A REVIEW ON NANOSUSPENSIONS: A GAME CHANGER IN SOLUBILITY ENHANCEMENT

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***Abstract*- Nano suspensions have emerged as a promising strategy to address the solubility and bioavailability challenges associated with poorly water-soluble drugs. This abstract provides an overview of recent advances in Nano suspension technology for drug delivery. We discuss the formulation methods, characterization techniques, and applications of Nano suspensions in pharmaceutical research and development. Nano suspensions, characterized by drug particles suspended at the nanometer scale in a liquid medium, offer enhanced drug dissolution and absorption properties. They have found applications in a wide range of therapeutic areas, from anticancer agents to antiretroviral. Furthermore, we explore the potential of Nano suspensions in personalized medicine and targeted drug delivery. The versatility and effectiveness of Nano suspensions make them a valuable tool in the field of pharmaceutical science, holding promise for improving drug efficacy and patient outcomes.**

Keywords: **Nano suspension, homogenization, Dissolution, targeting, therapeutic efficacy.**

Introduction:

The oral route is the most convenient and widely used route for drug delivery due to its ease of administration, high patient compliance, cost effectiveness, minimal safety constraints, and flexibility in dosage form design. About 50% of pharmaceutical compounds face the major challenge of formulating oral dosage forms with poor bioavailability. In recent years, much attention has been paid to nanotechnology for the delivery of formulations to improve the solubility and bioavailability of hydrophobic drugs. [1]. The nano size of the drug has the potential to increase the surface area and therefore the rate of dissolution, increase the rate of penetration, oral bio-availability and a faster onset of the therapeutic effect. Nanotechnology is one of the most important areas of modern science research and development, appearing in all fields of science, engineering and technology. A new interdisciplinary field of complex research that integrates medicine and other life sciences [2].

Nanosuspensions are colloidal dispersions of solid particles in a liquid phase, with an average particle size of less than 1 μm, using surfactants. Resistance is a major factor in drug efficacy regardless of the route of administration. Poorly soluble drugs are often a challenge for formulators in the industry. Conventional approaches to improve permeability are of limited use, especially when drugs are poorly soluble in aqueous and non-aqueous media. Nano suspension technology can be used to improve the stability and bioavailability of poorly soluble drugs. Nanosuspensions are two-phase systems consisting of pure drug particles dispersed in an aqueous vehicle and stabilized by surfactants. It is simple to prepare and more cost-effective than other approaches. Methods such as wet milling, high-pressure homogenization, emulsion solvent evaporation, and superfluidization have been used to prepare nanosuspensions [3].

An alternative and promising approach is to produce drug nanoparticles (i.e. nanosuspensions) to overcome this challenge. Nanosuspensions have emerged as a promising strategy for the efficient delivery of hydrophobic drugs due to their versatile properties and unique advantages. The unique properties of nanosuspensions allow them to be used in different doses, including special delivery systems such as mucoadhesive hydrogels. The main advantage of this technology is its general application to most drugs and its simplicity. [4].

Nanosuspension is defined as a submicron colloidal dispersion of pharmaceutical active particles in the liquid phase, less than 1 mm in size without matrix material, stabilized by surfactants and polymers. [5]

Advantages –

1) Improved biological performance
2) Ease of manufacture and scale-up
3) Long-term physical stability
4) Versatility
5) Increase in the oral absorption
6) Improved dose proportionality.

7) Its general applicability to most drugs & simplicity
8) It can be applied for poorly water soluble drugs.
9) It can be given by any route.
10) Reduced tissue irritation in case of subcutaneous/intramuscular administration.
11) Rapid dissolution & tissue targeting can be achieved by IV route of administration
12) Oral administration of Nano suspension provide rapid onset, reduced fed/fasted ratio & improved bioavailability.
13) The absorption form absorption window can be increased, due to reduction in the particle size.
14) Higher bioavailability & more consistent dosing in case of ocular administration & inhalation delivery.
15) Drug with higher log P value can be formulated as Nano suspensions to increase the bioavailability of such drugs.
16) Improvement in biological performance due to high dissolution rate & saturation solubility of the drugs.
17) Nano suspensions can be incorporated in tablets, pellets, hydrogel & suppositories are suitable for various routes of administration.

Disadvantage –
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**.**

➢ **Properties of Nano suspension:**

1. Long-Term Physical Stability:
Ostwald ripening is responsible for crystal growth and subsequent microparticle formation. Ostwald ripening is caused by changes in pore pressure / saturation temperature between small and large particles. Molecules diffuse from areas of high concentration around small particles (high solute in saturation) to large particles with greater affinity for the drug. This leads to the formation of a high concentration of the solution around large particles and thus the crystallization of the drug and the growth of large particles. Diffusion of drugs from small particles to large particles leaves a space around the small particles that is not saturated anymore, which causes the drug to diffuse out of the small particles, resulting in the complete disappearance of the small particles.. [6]

2. Internal Structure of Nano suspension:
The high energy input during the cleavage process causes structural changes in the drug particles. When drug particles undergo high-pressure homogenization, the particles change from a crystalline state to an amorphous state. When drug particles undergo high-pressure homogenization, the particles change from a crystalline state to an amorphous state. Exchange conditions depend on the hardness of the drug, the number of homogenization cycles, the chemical nature of the drug, and the energy density used by the homogenizer. [6]

3. Adhesiveness:
Compared to the coarse powder, there is a significant increase in the adhesion of the ultrafine powder. Adherence of small drug nanoparticles can be used for oral delivery of poorly soluble drugs. The best report is an increase in the bioavailability of diazole from 5% (as a microsuspension) to 82% (as a nanosuspension). [7].

4. Crystalline State and Morphology:
Possible changes in the crystal structure of the nano-suspension, that is, an increase in the amorphous fraction in the particles or the formation of transparent amorphous particles, are considered. In the production of nanosuspensions, the application of high pressure has been found to promote the amorphous state. [7]

5. Increase in Saturation Solubility and Velocity of Drug:
As the surface of drug particles increases from micrometer size to nanometer size, drug dispersion increases. According to the Noyes-Whitney equation, the melting rate increases as the surface area increases from micron-sized to nanometer-sized particles. $dx/dt = [(D \times A)/h] [Cs-X/V]$ ----- Equation (1) Where; D is the diffusion coefficient, dx/dt is the dissolution rate, A is the particle surface area, h is the thickness of the diffusion layer, V is the volume of the medium, and X is the surrounding concentration. liquid [8] .

➢ **Method of preparation:**

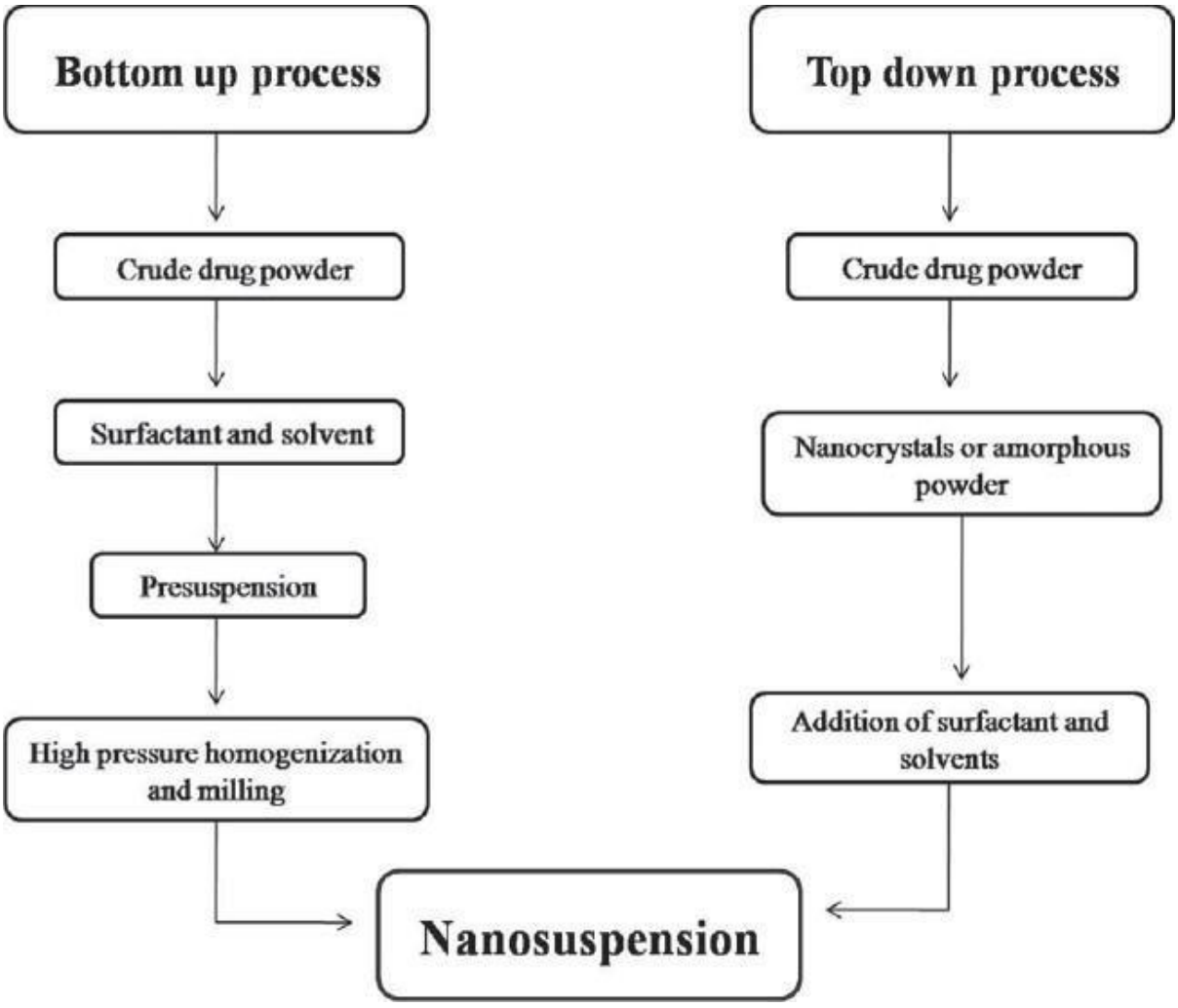

Fig: Preparation of Nano suspension

There are basically two ways to prepare nanosuspensions. Conventional precipitation methods (hydrosols) are called "low-tech". "High-Tech" is preferred over scattering methods and precipitation methods. Top Down technologies include media milling (nanocrystals), high pressure homogenization in water, high pressure homogenization in non-aqueous media (pure nano), and precipitation and high pressure homogenization. [9-16]

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

Bottom-Up Technology

The term "bottom-up technology" means that it starts at the molecular level and goes through the assembly of molecules to form solid particles. This refers to the quality of the solvent, such as adding a solvent to a non-solvent or changing the temperature or a combination of both. Precipitation is chemistry and medicine technology. [17-21]

Advantages

- Use of simple and low cost equipment.
- Higher saturation solubility is the advantage for precipitation compared to other methods of Nano suspension preparation.

Disadvantages

- The drug needs to be soluble poorly soluble in aqueous and in organic media).
- The solvent needs to be miscible with at least one nonsolvent.
- Solvent residues need to be removed, thus increasing production cost.
- It is an little bit tricky to preserve the particle character (i.e. size, especially the amorphous fraction) [22-24]

Top-Down Technology

The top down technologies include -

- Media milling
- High pressure homogenization

Media Milling Technique

Nano Milling Media Suspension is made using a high shear mill or a bead mill. The mill consists of a grinding chamber, a stirring horn, and a rotating chamber. This water solution is then put into a roller that contains small abrasive balls/beads. As these balls rotate at a very high shear rate at a controlled temperature, they fly through the crucible and strike the sample against the opposite wall of the crucible. The combined forces of friction and impact cause a reduction in particle size. Cellular media or spheres are made of ceramic fused alumina or zirconium oxide or high density polystyrene resin with high stomach resistance. Planetary ball mills (PM100 and PM200; Retsch GmbH and Co., KG, Haan, Germany) are examples of equipment that can be used to grind particles below 0.1 μm. Zn-insulin nano-suspension with an average particle size of 150 nm was prepared by wet milling. The main disadvantages of this technology are bead/bead erosion that can leave residues as contaminants in the final product, degradation of thermolabile drugs due to heat generated during the process, and significant particle size ≥5 μm.. [25-27]

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.

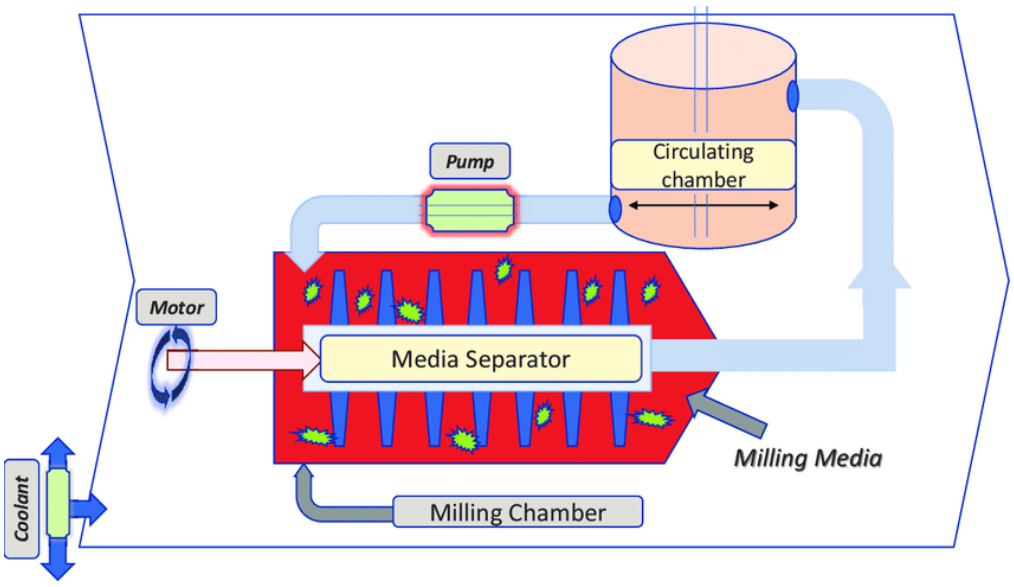

Fig 1: schematic representation of media milling

High pressure homogenization [28]

Homogenization involves applying pressure through a narrow nose valve. In this method, the surfactant and drug are concentrated under pressure through a nano-sized high-pressure homogenization aperture. The principle is based on voids in the water phase. The particle cavitation force is sufficient to convert drug microparticles into nanoparticles. Before the drug is subjected to the homogenization process, it is necessary to form a presuspension of the micronized drug in the surfactant solution using high-speed stirrers.

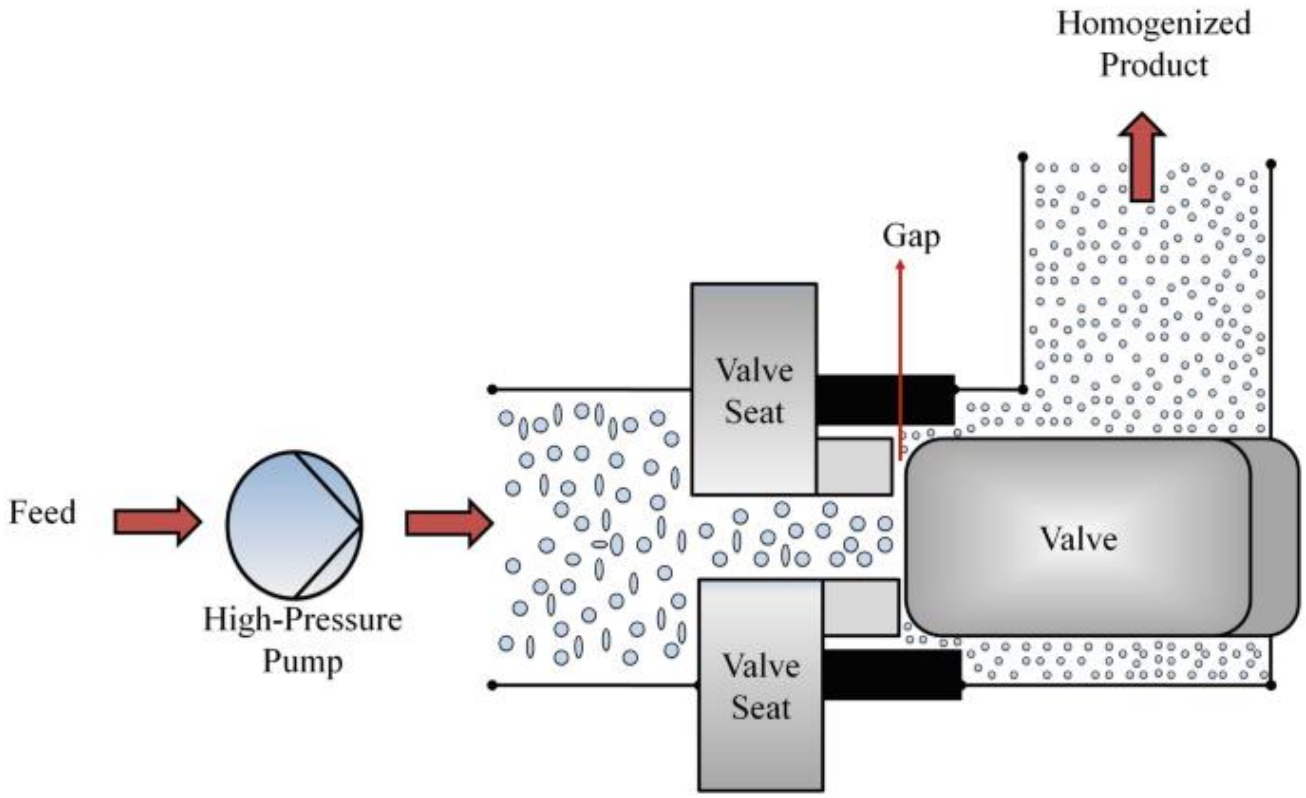

Fig 2: schematic representation of high pressure homogenization

Dissocubes

Homogenization involves applying pressure through a narrow nose valve. Dissocubes were developed by Muller et al. In this case, the drug suspension is passed into a small boat, which causes the static pressure to drop below the boiling water pressure, causing the water to boil and gas bubbles to form. When the normal air pressure is reached again after leaving the suspension space, the bubbles burst and the fraction containing the drug particles moves to the center and the colloid process, causing the particle size to decrease. This often requires several homogenization passes or cycles depending on the hardness of the drug, the desired medium particle size, and the desired homogeneity. This principle uses homogenizer APV Gaulin Micron LAB 40 (APV Homogenizer, Lubeck, Germany) and high pressure homogenizer NS 1001L-Panda 2K (Nirosuavi. S.P.A., Parma, Italy). To produce highly concentrated nano-suspensions, it is useful to start with very fine drug particles, which can be achieved by grinding the compound. The main advantage of medium pressure over high pressure homogenization is that it can be used for liquid and viscous suspensions and allows aseptic production. [29-32]

Nano pure

Nanoparticles are homogeneous suspensions in pure, anhydrous media or water mixtures. In Dissocubes technology, cavitation is the limiting factor of the process. But unlike water, fats and fatty acids have high vapor pressure and high boiling point. Therefore, the static pressure drop will not be enough to initiate cavitation. Patents related to the separation of polymeric materials by high-pressure homogenization show that high temperatures of about 800°C have facilitated the separation that cannot be used for thermolabile compounds. In nanopure technology, drug suspensions in non-aqueous media are homogenized at a temperature of 0°C or below freezing and are therefore called "deep freeze" homogenization. [33-34]

Nano edge

The basic principles of nano tip are similar to precipitation and homogeneity. The combination of these methods results in larger particle sizes and better stability in less time. The main disadvantages of precipitation techniques such as crystal growth and long-term stability can be solved by Nano edge technology. Suspension suspended in this method is more uniform; reduce particle size and prevent crystal growth. Precipitation is carried out using aqueous solvents such as methanol, ethanol and isopropanol. Although they can be tolerated to some extent in the formulation, it is desirable to completely eliminate this solvent. To efficiently produce nano-suspension using nano-edge technology, a high pressure homogenization followed by an evaporation step can be introduced to obtain the initial material modified solvent free. [35]

Nano jet

Called "counter-flow technology or Nano jet", this method uses a chamber in which the suspended flow is divided into two or more parts, which are combined under high pressure up to 4000 bar at speeds above 1000 m / s.[36] The high shear force produced during processing results in a reduction in particle size. Devices that use this principle include the M110L and M110S microfluidizers. Dear nanosuspension prepared from atovaco using microfluidization process. The main limitations of this method include the high flow rate of the microfluidizer (up to 75 passages) and the relative importance of rapid precipitation and high pressure homogenization of the product obtained. Baxter's patented Nano edge technology relies on the precipitation of baked-on materials to break down under high shear and/or thermal energy. Rapid addition of the drug solution to the antisolvent results in sudden supersaturation of the mixed solution and the formation of crystalline or amorphous bodies. Precipitation of amorphous material can be advantageous at high supersaturation when it exceeds the solubility of the amorphous state. [37]

Evaluation of nanosuspension

In-Vitro Evaluation

1. Particle size and size distribution.
2. Particle charge (Zeta Potential).
3. Crystalline state and morphology.
4. Saturation solubility and dissolution velocity.

1. Mean particle size and size distribution

The average particle size and the width of the particle size distribution (called the Polydispersity Index) were determined by Photon Correlation Spectroscopy (PCS). Particle size and polydispersity index (PI) govern saturated solutions; disintegration rate and biological performance. Changes in particle size have been shown to change solubility saturation and penetration rates. HK only measures the particle size between 3nm and 3 µm. PI governs the physical stability of the nanosuspension and should be as little as possible for long-term stability. (Must be close to zero). PCS is a versatile technique but has a low measurement range. In addition to PCS analysis, nanosuspensions were analyzed by laser diffractometry (LD). LD distributes the particle size and particle size from 0.05-80µm to 2000µm. An atomic force microscope is used to visualize the shape of particles.

2. Particle charge (Zeta Potential)

Particle charge determines the stability of nanosuspension. The minimum zeta potential should be ±30mV for electrostatically stable nanosuspensions and at least ±20mV for combined steric and electrostatic stabilization.

3. Crystalline state and particle morphology

Differential scanning calorimetry (DSC) determines the crystal structure. During the preparation of the nanosuspension, the drug particles will become amorphous, so it is necessary to measure the amount of amorphous drug formed during the preparation of the nanosuspension. X-ray diffraction (XRD) is also used to determine the physical state and phase changes of amorphous drugs.

4. Saturation solubility and dissolution velocity

The nanosuspension increase the saturation solubility as well as dissolution velocity. Saturation solubility is compound specific constant depending upon temperature and the properties of dissolution medium. Kelvin equation and the Ostwald-Freundlich equations can explain increase in saturation solubility.

Characterization of Nano suspension [38-39]

In-vitro evaluations

Colour, odour, Taste

These properties are particularly important for orally administered formulations. Changes in taste, especially in active ingredients, can be attributed to changes in particle size, crystal shape and subsequent particle dissolution. Changes in color, smell, and taste may also indicate chemical instability.

Particle Size Distribution

Particle size distribution determines the physicochemical behavior of the formulation such as saturation solubility, dissolution rate, physical stability, etc. Particle size distribution can be determined by photon correlation spectroscopy (PCS), laser diffraction (LD) and coulter counter multisizer. The PCS method can measure particles in the size range of 3 nm to 3 µm, and the LD method has a measurement range of 0.05-80 µm. The blade counter multisizer gives the absolute number of particles, unlike the LD method, which only provides a relative size distribution. For IV use, particles should be less than 5 µm, with the smallest capillary size being 5-6 µm, and therefore larger particle size can lead to capillary blockage and embolism.

Zeta Potential

Zeta potential is an indicator of suspension stability. A minimum zeta potential of ±30 mV is required for a stable suspension stabilized by electrostatic repulsion alone, while a zeta potential of ±20 mV would be sufficient for a combined electrostatic and steric stabilizer.

Crystal Morphology

Techniques such as X-ray diffraction analysis combined with differential scanning calorimetry or differential thermal analysis can be used to characterize the polymorphic changes due to the effect of high-pressure homogenization in the crystalline structure of the drug. Nanosuspensions can undergo a change in the crystalline structure, which can be in an amorphous form or in another polymorphic form due to high-pressure homogenization.

Dissolution, Velocity and Saturation Solubility

Nanosuspensions have an important advantage over other techniques in that they can increase the dissolution rate as well as the solubility at saturation. These two parameters should be determined in different physiological solutions. Evaluation of saturation solubility and dissolution rate helps in determining the in vitro behavior of the formulation. Böhm et al. reported an increase in dissolution pressure as well as dissolution rate as the particle size decreased to the nanometer range. A decrease in size leads to an increase in dissolution pressure.

Density

The specific gravity or density of the formulation is an important parameter. A decrease in density often indicates the presence of air trapped in the structure of the formulation. Density measurements at a given temperature should be made using a well-mixed, uniform formulation; an accurate hydrometer makes such measurements easy.

PH Value

The pH of the aqueous formulation should be measured at a given temperature and only after settling equilibrium has been reached to minimize "pH drift" and coating of the electrode surface with suspended particles. Electrolyte should not be added to the external phase of the preparation to stabilize the pH.

Droplet Size

The droplet size distribution of micro emulsion vesicles can be determined by either light scattering technique or electron microscopy.

Dynamic light scattering spectrophotometer which uses a neon laser of wavelength 632 nm

Viscosity Measurement

The viscosity of lipid-based formulations of several compositions can be measured at different shear rates at different temperatures using a Brookfield-type rotary viscometer. The sample room of the device must be kept at 370C thermal bath and the samples for measurement immersed in it.

Stability of Nano suspension

The high surface energy of Nano-sized particles induces agglomeration of drug crystals. The main function of the stabilizer is to thoroughly wet the drug particles to prevent Ostwald ripening and agglomeration of the nano suspension and to form a physically stable formulation by providing a steric or ionic barrier. Typical examples of stabilizers used in nanosuspensions are cellulose, poloxamer, polysorbates, lecithin, polyoleate and povidone. In the development of a parenteral Nano suspension, lecithin may be preferred.

In-Vivo Biological Performance

Establishing an in-vitro/in-vivo correlation and monitoring drug efficacy in vivo is an essential part of the study, regardless of the route and administration system used. This is most important in the case of intravenous injection Nanosuspension, because the in vivo behavior of a drug depends on organ distribution, which in turn depends on its surface properties, such as surface hydrophobicity and interaction with plasma proteins. In fact, the qualitative and quantitative composition of the protein absorption profile observed after intravenous injection of nanoparticles is considered to be a crucial factor for organ distribution. Thus, appropriate techniques need to be used to evaluate surface properties and protein interactions to gain insight into in vivo behaviour. Techniques such as hydrophobic interaction chromatography can be used to determine surface hydrophobicity, while 2-D PAGE can be used to quantitatively and qualitatively measure protein adsorption after intravenous injection of drug nanosuspensions in animals.

APPLICATION OF NANOSUSPENSION -

Bioavailability enhancement

A drug with poor solubility, poor permeability, or poor solubility in the gastrointestinal tract will result in poor oral bioavailability. Nanosuspensions solve the problem of poor bioavailability by solving the problem of poor solubility and poor permeability through membranes. The dissolution rate was enhanced for diclofenac when it was formulated as nanosuspensions. The dissolution rate of Diclofenac 1 Nano suspension after 60 minutes in SGF and H_2O is 25% and 10% in SIF compared to the relative crude suspension and the dissolution rate of Diclofenac 2 after 60 minutes in SGF and H_2O is 50% and 35% in SIF compared to coarse suspension.[40]

Oral Drug Delivery

Poor solubility, incomplete dissolution and lack of efficacy are the main problems of oral drug administration. Due to the smaller particle size and much larger surface-to-volume ratio, oral nanosuspensions are specifically used to increase the absorption rate and bioavailability of poorly soluble drugs. [41] In the case of azithromycin nanosuspensions, it was found that more than 65% of the drug was dissolved in 5 hours compared to 20% of the micronized drugs. Nano suspension has advantages such as improved oral absorption, dose proportionality and low intersubject variability. Using standard manufacturing techniques, drug nanosuspensions can be easily incorporated into a variety of dosage forms such as tablets, capsules, and quick dissolves. A nano-suspension of ketoprofen was successfully incorporated into pellets for sustained drug release for 24 hours. [42]

Parental Drug Delivery

The present approaches for parental delivery include micellar solutions, salt formation, solubilization using cosolvents, cyclodextrin complexation, and more recently vesicular systems such as liposomes and niosomes. But these methods have limitations like solubilization capacity, parental acceptability, high manufacturing cost, etc. To solve the above problems, the Nano suspension technology is used. Nanosuspensions are administered through various parental routes such as intraarticular, intraperitoneal, intravenous, etc. Additionally, nanosuspensions increase the efficacy of parenterally administered drugs. Paclitaxel Nano suspension was reported to have their superiority in reducing the median tumour burden. [43]

Pulmonary Drug Delivery

For pulmonary administration, nanosuspensions can be nebulized using mechanical or ultrasonic nebulizers. Due to the presence of many small particles, all aerosol droplets contain drug nanoparticles. Budesonide corticosteroid was successfully prepared in the form of Nano suspension for pulmonary application. [44] Aqueous drug suspensions can be easily nebulized and administered via the pulmonary route because the particle size is very small. Different types of nebulizers are available for the administration of liquid preparations. Some of the drugs successfully tried by the pulmonary route are budesonide, ketotifen, ibuprofen, indomethacin, nifedipine, itraconazole, interleukin-2, p53 gene, leuprolide, doxorubicin, etc. [45]

Ocular Drug Delivery

Nanosuspensions are used in the ocular delivery of sustained release drugs. Liang and co-workers prepared a suspension of cloricromene Nano for ophthalmic application using Eudragit. The experiment showed a higher availability of the drug in the aqueous humour of the rabbit eye. Thus, nanosuspension formulation offers a promising way to improve drug storage and bioavailability after ocular application. [46]

Targeted Drug Delivery

Due to their surface properties, nanosuspensions are suitable for targeting specific organs. Along with this, it is easy to change the in vivo behavior by changing the stabilizer. The drug will be taken up by the mononuclear phagocytic system, which allows for site-specific delivery. This can be used to target antifungal, antimycobacterial or antileishmanial drugs to macrophages when pathogens persist intracellularly. [47]

Mucoadhesion of the nanoparticles

Nanoparticles have the ability to adhere to the mucosal surface due to the small particles. Particle adhesion is the first step before particle absorption. To further extend adhesion time, nanosuspensions are formulated with hydrogels made from mucoadhesive polymers, e.g., various types of carbopol and chitosan. The adhesiveness of the nanosuspension not only helps improve bioavailability, but also improves targeting of parasites persisting in the GIT, e.g. cryptosporidium parvum. Mucoadhesive nanosuspensions of bupravaquone have been reported to show benefit in alpha TRC-deficient mice infected with cryptosporidium parvum oocytes [48]

Topical formulations

Drug nanoparticles can also be incorporated into anhydrous ointments and creams that have increased saturation solubility and increased diffusion of the drug into the skin [49-50]

Future perspectives and challenges

The future prospects of nanosuspensions are encouraging as they can contribute as a valuable tool for product development scientists to overcome various formulation and drug delivery challenges. Although several studies have been published on nanosuspensions, important aspects of stability problems related to nanosuspensions are still unresolved. The stabilizing ability of electrostatic and steric stabilizers and their properties in relation to API, maximum particle size and physical stability are important factors to be further investigated. Advances in biotechnology and breakthrough tools such as drug-antibody conjugates and nanobodies are likely to lead to highly concentrated monoclonal (mAb) and biosimilar products with enhanced biopharmaceutical properties and safety. Recently, Johnston et al. [51]

CONCLUSION: The remarkable advancements in Nano suspension technology have indeed made it a game changer in the field of solubility enhancement. With the ability to convert poorly water-soluble drugs into highly bioavailable formulations, nanosuspensions offer a promising solution to a longstanding challenge in pharmaceutical sciences.

Through a comprehensive exploration of preparation methods, characterization techniques, stabilization strategies, and real-world applications, it is evident that nanosuspensions have revolutionized drug delivery. These tiny, well-dispersed particles not only enhance drug solubility but also open doors to targeted and controlled drug release, ultimately leading to improved therapeutic outcomes for patients.

However, it is essential to acknowledge that challenges remain, including issues related to physical stability, scalability of manufacturing processes, and regulatory considerations. Researchers, pharmaceutical companies, and regulatory agencies must work collaboratively to address these hurdles and fully harness the potential of nanosuspensions. As we move forward, it is clear that the potential of nanosuspensions in enhancing drug solubility and bioavailability is vast. The versatility and efficacy of this technology make it a critical player in the ever-evolving landscape of pharmaceutical sciences. Nanosuspensions are not only a game changer but also a catalyst for innovation in drug delivery, offering hope for improved treatment options and better patient outcomes in the future.

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