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NANOSUSPENSION: A RISING DRUG DELIVERY SYSTEM

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ABSTRACT
Solubility proves to be an important limitation for the development and commercialization of new drug products. Due to this limitation, many pharmacologically active substances have failed to attain the market. Therefore, Nanosuspensions have emerged as a promising strategy for the efficient delivery of poorly water soluble substances due to their versatile characteristics and unique advantages. Various methods such as media milling and high pressure homogenization have been utilized for commercial production of nanosuspensions. Recently, the formulaion of nanosuspensions using emulsions and microemulsions as templates has been addressed in the literature. The unique features of nanosuspensions have enabled their use in several dosage forms, along with specialized delivery system such as mucoadhesive hydrogels. Rapid strides have been made in the delivery of nanosuspensions with the aid of parenteral, per-oral, ocular and pulmonary routes. Currently, efforts are being taken to extend their role in site-specific drug delivery.[1]

KEYWORDS: Nanosuspension, Bioavailability, High pressure homogenization, Media milling, Solubility, Ostwald ripening.

INTRODUCTION
Industries in pharmacy are constantly searching new approaches to obtain enough oral bioavailability as most of biological properties exhibiting new chemical entities are poorly water soluble.[2] Practically 40% of New chemical entities (NCEs) which are produced via various drug discovery programs are mostly lipohilic or poorly water soluble compounds. It has always been challenging problem to produce poorly water soluble compound. Formulating the nanosized particles can be applied to all drugs belonging to biopharmaceutical classification system (BCS) from class II to IV.[3,4] Recently, the formulation of such drugs as nanoscale structures (which have a dimension under 1µm) has hastily developed as a new and novel drug delivery system. The primary characteristic of these system is the fast dissolution rate, which increase bioavailability after oral administration.[5]

Defination: A pharmaceutical nanosuspension is defined as "finely dispersed solid drug particles in an aqueous vehicle or solvent, which are stabilized by surfactants, for either topical & oral use or parentral and pulmonary administration, with reduced particle size, leading to increase in surface area, dissolution rate, hence enhancing the bioavailability".[1] The diameter of the suspended particle is less than 1 µm in measurement (i.e. 0.1nm-1000 nm).[6,7] Average particle size is ranging from 200 to 600 nm.[1,2] An increase in the dissolution rate of nonosized particles is associated to an increase in the surface area and therefore the dissolution velocity.

Need of Nanosuspension: As many drugs are hydrophobic, so they have a limitation during making formulation. The formulation of nanosuspension is mainly preferred for a drugs that are insoluble in aqueous solvent with high lop P value. There are many ways to solve the problem of low solubility, low permeability and low bioavailability such as co-solvency, oily solutions, micronization and salt formation. Some other approaches are formulation of liposomes, microemulsion, emulsion, beta-cyclodextrin complex etc. But many of these methods lack in universal acceptability in all drugs.[8] In such cases, nanosuspensions are preferred. Surface active agents are added to stabilize the nanosuspension. Nanosuspesion is widely used for the drugs having high log P, high melting point and high dose. Major issues associated with less or poor water-soluble drugs:[1]

- Less Bioavailability.

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

Nanosuspension solve the above mentioned problems and used to increase the bioavailability as well as rate of absorption. It may also reduces the dose of the conventional crude suspension. The increase in dissolution rate is a result of increased surface area by reducing the particle size as described by Nernst-Brunner and Levich modification of Noyes Whitney equation.[9] The key difference between the conventional suspension and nanosuspension is particle size distribution. In nanosuspensions, the overall bioavailability is enhanced by an increase in surface area and saturation solubility via particle size reduction. This system cannot be achieved by the conventional milling techniques (Fig.1).[11]

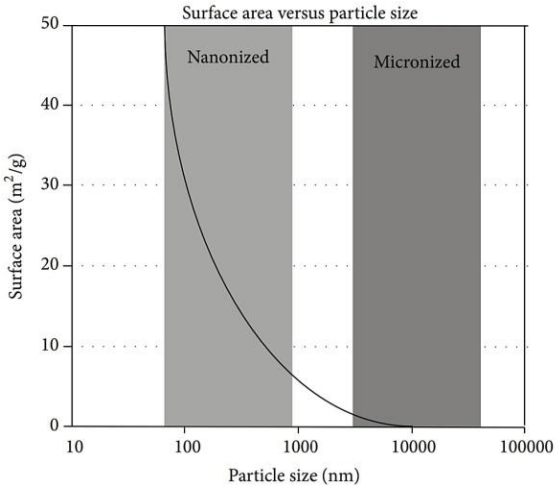


Figure 1: The plot demonstrates that, the increase in surface area when micron-size drug paraticle are broken into nanometer-size range. It enhance the overall performance of poorly soluble drugs.[10]

Advantages[8,12]

- Nanosuspension may enhances the dissolution velocity and saturation solubility of the drug.
- Nano suspension Provide passive targeting.
- Decreased tissue irritancy in case of subcutaneous/intramuscular administration.
- Nanosuspension provide Versatility
- As Ostwald ripening is absent, long term physical stability.
- Ease of manufacture and scale-up
- The absorption from absorption window of the drugs may be enhanced, due to reduction in the size of particles.
- Biological performance is enhanced due to high dissolution rate and saturation solubility of drug molecule.
- Increased bioavailability and more consistent dosing in case of ocular and inhalational delivery.
- Surface-modification of nanosuspension is possible for site specific delivery.

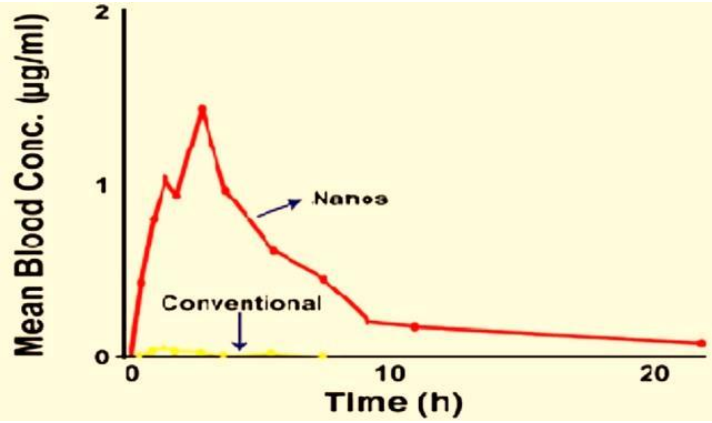


Figure 2: Bioavailability of hydrophobic compound formulated as nanosuspension (red) or conventional suspension (yellow).[1,11]

FORMULATION CONSIDERATIONS

Stabilizer: Stabilizer have very important role in the formulation of physically stable nanosuspension. The physical stability and the in-vivo behavior of nanosuspension can be affected by the amount and type of stabilizer. As we reduced the particle size to nano range, the surface free energy is tend to increase which results into agglomeration of drug particles. Stabilizers mainly used to wet the surface of drug particle to resist Ostwald ripening and agglomeration. It provides good physical stability by providing ionic and steric barriers. The drug-to-stabilizer ratio in the formulation may vary from 1:20 to 20:1 and should be investigated for a selected case.[13] Examples of stabilizers used in preparation of nanosuspension are Cellulosics, Poloxamers, Polysorbates, Lecithin and Povidones.[8]

Organic Solvents: When nanosuspension is prepared by using emulsion or microemulsion template then organic solvents are employed in formulation. Organic solvents may be hazardous in physiologic and environmental means. One should have to consider the toxicity potential of organic solvent and ease of their removal from the formulation when nanosuspension is formulated from emulsion and microemulsion as a template.

Table 1: Examples of solvents used in formulation of nanosuspension.[1]

Type of Solvent	Name	Remark
Water Soluble Solvent	Iso-Propanol, Ethanol	Less Hazardous, Pharmaceutically accepted
Partially Water Soluble Solvents	Ethyl Acetate, Ethyl formate, Butyl lactate, triacetin, propylene carbonate, benzyl alcohol	Preferred in the formulation over the conventional hazardous solvents, such as dichlormethane

Surfactant: Surfactants or surface active agents are incorporated to reduce the interfacial tension. They also act as wetting or deflocculating agents. Examples - Tweens and Spans are widely used surfactants.[15]

Co-surfactant: The choice of co-surfactant is vital when using microemulsion to formulate. Since co-surfactants can significantly affect phase behavior, the effect of co-surfactant on uptake of the interior phase for selected microemulsion composition and on drug loading need to be investigated. e.g. Transcutol, glycofurol, ethanol and iso-propanol – are safely used as co-surfactants. Also, bile salts and Dipotassium glycerrhizinate are frequently used as co-surfactants.[1]

Other Additives: Addition of other ingredients is depend on physical and chemical properties of drug candidates or route by which drug is administered. Normally additives like buffers, polyols, osmogent and cryoprotectants are added.[13] Buffers (such as acetate, phosphate), cryprotectants (like sucrose as sugar) and osmogent (such as mannitol, sorbitol).[14]

METHODS OF PREPARATION OF NANOSUSPENSION

Nanosuspension preparation is a simple alternative to that of liposomes & other conventional colloidal drug but results to be more cost effective. There are two methods for preparation of nanosuspension.

A. Top down process technology
B. Bottom up process technology

Top down process involves the disintegration of large particle, microparticles to nanosized particles. 'Top Down Technologies' include Media Milling (Nanocrystals), High Pressure Homogenization in water (Disso cubes), High Pressure Homogenization in nonaqueous media (Nanopure) and combination of Precipitation and High-Pressure Homogenization (Nanoedege). Some other methods used for preparation of nanosuspensions are emulsion as templates, microemulsion as templates etc.[12] It is preferred over bottom up process.

Bottom up technology includes conventional precipitation methods (hydrosols). In this method, drug is dissolved in an organic solvent and this solution is mixed with a miscible antisolvent. In the water-solvent mixture the solubility is low and the drug precipitates.[12] The limitation of this precipitation technique is that the drug should be soluble in at least one solvent and this solvent needs to be miscible with nonsolvent.[15]

TOP DOWN PROCESS

HIGH PRESSURE HOMOGENIZATION (DISSOCUBES)

Dissocube technology was developed by R. H. Muller in 1999. The instrument can be operated at pressure varing from 100 –1500 bars (2800–21300psi) to the 2000 bars with volume capability of 40ml (for laboratory scale). High pressure homogenization used to produce nanosuspension of many hydrophobic drugs. In the high pressure homogenization method, the suspension of a drug and surfactant is compelled underneath pressure via a naosized aperture valve of high pressure homogenization. Different techniques developed primarily based on this principle for production of nano suspensions are Dissocubes, Nanopure, Nanoedge, Nanojet technology.

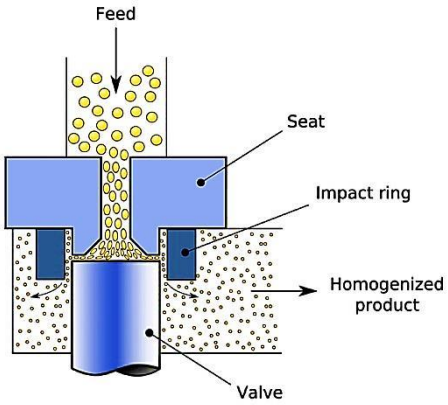


Figure 3: Schematic representation of High Pressure Homogenization process.

Principle

Based on cavitation in the aqueous phase. The particles cavitations forces are sufficiently excessive to convert the drug micro particles into nano particles. The issue with this method is the requirement for small sample particles earlier than loading and the reality that many cycles of homogenization are required.[12]

Advantages[2,12]

1. The main benefit is that it may be used with drugs that are poorly soluble in both aqueous and organic solutions.
2. Prevents processed materials from eroding.
3. It may be used to both diluted and concentrated suspensions, and it may allows aseptic preparation.
4. The nanosized drug present in the final product has a narrow size distribution.
5. Scalability is simple, and batch-to-batch variance is minimal.

Disadvantages[2]

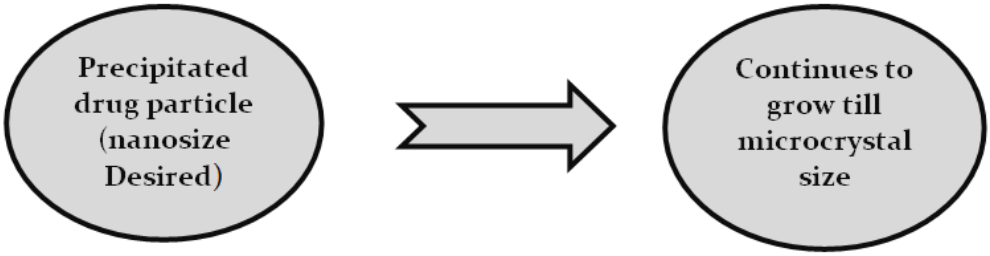
1. The use of high-cost instrument, which raises the cost of the dosage form.
2. Before loading the drug, it must be pre-processed.

NANOPURE (HOMOGENIZATION IN NON – AQUEOUS MEDIA)

Suspensions that have been homogenized in water-free medium or water mixtures such as PEG 400, PEG 1000, and others. Drug suspensions in non-aqueous media were homogenized at 0^{o}Celsius or even below the freezing point in nanopure technology, and thus homogenizations are referred to as "deep – freeze" homogenizations. At milder conditions, it can be utilised for thermolabile compounds. The drug nanocrystals can be directly filled as drug suspensions into HPMC capsules or gelatin by dispersing them in liquid polyethylene glycol (PEG) or different oils.[2,17]

NANOEDGE (COMBINED PRECIPITATION AND HOMOGENIZATION)

The drug is dissolved in an organic solvent and this solution is mixed with a miscible anti-solvent for precipitation. Within the water-solvent mixture, the solubility is low and the drug precipitates. Precipitation has also been including high shear processing. This is often accomplished by a combination of rapid precipitation and high pressure homogenization.



The Nanoedge technology was patented by Baxter depends on the precipitation of friable materials for fragmentation under conditions of high shear and/or thermal energy. Rapid addition of a drug solution to an antisolvent results in sudden super saturation of the mixed solution, and generation of fine crystalline or amorphous solids. Precipitation of an amorphous material might be favored at high super saturation when the solubility of the amorphous state is exceeded.[1]

NANOJET

It is also referred as opposite stream technology, in which a stream of suspension is divided into two or more parts using a chamber, where the suspension collides with each other at high pressures of up to 4000 bar at high velocity of 1000m/s. Particle size is reduced as a result of the high shear forces generated in this process. The main drawback is that the microfluidizer requires a large number of passes approximately 75, and the

resulting product contains a large percentage of microparticles. This procedure also needs a long production period.[17]

MEDIA MILLING (NANOCRYSYALS)

Liversidge et al. invented this patent-protected technique in 1992. The technology was previously held by Nano Systems, however it was recently acquired by Elan Drug Delivery. Nanosuspensions are made by utilizing high-shear media mills or pearl mills in this process.[18] A milling chamber, a milling shaft, and a recirculation chamber constitute up the media mill. The milling chamber is charged with milling media, water or an appropriate buffer, drug, and stabiliser throughout the media milling process.

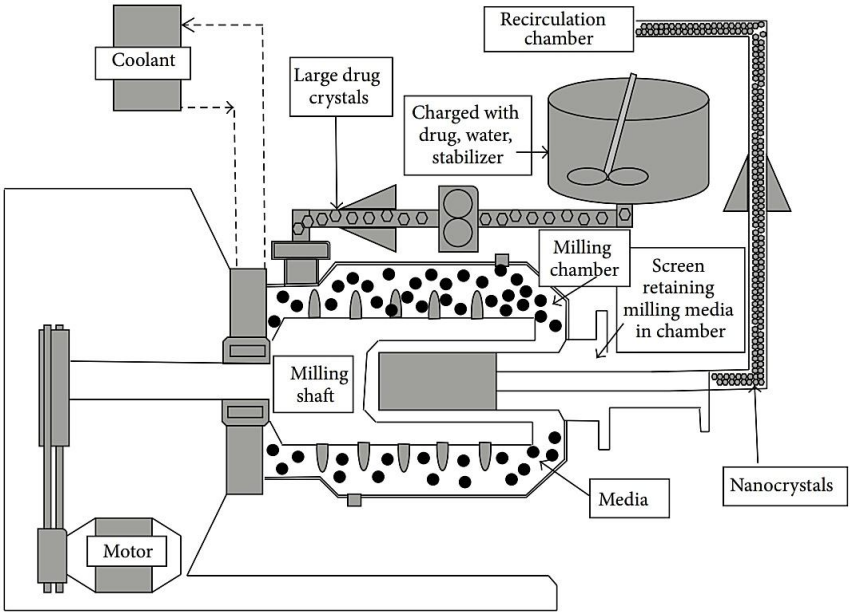


Figure 4: Schematic Diagram of Media Milling Process.[10]

Principle

The high energy input required to break the microparticulate drug into nano-sized particles is provided by the high energy and shear forces generated by the milling media impaction with the drug. Glass, zirconium oxide, or highly cross-linked polystyrene resin make up the milling medium. The process can be performed in either batch or recirculation mode. It takes 30–60 minutes in batch mode to obtain dispersions with unimodal distribution profiles and mean diameters of less than 200nm.[13]

Advantages

1. Poorly soluble drugs can be formulated.
2. Narrow size distribution of the final nanosized product and flexibility in handling the drug quantity.

Disadvantage

1. Potential erosion of material from the milling pearls.

EMULSIFICATION SOLVENT EVAPORATION TECHNIQUE

Emulsification-solvent evaporation technique, this method involves preparation of a solution of drug followed by its emulsification in another liquid that is a non-solvent for the drug. Evaporation of the solvent results in precipitation of the drug. Crystal growth and particle aggregation are often controlled by creating high shear forces using a high-speed stirrer.[1,2]

DRY-CO-GRINDIG

Dry-co-grinding is an another method. It is simple and inexpensive, but it must be done without the use of organic solvents. Because of the enhancement in surface polarity and conversion from a crystalline to an amorphous drug, this technique aids in improving the physicochemical characteristics and dissolving of poorly water soluble drugs.

BOTTOM UP PROCESS

SUPER CRITICAL FLUID METHOD

It is one of the best ways to make nanoparticles from a drug solution. The rapid expansion of supercritical solution (RESS) and the supercritical anti-solvent technique (PCA) are two of the approaches employed. The drug solution expands in a supercritical fluid through a nozzle, leading in a loss of the supercritical fluid's solvent power and the precipitation of the drug as tiny particles. In the PCA technique, medication solution is atomized and injected into a chamber containing pressurised CO_2. As the solvent system is removed, the solution becomes supersaturated and precipitates as fine crystals.[2]

EMULSIONS AS TEMPLATES

Emulsions can be utilised as templates to make nanosuspensions in contrast to being employed as drug delivery vehicles. For drugs that are soluble in either a volatile organic solvent or a partially water-miscible solvent emulsions can be used as templates.[13]

Principle

An organic solvent or mixture of solvents loaded with the drug is dispersed in the aqueous phase containing suitable surfactants to form an emulsion. The organic phase is then evaporated at a low pressure, causing the drug particles to precipitate instantly and form a surfactant-stabilized nanosuspension. Since each emulsion droplet produces a single particle, the particle size of the nanosuspension can be controlled by adjusting the emulsion droplet size.[12]

Advantages

1. Controlling the size of the emulsion droplet is a simple way to regulate particle size.
2. It is not essential to use special instruments.
3. Ease of scale-up if formulation is optimized properly.

Disadvantages

1. This method cannot be used for the drugs that are poorly soluble in aqueous and organic media.
2. In comparison to the previous manufacturing procedures, a large amount of surfactant/stabilizer is needed.
3. Diultrafiltration is required for the purification of the drug nanosuspension, which might make the process expensive.
4. Because dangerous solvents are used in the process, there are safety issues.

MICROEMULSION AS TEMPLATE

Microemulsions are isotropically transparent and thermodynamically stable dispersions of two immiscible liquids, such as oil and water, that are stabilised by an interfacial film of surfactant and co-surfactant (Eccleston 1992).[12]

Principle

The drug may be loaded into the internal phase or pre-formed microemulsions may be saturated with the drug by intimate mixing. The nanosuspension of drug is produced by dilution of the microemulsion to the appropriate concentration. If all of the chemicals used to prepare the nanosuspension are present at a concentration that is suitable for the chosen route of administration, then simple centrifugation or ultracentrifugation is one that is required to separate the nanosuspension.[20]

Advantages

1. They are an ideal drug delivery vehicle because of their high drug solubilization, extended shelf life, and simplicity of production.
2. The benefits and drawbacks are similar to those of emulsion as templates. The one additional benefit is that microemulsions use less energy for the generation of nanosuspensions.

POST PRODUCTION PROCESSING

Post-production processing of nanosuspensions becomes essential when the drug candidate is very vulnerable to hydrolytic cleavage or chemical degradation. Processing may also be required when the good possible stabilizer is not able to stabilize the nanosuspension for long period of time or there are acceptability restrictions with relation to the desired route. Considering these aspects, techniques like lyophilization or spray drying might be employed to supply a dry powder of nano-sized drug particles. Rational selection has to be made in these unit operations considering the drug properties and economic aspects. Generally, spray drying is more economical and convenient than lyophilization. The effect of post-production processing on the particle size of the nanosuspension and moisture content of dried nanosized drug should be given due consideration.[1,2]

Solidification Technique

In this case, solid dosage forms are considered more attractive, because of their patient convenience (marketing aspects) and good stability. Therefore, transformation of nanosuspensions into the solid dosage form is desirable. Solidification methods of the nanosuspensions include some unit operations like granulation, spray drying or lyophilization. As the primary objective of the nanoparticulate system is rapid dissolution, disintegration of the solid form and redispersion of the individual nanoparticles should be rather rapid, in order that it doesn't impose a barrier on the integrated dissolution process. Drying of nanoparticles can create stress on the particles which will cause aggregation. As an example, drying may cause crystallization of the polymers like Poloxamers, thereby compromising their ability to stop aggregation. Drying also can create additional thermal stresses which will destabilize the particles. As a result of the above considerations, adding matrix-formers to the suspension before solidification is important. Microcrystalline cellulose has been successfully wont to displace sucrose as a matrix former during freeze-drying of itraconazole nanosuspensions. Additionally, the effect of surface hydrophobicity on drug dissolution behavior upon redispersion had been investigated, indicating the more intense hydrophobicity, the more aggregation of the nanoparticles and therefore the slower the drug's dissolution after solidification.[1,7]

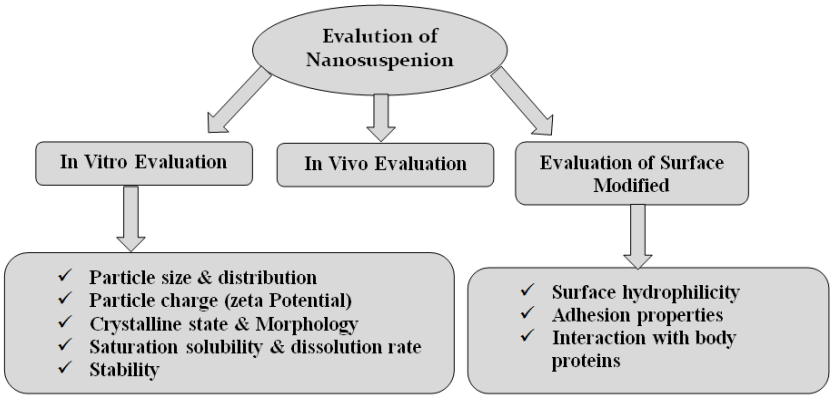
Surface Modification Technique

Nanosuspensions have the actual characteristics to raise the saturation solubility and dissolution rate for the poorly soluble drugs. But in some cases, the rapid or burst release of nanosuspensions may lead to the side effect and toxicity. As a colloid nanoparticle system,

nanosuspensions usually can target the Monocyte Phagocytic system (MPS), which may aid within the treatment of lymphatic-mediated diseases like tubercle bacillus, Listeria monogyna, Leishmania sp. The action is named as 'passive targeting'. However, the passive targeting process could pose an obstacle when either macrophages aren't the specified targets or accumulated drug is toxic to MPS cells. Hence, so as to bypass the phagocytic uptake of the drug, its surface properties got to be tuned, similar to stealth liposomes and nanoparticles. Faced with the above problems, the surface modification of nanosuspensions are going to be very necessary. Within the case of burst release and passive targeting, the controlled release and long residence at site of action might be effective. For example, Tan et al. had prepared layer-by-layer self-assembly coated procaine hydrochloride.[1,7]

CHARACTERIZATION OF NANOSUSPENSION

The appearance, colour, odour, assay, related impurities, particle size, zeta potential, crystalline status, dissolution studies, and in vivo studies of nanosuspensions are all evaluated. The most important characterization techniques were discussed below.



IN-VITRO EVALUATION

1. Mean particle size and size distribution

The physical stability, dissolution rate, saturation solubility, and even in-vivo behaviour of nanosuspensions are all influenced by the mean particle size and distribution. The saturation solubility and dissolution velocity of a drug can vary significantly depending on its particle size. Photon correlation spectroscopy (PCS), laser diffraction (LD), and coutler counter multiliser may all be used to assess particle size distribution. Poly-dispersity Index PI) is a critical parameter that controls the physical stability of nanosuspension and should be kept as low as possible. For assessing the contamination of nanosuspensions by microparticulate drugs, the coulter-counter gives the absolute number of particles per volume unit for the various size classes, and it is a more efficient and suitable approach than LD.[2]

2. Particle charge (zeta potential)

The zeta potential of a nano suspension must be determined because it provides information about the nano suspension's physical stability. Both the stabilizer and the drug determine the zeta potential of a nano suspension. A minimum zeta potential of ±30 mV is necessary for an electrostatically stabilised nano suspension, whereas a minimum zeta potential of ±20 mV is desired for a combined electrostatic and steric stabilised nano suspension.[1,12]

3. Crystalline state and particle morphology

It is important to understand the crystal morphology of the drug within the nanosuspension. Polymorphic or morphological changes in drug that occur during nano-sizing are often determined by the knowledge of crystalline state and particle morphology. Amorphous state of the drug formed during preparation of nanosuspension is decided by X-ray diffraction analysis. It gives information about the changes within the physical state of the drug particles as well as the extent of the amorphous fraction. Differential scanning calorimetry are often used additionally. Scanning electron microscopy (SEM) is additionally wont to get exact information about particle morphology.[1] Effect of high pressure homogenization on the crystalline structure of the drug is estimated by X-ray diffraction analysis together with differential scanning calorimetry. Techniques like scanning electron microscopy (SEM), atomic force microscopy (AFM) or transmission electron microscopy (TEM) are preferred for determining the precise size and morphology of nanoparticles in suspension.[1,12]

4. Saturation solubility and dissolution velocity

The determination of the drug's saturation solubility and dissolution velocity is critical because these two parameters help together to predict any changes in the drug's in-vivo performance (blood profiles, plasma peaks, and bioavailability). As nanosuspensions are known to enhance drug saturation solubility, determining saturation solubility rather than increasing saturation solubility is an essential investigative parameter. The drug's saturation solubility in various physiological buffers and at various temperatures should be determined using methods published in the literature. The examination of nanosuspensions' dissolving velocity

indicates the benefits that can be obtained over conventional formulations, particularly when developing sustained-release dosage forms based on nanoparticulate drugs. Methods published in the pharmacopoeia should be used to determine the dissolution velocity of drug nanosuspensions in various physiological buffers.[12]

5. Stability

In nanosuspensions, the particle size of the suspended particles affects the stability. The surface energy of the particles increases as particle size decreases to the nano range, and the tendency of the particles to agglomerate increases. As a result, stabilisers are employed to reduce the risk of Ostwald ripening and to improve suspension stability by acting as a steric or ionic barrier. Cellulosic, Poloxamers, Polysorbates, lecithin, polyoleate, and other stabilizer. In nanosuspensions, povidones are commonly employed. In the formation of parentral nanosuspensions, lecithin is recommended. Nanosuspensions may be stored under various stress conditions such as temperature (15, 25, 35, 45°C), thermal cycling, and mechanical shaking and the change in their mean particle size can be followed for three months. To examine the effect of stabilizer type and micellar solubilized drug on Ostwald ripening, different concentrations of small molecule surfactants (like sodium lauryl sulphate (SLS) and dowfax 2A1 (DF)) and polymeric stabilizer (like Hydroxypropyl methylcellulose (HPMC)) can be evaluated.[1]

6. pH value

To reduce "pH drift" and electrode surface coating with suspended particles, the ph of an aqueous formulation should be measured at a specific temperature or when equilibrium is reached. To keep the pH stable, no electrolyte should be added during in the external phase of the formulation.[12]

7. Osmolarity

Practically, Osmolarity of nanosuspension are often measured by using Osmometer.[1]

8. Drug Content

Drug content of nanosuspension formulation is achieved by extracting nanosuspension by appropriate solvent mixture like Methanol:THF(1:1) mixture, shake well & centrifuge. The supernatants are separated and diluted with same solvent mixture and absorbance is measured at suitable λmax. The drug content is calculated using the calibration curve.[1,21]

IN VIVO EVALUTION

The in vivo evaluation of nanosuspensions is required for particular drug and route of administration. In most cases, the formulations are administered by the prescribed route, and plasma drug concentrations are measured using HPLC-UV visible spectrophotometry. In vivo parameters are used to examine surface hydrophilicity/hydrophobicity (which determines interaction with cell prior to phagocytosis), adhesion properties, and interactions with body proteins. In order to produce a successful preparation, it is necessary to monitor the Nanosuspensions' in-vivo performance and establish a relationship between in-vitro release and in-vivo absorption regardless of the route of administration and delivery systems. In-vivo biological performance of oral nanosuspensions is influenced by their rate of dissolution. The organ distribution for intravenously injected nanosuspensions is determined by the size of the nanoparticles and their surface characteristics. Hydrophilicity/hydrophobicity, as well as particle interactions with plasma proteins, influence the nanosuspension's in-vivo organ distribution behaviour. After intravenous injection of drug nanosuspension in animals, surface hydrophobicity is determined by hydrophobic interaction chromatography, and protein absorption is quantitatively and qualitatively determined by 2-D PAGE.[1,22]

EVALUATION OF THE SURFACE MODIFIED PARTICLES

Surface hydrophilicity

Hydrophobicity/hydrophilicity of the surface it's a crucial parameter that influences in vivo organ distribution upon intravenous administration. Surface hydrophobicity influences the adsorption of plasma proteins, which is a significant determinant in organ distribution, as well as the interaction with cells before to phagocytosis. To avoid artefacts, the surface hydrophobicity in the aqueous dispersion medium must be measured. Hydrophobic interaction chromatography (HIC) is the best technique used to determine the hydrophobicity of bacteria and subsequently shifted to the characterization of nanoparticulate drug carriers.[2,9]

Adhesion Properties

Male Wistar rats may be utilised in in-vivo bioadhesive studies. In general, each rat receives a single dose of 10 mg nanoparticles mixed with drug (about 45 mg particles/kg body weight). Once the animal is cut, the abdominal cavity is opened, and the stomach, small intestine, and cecum are removed and cleaned with phosphate saline buffer. The stomach, small intestine, and cecum are cut into 2cm lengths and digested in alkali for 24 hours, after which 2ml methanol is added, and the mixture is centrifuged. To determine the number of nanoparticles adhering to mucosa, a 1 ml sample of supernatant will be assayed for drug by spectroflurimetry. Standard curves can be prepared for calculation if necessary.[2]

Interaction with body proteins

Incubating nanoparticles and mucin (4:1 weight ratio) in neutral or acidic media can be used to study the in-vitro interaction between mucin and nanoparticles. The incubation is carried out at a temperature of 370°C with constant stirring. The dispersion is then centrifuged and 150 of each supernatant is deposited in a test plate. After adding BCA Protein Assay Reagent Kit to the supernatants, the plate is incubated for 2 hours at 37° C.

By following this procedure absorbance of mucin is measured at λmax of the drug. The difference between the initial concentration of mucin and the concentration in dispersion after incubation and centrifugation is used to determined the total amount of mucin absorbed to nanoparticles.[1,2]

APPLICATIONS OF NANOSUSPENSION

Oral drug delivery

The oral route has a number of advantages over other options. The efficacy of an orally ingested drug is determined by its absorption via the GI tract and solubility. The oral absorption and bioavailability of a drug can be increased by nanosizing it. Increased bioavailability will result in a reduction in drug dose, resulting in more cost-effective therapy.[1,22]

Pulmonary drug delivery

Commercially available nebulizers can be nebulize the drug nanosuspension. The size distribution of the produced aerosol droplets can be used to control disposition in the lungs. The mucoadhesiveness of drug nanocrystals is increased, resulting in a longer residence duration at the mucosal surface of the lung. Hernandez-Trejo and Cowotkers developed physically stable nanosuspensions for nebulization to deliver bupravaquone to the site of a lung infection.[12,25]

Ocular drug delivery

Drugs which have poor solubility in lachrymal fluid can be formulated as nanosuspension. Advantages of nanosuspension in ocular drug delivery are as follows –

- It can remain for longer duration in cul-de-sac.
- Avoids the tonicity produced by the hydrophilic drugs.
- In order to provide sustained release of drug, nanosuspension may incorporate with appropriate hydrogel base or mucoadhesive base. Effect of nanosuspension is related to the intrinsic solubility of drug in lachrymal fluid.[2,24]

Parenteral drug delivery

Nanosuspensions are often wont to transform poorly soluble non-injectable drugs into a formulation suitable for intravenous administration. Although the formulation of Nanosuspension for parenteral use is critical, current developments during this technology have proved its utility as injectable formulations. The methods used for preparation of Nanosuspension are now precisely controlled, and are ready to produce uniform particles with better control over maximum particle size. Various research reports are available which emphasize the applicability of Nanosuspensions for parenteral administration.[1,22]

Topical formulation

The nanocrystalline form possesses increased saturation solubility leading to enhanced diffusion of the drug into the skin. Nanocrystals also exhibit various properties like increased penetration into a membrane, enhanced permeation and bioadhesiveness which might be very useful for dermal application and the nanoparticles can be incorporated in to the creams and oil as well as water free ointments.[12,23]

Drug targeting

Nanosuspensions offer a great potential for drug delivery, especially in targeting the brain. The surface properties and invivo behaviour of nanosuspensions can be changed by altering the stabiliser, therefore they're suitable candidates for drug administration.[2,12]

Mucoadhesion of 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 mentioned as "bioadhesion." From this moment on, the concentrated suspension acts as a reservoir of particles and an adsorption process takes place very rapidly. The direct contact of the particles with the intestinal cells through a bioadhesive phase is that the first step before particle absorption.[1,22]

Bioavailability enhancement

Nanosuspensions improve the drug's solubility and permeability across the membrane, resulting in greater bioavailability.[12]

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CONCLUSION

Nanosuspensions appear to be a novel and commercially viable solution to addressing issues like poor bioavailability associated with the administration of hydrophobic medicines, such as those that are poorly soluble in both aqueous and organic mediums. Large-scale production of nanosuspensions has been completed using techniques such as media milling and high-pressure homogenization. Advances in production methodologies that use emulsions or microemulsions as templates have resulted in even more simple and direct methods of production, but they are not without drawbacks. In this regard, more research is required. Increased dissolution velocity, increased saturation solubility, improved bioadhesivity, versatility in surface modification, and ease of post-production processing are just a few of the attractive characteristics of nanosuspensions. Nanosuspensions have been used in pulmonary and ocular delivery, and their application in parentral and oral routes have been investigated thoroughly. However, their use in buccal, nasal, and topical administration is still being researched. The development of stealth nanosuspensions laced with functionalized surface coatings capable of evoking

passive or active targeting as needed is a further step in nanosuspension research.[1,12]

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