. These solvents can be used as the emulsion's dispersed phase. To create an emulsion, an organic solvent or combination of solvents containing the drug is dispersed in an aqueous phase containing the appropriate surfactants while being stirred. High pressure homogenization was used to further homogenise the obtained emulsion. The emulsion was diluted with water and homogenised by a homogenizer after homogenization cycles in order to diffuse the organic solvent and turn the droplets into solid particles. Since one particle is created in each emulsion droplet, it is

possible to regulate the size of the emulsion, which increases the amount of organic phase that is taken in and, ultimately, the amount of drug loading in the emulsion. Initially, organic solvents like methanol, ethanol, ethyl acetate, and chloroform were used.[41-45]

Advantages

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

Disadvantages

- Drugs that are poorly soluble in both aqueous and organic media cannot be formulated by this technique.
- Safety concerns because of the use of hazardous solvents in the process.
- Need for diultrafiltration for purification of the drug Nanosuspension, which may render the process costly.
- High amount of surfactant/stabilizer is required as compared to the production techniques described earlier.[41-44]

Micro emulsion template

This method involves dispersing a drug-loaded organic solvent or mixture of solvents into an aqueous phase with the right surfactants to create an emulsion. The organic phase is then quickly evaporated under reduced pressure, causing the drug particles to instantly precipitate and create the surfactant-stabilized Nanosuspension. In a different method, the dispersed phase is made up of solvents that are only partially water-soluble, such as butyl lactate, benzyl alcohol, and triacetin.[42-45]

Advantages

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

Disadvantages

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

Supercritical fluid method

Drug solutions can be used to create nanoparticles using supercritical fluid technology. Three different approaches have been tried: precipitation with compressed anti-solvent process, supercritical anti-solvent process, and rapid expansion of supercritical solution (RESS) (PCA). The RESS involves expanding the drug solution in supercritical fluid through a nozzle, which causes the supercritical fluid to lose solvent power and cause the drug to precipitate as tiny particles. This method was used by Young et al. to create cyclosporine nanoparticles between 400 and 700 nm in size. The drug solution is atomized into a chamber that contains compressed CO 2 in the PCA method. The solution becomes supersaturated as the solvent is removed, which causes it to precipitate as tiny crystals. A drug that is poorly soluble in a supercritical fluid is used in the supercritical anti-solvent process along with a drug solvent that is also miscible with the supercritical fluid. When the drug solution is injected into the supercritical fluid, the solvent is extracted and the drug solution becomes supersaturated as a result. After that, the drug precipitates as tiny crystals. This technique was used by Chattopadhyay et al. to create nanoparticles of griseofulvin, a drug with poor solubility.[40-45]

Disadvantages

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

Melt emulsification method

In this procedure, the drug is mixed with the stabilizer's aqueous solution, heated above the drug's melting point, and homogenised to create an emulsion. The sample holder was wrapped in a heating tape with a temperature controller during this procedure, and the temperature of the emulsion was kept above the drug's melting point. The emulsion was then gradually cooled to room temperature or placed in an ice bath.[44-45]

Advantage

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

Dry Co-Grinding

Recently, dry milling techniques have made it possible to create nanosuspensions. It has been reported that stable Nanosuspensions can be made by dry-grinding insoluble drugs with soluble polymers and copolymers after dispersing them in a liquid medium. There are numerous soluble polymers and co-polymers that have been used, including PVP, polyethylene glycol (PEG), hydroxypropyl methylcellulose (HPMC), and derivatives of cyclodextrin.[45-46]

Table 1: Advantages and disadvantages of various preparation techniques of nanosuspensions[47]

Method	Benefits	Drawbacks
High-pressure Homogenization	Widely applying regions, ease of scale-up and little batch to batch variation, narrow size distribution in the final product, allowing aseptic production of nanosuspensions for parenteral administration and flexibility in handling the drug quantity	Pretreatment of micronized drugparticles and pre-suspending materialsbefore subjecting it to homogenization
Milling	The same as those for high-pressure homogenization	Potential erosion of material from the milling pearls
Microprecipitation	Low need of energy, stable products and simple process	narrowly applying space, wide size distribution and potential toxicity of non-aqueous solvents
Emulsion and Microemulsion	Low need of energy, stable products, simple process, small size of particles and uniform particle distribution	high concentration undesired surfactants and residual solvents
Microprecipitation -high pressure homogenization	much smaller, more uniform and more stable compared to that by the Microprecipitation; less mechanical force and energy compared with the high-pressure homogenization	The manufacturing process is complicated
Dry Co-grinding5	Easy process No organic solvent Require short grinding time	Generation of residue of milling media

APPLICATIONS OF NANOSUSPENTION[48-55]

1. Oral

Oral drug administration is the most commonly used method of drug administration. However, some drugs have low bioavailability due to poor solubility and absorption, which reduces their efficacy. In such cases, Nanosuspension can help to improve the dissolution rate and absorption due to increased surface area and improved adhesiveness. Nanosuspension can lead to increased mucoadhesion which can increase gastrointestinal transit time and lead to increased bioavailability. The improved oral bioavailability can be attributed to the drug Nanosuspension's increased surface area, saturation solubility, and adhesiveness. It is also simple to mask the taste of a particulate system.

2. Parenteral

Poorly soluble non-injectable drugs can be converted using nanosuspensions into a formulation suitable for intravenous administration. Despite the importance of producing Nanosuspension for parenteral use, recent advancements in this technology have demonstrated the value of its injectable formulations. Today's precise control over the preparation processes for nanosuspension allows for the production of uniform particles with improved control over maximum particle size. There are numerous research reports that highlight Nanosuspensions' suitability for parenteral administration.

3. Ocular delivery

Drugs with poor lachrymal fluid solubility may benefit from nanosuspension. Due to their innate capacity to enhance drug saturation solubility, nanosuspensions represent an ideal method for the ocular delivery of hydrophobic drugs. For some glucocorticoid medications, Kassem et al. have developed a nanosuspension delivery system.

4. Pulmonary

Drugs with poor pulmonary secretion solubility may benefit from delivery via nanosuspensions. Aerosols and dry powder inhalers, which are currently used for pulmonary delivery, have some drawbacks like limited diffusion at the required site, a short residence time, etc. that can be fixed by nanosuspensions. The formulation of fluticasone and budesonide as a nanosuspension for pulmonary delivery has been successful.

5. Dermal

Increased saturation solubility in the nanocrystalline form leads to improved drug diffusion into the skin. Additionally, nanocrystals display a number of qualities, including improved permeation, bioadhesiveness, and increased membrane penetration, all of which could be very helpful for dermal application.

6. Targeting

The size of the drug nanoparticles affects how well they are absorbed. The in vivo behaviour of the nanoparticles can be altered and they can be used as a targeted delivery system by altering their surface properties. By creating smart crystals, or drug particles smaller than 100 nm, which can be used as a targeted drug delivery system, it is possible to prevent the phagocytotic uptake of nanocrystals. The creation of nanosuspension is a commercially viable option for targeted delivery because of the method's simplicity. Targeting of Cryptosporidium parvum was reported to be accomplished with mucoadhesive nanosuspension. The distribution of an organ depends on the surface characteristics of a particle, such as surface hydrophobicity, charge, presence, and

concentration of specific functional groups. Tween 80-coated nanocrystals can therefore be used to target the brain.

7. Mucoadhesion of nanoparticles

Nanoparticles administered orally in the form of a suspension diffuse into the liquid media and quickly come into contact with the mucosal surface. The particles are immobilised at the intestinal surface thanks to an adhesion mechanism known as mucoadhesion.

Table 2: Benefits and Drawbacks of nanosuspensions over conventional formulations.

Administration Mode	Drawbacks of Conventional Formulations	Benefits of Nanosuspensions
Oral	Slow onset of action/ poor absorption	Rapid onset of action/ improvedsolubility so improved bioavailability Reduced fed/fasted ratio
Ocular	Lacrimal wash off/ low bioavailability	Higher bioavailability/ doseconsistency Lesser irritation
Intravenous	Poor dissolution/ non-specific action	Rapid dissolution/ tissue targetingProlonged retention time in systemic circulation
Intramuscular	Low patient compliance due topain	Reduced tissue irritationHigh bioavailability Rapid onset of action
Inhalations	Low bioavailability due to low Solubility	Rapid dissolution/ high bioavailability/ dose regulation

FORMULATION OF NANOSUSPENTION

1) STABILIZER

Nanosuspensions are made with the help of stabilisers, which is crucial. The high surface energy of nanoparticles can cause the drug crystals to aggregate if an appropriate stabiliser isn't present. The main purposes of a stabiliser are to completely wet the drug particles, to prevent ostwald's ripening and agglomeration of nanosuspensions, and to provide steric or ionic barriers in order to produce a physically stable formulation. Physical stability and in-vivo behaviour of nanosuspensions are significantly influenced by the type and quantity of stabiliser. To create a stable nanosuspension, a combination of stabilisers may be necessary in some circumstances.

2) Organic solvents

If nanosuspensions are to be created using an emulsion or microemulsion as a template, organic solvents may be needed in the formulation. Due to the nascent nature of these techniques, detailed information on formulation considerations is not yet available. When creating a nano suspension using emulsions or microemulsions as templates, it is important to take into account the organic solvents' acceptability in the pharmaceutical industry, their potential for toxicity, and how simple it is to remove them from the formulation.

3) Co-surfectants

When creating nanosuspensions using microemulsions, the choice of co-surfactant is crucial. The impact of co-surfactant on internal phase uptake and drug loading for particular microemulsion compositions should be studied because it has a significant impact on phase behaviour. Although bile salts and dipotassium glycerrhizinate are mentioned in the literature as co-surfactants, other solubilizers, including Transcutol, glycofurol, ethanol, and isopropanol, can be used in the creation of microemulsions without risk.[56,57]

4) Other additives

considerations for formulation Depending on the administration method or the characteristics of the drug moiety, nanosuspensions may contain additives like buffers, salts, polyols, osmogent, and cryoprotectant.[58]

CHARACTERIZATION OF NANOSUSPENTION[23-61]

In-vitro evaluations

- Color, Odor, Taste
- Particle size distribution
- Particle charge (Zeta Potential)
- Crystal morphology
- Dissolution velocity and Saturation solubility
- Density
- pH Value
- Droplet Size
- Viscosity Measurement
- Stability of Nanosuspension

In-vivo biological performance

Evaluation for surface-modified nanosuspension

- Surface hydrophilicity
- Adhesion properties
- Interaction with body proteins

In-vitro evaluations

- **Color, Odor, Taste**

These qualities are particularly crucial in formulations intended to be taken orally. Changes in particle size, crystal habit, and subsequent particle dissolution can all be linked to variations in taste, particularly of active ingredients. Changes in colour, odour and taste can also indicate chemical instability.

❖ **Particle size distribution**

The physiochemical behaviour of the formulation, such as saturation solubility, dissolution velocity, physical stability, etc., is determined by the particle size distribution. The particle size distribution can be determined by photon correlation spectroscopy (PCS), laser diffraction (LD) and coulter counter multisizer. The PCS method has a measuring range of 3 nm to 3 m, while the LD method has a range of 0.05 to 80 m. The LD method only provides a relative size distribution; in contrast, the coulter counter multisizer provides the precise number of particles. Given that the smallest capillaries are between 5 and 6 micrometres in diameter and that a higher particle size can cause capillary blockade and embolism, particles used for IV therapy should be less than 5 micrometres.

❖ **Particle charge (Zeta potential)**

The stability of the suspension is indicated by the zeta potential. A minimum zeta potential of 30 mV is required for a stable suspension stabilised only by electrostatic repulsion, whereas a zeta potential of 20 mV would be sufficient in the case of an electrostatic and steric stabiliser working together.

❖ **Crystal morphology**

Techniques like X-ray diffraction analysis combined with differential scanning calorimetry or differential thermal analysis can be used to characterise the polymorphic changes brought on by high-pressure homogenization in the drug's crystalline structure. Due to high-pressure homogenization, nanosuspensions may change in crystalline structure, possibly becoming amorphous or taking on other polymorphic forms.

❖ **Dissolution Velocity and Saturation solubility**

Nanosuspensions have a significant advantage over other techniques in that they can increase both dissolution velocity and saturation solubility. In different physiological solutions, these two parameters should be determined. The assessment of saturation solubility and dissolution velocity aids in determining the formulation's in vitro behaviour. Böhm et al. discovered an increase in dissolution pressure and velocity as particle size was reduced to the nanometer range. 17 As the size of the particles decreases, the dissolution pressure rises.

❖ **Density**

The formulation's specific gravity or density is an important parameter. A decrease in density frequently indicates the presence of entrapped air within the formulation's structure. Density measurements at a given temperature should be performed with a well-mixed, uniform formulation; precision hydrometers make such measurements possible.

❖ **pH Value**

To reduce electrode surface coating with suspended particles and "pH drift." No electrolyte should be included in The pH of an aqueous formulation should be measured at a specific temperature and only after the external phase of the formulation has reached settling equilibrium, stabilising the pH.

❖ **Droplet Size**

Either light scattering technique or electron microscopy can be used to determine the droplet size distribution of micro emulsion vesicles. spectrophotometer for dynamic light scattering that makes use of a neon laser with a 632 nm wavelength.

❖ **Viscosity measurement**

The viscosity of lipid based formulations of several compositions can be measured at different shear rates at different temperatures using Brookfield type rotary viscometer. The samples for the measurement must be submerged in the thermobath that keeps the sample room of the instrument at 370C. Using a Brookfield type rotary viscometer, the viscosity of lipid-based formulations of various compositions can be measured at various shear rates and temperatures. The samples for the measurement must be submerged in the thermobath that keeps the sample room of the instrument at 370C.

❖ **Stability of nanosuspension**

The agglomeration of the drug crystals is caused by the high surface energy of nanoscale particles. The stabilizer's primary job is to thoroughly saturate the drug particles in order to prevent Ostwald ripening and Nanosuspension agglomeration and to create a physically stable formulation by acting as a steric or ionic barrier. Stabilizers like cellulosics, poloxamer, polysorbates, lecithin, polyoleate, and povidones are frequently used in nanosuspensions. When creating parenteral Nanosuspensions, lecithin may be preferred.

In-Vivo biological performance

Regardless of the route and delivery system used, establishing an in-vitro/in-vivo correlation and monitoring the drug's in-vivo performance are crucial components of the study. Since the drug's in-vivo behaviour depends on the organ distribution, which in turn depends on its surface characteristics, such as surface hydrophobicity and interactions with plasma proteins, it is crucial in the case of intravenously injected Nanosuspensions. In fact, the essential component for organ distribution is acknowledged to be the qualitative and quantitative composition of the protein absorption pattern observed after the intravenous injection of nanoparticles. Therefore, it is necessary to use appropriate techniques to assess surface characteristics and protein interactions in order to gain an understanding of in-vivo behaviour. Surface hydrophobicity can be measured using methods like hydrophobic interaction chromatography, and protein adsorption after intravenous injection of drug nanosuspensions in animals can be measured quantitatively and qualitatively using 2-D PAGE.

Properties of nanosuspention

Physical Long-term stability[22]

The absence of Ostwald ripening, which is indicative of their long-term physical stability, is another unique quality of nanosuspensions. Crystal growth and subsequent particle formation are both caused by the Ostwald ripening process. Ostwald ripening is brought on by variations in small- and large-particle dissolution pressure/saturation solubility. Molecules diffuse from areas around small particles with higher concentrations of drug to areas around larger particles with lower concentrations of drug (higher saturation solubility). This causes a supersaturated solution to form around the large particles, which in turn causes the drug to crystallise and the large particles to grow. The process by which the drug diffuses from the small particles to the large particles leaves an area around the small particles that is no longer saturated, which ultimately causes the drug to dissolve from the small particles and causes their complete disappearance.

Internal structure of nanosuspensions[6]

The drug particles' internal structure changes as a result of the high energy input during the disintegration process. The drug's crystalline state is changed to an amorphous state when it is subjected to high-pressure homogenization. The amount of homogenization cycles, chemical makeup of the drug, and power density used by the homogenizer all affect the state change.

Adhesiveness[6]

When compared to coarse powders, ultra-fine powders have a noticeably higher adhesiveness. Small drug nanoparticles' ability to stick together can be used to enhance the oral delivery of drugs that aren't very soluble. The increase in bioavailability for danazol from 5% (as macrosuspension) to 82% is a remarkably noteworthy report (as nanosuspension).

Crystalline state and morphology[6]

Consideration should be given to a potential alteration in the crystalline composition of nanosuspensions, such as an increase in the proportion of amorphous particles or even the production of entirely amorphous particles. High pressures were found to encourage the amorphous state during the creation of nanosuspensions.

Increase in Saturation Solubility and Dissolution Velocity of drug[7]

The increase in drug surface area from micrometre to nanometer size causes a greater increase in drug dissolution. The Noyes-Whitney equation (Equation no. 1) states that the increase in surface area from micron-sized to nanometer-sized particles causes an increase in the dissolution velocity.

$$dx/dt = [(D \times A)/ h] [Cs-X/V] \text{ - Equation (1)}$$

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

Research Work and Successful formulations based on nanosuspensions

- A suspension containing 20 nm silica particles in ethylene glycol was subjected to electrohydrodynamic atomization (EHDA) in the stable cone-jet mode using a ring-shaped ground electrode. The droplets produced were sized by laser diffraction and were in the range 0.5-20 mum. Immediately after deposition, droplet relics were analysed by optical microscopy and were found to be in the size range 1-80 mum. Subsequently, usinga pointed rod-electrode (rather than a ring), and by increasing the intensity of the electric field and by reducing the flow rate of suspension subjected to EHDA, relics of similar to 50 mum in size were deposited using a patterning device. In both of the above instances, the relics contained two distinct zones, an outer ring of ethylene glycol and a much smaller dense inner region of silica nanoparticles. These results show that, by using EHDA, a novel controlled deposition method of nanosuspensionshas been developed.[63]

- All-Trans Retinoic Acid (ATRA) nanosuspensions were prepared with a modified precipitation method. The ATRA solution in acetone was injected into pure water by an air compressor under the action of ultrasonication. Photon correlation spectroscopy results showed that the mean particle size of ATRA nanoparticles in nanosuspensions reduced from 337 nm to 155 nm as the injection velocity increased and the polydispersity index was 0.45-0.50. The morphology of ATRA nanoparticles varied with the different concentration of ATRA solution in acetone. ATRA nanoparticles showed an amorphous state and stable in 6 months. It could be concluded that this modified precipitation method could produce stable and controllable ATRA nanosuspension to a certain extent, thus benefit for higher saturation solubility.[64]

- Albendazole, an anthelmintic drug belonging to BCS class II, has poor bioavailability. Bioavailability is dissolution rate dependent and hence needs novel approach for enhancement of bioavailability. The aim of the study was to develop nanosuspension of albendazole by using various

techniques like nanoprecipitation, emulsion template and sonication. Nanosuspensions were prepared using polyvinylpyrrolidone K30 as a stabilizer and Tween 80 as a surfactant. Average particle size, zeta potential, particle size distribution, pH, viscosity, photomicrography, sedimentation, redispersibility and % drug content were determined to characterize prepared nanosuspensions. In vitro release study was performed in 0.1N HCl using cellophane membrane and with marketed product. Residual solvent compared determination was carried out by gas chromatography for nanosuspensions prepared by nanoprecipitation and emulsion templatetechniques. All the results obtained for characterization were satisfactory. The prepared nanosuspensions showed particle size 673±9.18 nm to 893±21.6 nm, zeta potential -8.70±0.5mV to - 8.96±0.8, polydispersity index 0.204±0.04 to 0.644±0.07. In vitro release study of the nanosuspensions showed 33.80% to 42.92% drug release in first hour which was higher than the marketed suspension (16.19% release in first hour). The optimized nanosuspensions showed up to 97.05% drug release within 6-8 hours while marketed product showed up to 91.03% drug release within 10 hours.[65]

- Oleanolic acid is a naturally derived triterpene used clinically in the treatment of hepatitis in China, but its poor solubility often leadsto poor bioavailability. In the present study, oleanolic acid nanosuspensions were prepared by the nanoprecipitation method and then systematically characterized. The average particle size of the obtained nanosuspensions was 284.9 nm, with a polydispersity index of 0.216. Transmission electron microscopy and atomic force microscopy showed that the drug existed as spherical or near- spherical nanoparticles in the nanosuspensions. Differential scanning calorimetry and X-ray diffraction studies indicated that oleanolic acid was present in an amorphous state in the lyophilized nanosuspensions. At 25ºC, the saturation solubility of oleanolic acid was increased by about 6 times after nanoation (25.72 microg mL(-1) vs 4.37 microg mL(-1)). In the in-vitro drug release experiments, the lyophilized nanosuspensions showed a faster drug dissolution rate than that ofthe coarse drug powder (approx. 90% vs 15% during the first 20 min), and nearly 95% of the oleanolic acid was released by 120 min. As evidenced by the lower serum alanine aminotransferase activity and liver malondialdehyde content, pre-treatment with oleanolic acid nanosuspensions significantly enhanced the hepatoprotective effect of oleanolic acid against carbon tetrachloride-induced liver injury.[66]

- A study was performed to investigate potential of Eudragit RLPO-based nanosuspension of glimepiride (Biopharmaceutical Classification System class II drug), for the improvement of its solubility and overall therapeutic efficacy, suitable for peroral administration. Nanoprecipitation method being simple and less sophisticated was optimized for the preparation of nanosuspension. Physicochemical characteristics of nanosuspension in terms of size, zeta potential, polydispersity index, entrapment efficiency (% EE) and *in vitro* drug release were found within their acceptable ranges. The size of the nanoparticles was most strongly affected by agitation time while % EE was more influenced by the drug/polymer ratio. Differential scanning calorimetry and X-ray diffraction studies provided evidence that enhancement in solubility of drug resulted due to change in crystallinity of drug within the formulation. Stability study revealed that nanosuspension was more stable at refrigerated condition with no significant changes in particlesize distribution, % EE, and release characteristics for 3 months. *In vivo* studies were performed on nicotinamide–streptozotocin-induced diabetic rat models for pharmacokinetic and antihyperglycaemic activity. Nanosuspension increased maximum plasma concentration, area under the curve, and mean residence time values significantly as compared to aqueous suspension. Oral glucose tolerance test and antihyperglycaemic studies demonstrated plasma glucose levels were efficiently controlled in case of nanosuspension than glimepiride suspension. Briefly, sustained and prolonged activity of nanosuspensions could reduce dose frequency, decrease drug side effects, and improve patient compliance. Therefore, glimepiride nanosuspensions can be expected to gain considerable attention in the treatment of type 2 diabetes mellitus due to its improved therapeutic activity.[67]

Patents on nanosuspensions

There are numerous patents on nanosizing because it is such a flexible technology.

Table 3: An overview of the technologies and patents/patent applications that underpin the different homogenization processes.[10]

Nanocrystal	Company	Patent/patent application examples
Hydrosol	Novartis (Prev. Sandoz)	GB 22 69 536 GB 22 00 048
Nanomorph™	Soligs/Abbott	D 1963 7517
NanoCrystal™	Élan NanoSystems	US 5,145,684

DissoCubes®	SkyePharma	US 5,858,410
Nanopure	PharmaSol	PCT/EP00/0635
Nanoedge™	Baxter	US 6,884,436

Current marketed pharmaceutical products

Table 4: Recent marketed product approved by FDA.[68]

Drug	Application	Formulation
Methylphenidate HCl	ADHD	Nanocrystal
Aprepitant	Chemotherapy induced nausea	Nanocrystal
Megestrol Acetate	Anti -anorexic	nanocrystal
Sirolimus	immunosuppressant	Nanocrystal
Tizanidine HCL	Muscle relaxant	Nanocrystal

Table 5: Recent Marketed Pharmaceutical Products Utilizing Nano-crystalline Formulation.

Product	Drug compound	Indication	Company	Nanoparticle technology
RAPAMUNE®	Sirolimus	Immunosuppressant	Wyeth	Élan Drug Delivery Nanocrystals®
EMEND®	Aprepitant	Anti-emetic	Merck	Élan Drug Delivery Nanocrystals®
TriCor®	Fenofibrate	Hypo-cholesteremic	Abbott	Élan Drug Delivery Nanocrystals®
MEGACE ES®	Megestrol Acetate	Appetite stimulant	PAR Pharmaceutical	Élan Drug Delivery Nanocrystals®
TRIGLIDE™	Fenofibrate	Hypo-cholesteremic	First Horizon Pharmaceutical	SkyePharma IDD®-Ptechnology

Table 6: A Novel drug application based on nanosuspensions reported.[7]

Drugs	Indication	Author or Company	Status	Route
Danazol	Hormone	Rogers T.L.	Reported	Oral
Naproxen	Anti-inflammatory	AnchaleeAin-Ai	Reported	Oral/parenteral
Probucol	Lipid lowering	JyutaroShudo	Reported	Oral
Loviride	Antivirotic	B. Van Eerdenbrugh	Reported	Intravenous
Budesonide	Asthma	Jerry Z. Yang	Reported	Pulmonary
Fluticasone	Asthma	Jerry Z. Yang	Reported	Pulmonary
Clofazimine	Antimycobacterials	K. Peters	Reported	Intravenous
Buparvaquone	Antibiotic	Müller R. H.	Reported	Oral
Oridonin	Anticancer	Lei Gao	Reported	Intravenous
AZ68	Anticancer	Kalle S.	Reported	Oral/I.V.
Ascorbylpalmitate	Ascorbylpalmitate	Veerawat T.	Reported	Intravenous
Hydrocortisone	Glucocorticoid	M.A. Kassem	Reported	Ophthalmic
Prednisolone	Glucocorticoid	M.A. Kassem	Reported	Ophthalmic
Hexadecadrol	Glucocorticoid	M.A. Kassem	Reported	Ophthalmic
Aphidicolin	Antileishmanial	O. Kayser	Reported	Oral
Dihydroartemisinin	Antimalarial	Jiraporn C.	Reported	Intravenous
Cilostazol	Antiplatelet agent	Jun-ichiJinno	Reported	Oral
Carbamazepine	Psychotolytic	D. Douroumis	Reported	Oral
Omeprazol	Proton pump inhibitor	Jan Möschwitzer	Reported	Intravenous
Mitotane	Adrenal Cortex Hormones	Michele Trotta	Reported	Oral
Griseofulvin	Antifungal	Boris Y. Shekunov	Reported	Oral
Tarazepide	Selective CCKa-antagonist	C. Jacobs	Reported	Oral
Albendazole	Anthelmintic drug	Mittapalli P. K.	Reported	Oral
Azithromycin	Antimicrobial	Dianrui Zhang	Reported	Oral
Ketoprofen	Analgesic	Remon J.P.	Reported	Oral

Table 7: List of Drugs and Other information.[7]

S. No	Model drug	Polymer used	Method of preparation	Purpose	Route	Reference
1.	Ibuprofen	Tween 80 and PVP K25	Melt emulsification method	Enhancing dissolution rate	lyophilized powder or granules	Kocbek *et al*[58]
2.	Ibuprofen	Eudragit RS100	Quasi-emulsion solvent diffusion technique	Improving the bioavailability	Topical application	Rosario Pignatello *et al*[59]
3.	Flurbiprofen (FLU),	Eudragit RS100 and RL100	Quasi-emulsion solvent diffusion technique	Improving the availability	Eye-drop formulation	Pignatello *et al*[60]
4.	Spironolactone	Nanosized,micronized, and coarse drug material and surfactant.	Disso Cubes	Bioavailability	Oral and i.v. formulations	Langguth *et al*[61]
5.	Piposulfan (alkylating agent), Etoposide (topoisomerase II inhibitor), Camptothecin (topoisomerase I inhibitor)	2% w/v solids suspension containing 1 % w/v surfactant	Wet milling technology	Retain biological effectiveness	Intravenous injection.	Merisko Liversidge *et al*[62]
6.	Diclofenac sodium	Poly(lactide-co-glycolide) and poly(lactide-co-glycolide-leucine) {poly[Lac(Glc-Leu)]} biodegradable polymers	Emulsion and solvent evaporation technique	Improving the ocular availability	Ophthalmic application	Sagar *et al*[63]
7.	Celecoxib	Tween 80, PVP K-30 and SDS	Emulsion-diffusion method	Increase drug dissolution rate	Dry powder suitable for tabletting.	Andrej Dolenc *et al*[64]
8.	Risperidone	Poly (D, L-Lactide	Nanoprecipitation method	High encapsulation efficiency	Parenteral drug delivery	Muthu and Singh[65]
9.	Asulacrine	Lyophilized to obtain the dry ASL	High pressure homogenization	Dissolution and saturation solubility were enhanced	Intravenous (i.v.) administration	Srinivas Ganta *et al*[66]
10.	Azithromycin		High pressure homogenization	Increasing its saturation solubility and dissolution velocity	Freeze-dried powder	Dianrui Zhang *et al*[67]
11.	Atorvastatin calcium		High pressure homogenization technique	Enhance its solubility and dissolution characteristics	Anhydrous form	Arunkumar *et al*[68]
12.	Oridonin		High-pressure homogenization	Increased drug saturation solubility and dissolution velocity.	Crystalline state	Lei Gao *et al*[69]

CONCLUSION

Poorly water soluble drugs are administered using nanosuspensions, which have largely solved the dissolution issues and improved drug absorption and bioavailability. Tablets, capsules, and pellets are some examples of conventional dosage forms that can be combined with nanosuspension technology, as well as parenteral products. When formulation development work is abandoned, drugs with poor solubility and low bioavailability are referred to as "brick dust" candidates. Nanosuspensions technology can save these drugs. In addition to addressing the issues of poor solubility and bioavailability, a nanosuspension modifies the drug's pharmacokinetics, enhancing drug efficacy and safety. As oral formulations and non-oral administration advance in the future, nanosuspensions will continue to be of interest to take advantage of their drug delivery capabilities, straightforward formation technologies, and variety of applications. For the mass production of nanosuspensions, methods of production like media milling and high-pressure homogenization have been used successfully. The development of production techniques that use emulsions or microemulsions as templates has led to even simpler, albeit constrained, production methods. In this regard, more research is still required. The applications of nanosuspensions for different routes have expanded due to their appealing properties, including increased dissolution velocity, increased saturation solubility, improved bioadhesivity, versatility in surface modification, and ease of post-production processing. Hydrophobic drugs and medications that are poorly soluble in aqueous and organic solutions have poor bioavailability issues that have been resolved by nanosuspension. For the mass production of nanosuspensions, production methods like media milling and high pressure homogenizer are employed. The administration of nanosuspensions can be done orally, parenterally, pulmonaryly, ocularly, or topically. Since nanotechnology is straightforward, there are fewer excipient requirements, higher dissolution rates, and saturation solubility, many drugs with low bioavailability are formulated in nanosuspension form.

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