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Nanosuspension as Novel Drug Delivery Approach: A Review

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ABSTRACT: The solubility of drugs is a common problem observed during formulation development to overcome this issue nanosuspension is possibly a solution. Over the last decade, there has been growing interest in formulatingthepoorly soluble drugswith nanosuspensions. Nanosuspension are cost-effective and simple to manufacture in comparison to liposomes and other colloidal drug carriers, which make them an attractive option for eliminating solubility issues. Basically, nanosuspensions containan aqueous vehicle in which pure drug particles are dispersed which arestabilized by addition ofsurface-active agents. This approach to drug formulation is straightforward and offers several advantages over other methods. Nanosuspensions, can be used for oral, topical, parenteral, and pulmonary route of administration of drug delivery.Nanosuspensions can also be incorporated into ocular inserts and mucoadhesive hydrogels for targeted drug delivery. In nanosuspensions reducing particle size is the main reasonfor increase dissolution rate and improve drug delivery. This review is mainly focused on the methods of nanosuspension formulation, formulation considerations, production methods, evaluation parameters and applications in pharmaceutical drug delivery.

KEY WORDS: Nanotechnology, Nanosuspension, Solubility, Techniques, Bioavailability

I. INTRODUCTION

Nanosuspensions are prepared using nanotechnology. Nanotechnology is the field of science and engineering. It deals with the alteration of matter at atomic or molecular scale, typically ranging between 1 to 100 nanometres. At this size range, materials show unique properties that are different from those at larger scales because of the quantum mechanical effects. Nanotechnology deals with the designing, synthesis, characterization, of particles by controlling shape and size to the nanometer range. Nanotechnology helps in targeted drug delivery, imaging, and diagnostics at the cellular or molecular level, which helps in effective treatments with fewer side effects.[1]

Nanosuspension:

Nano-suspensions are colloidal dispersions of nanoscale particles in a liquid medium. Nanosuspensions are a type of drug formulation with very small drug particles stabilized by surfactants. These are primarily a mixture of drug particles and antisolvent (most likely water), with the particle size less than 1µm. The particles of nano-suspensions are usually in the range of 1 to 100 nanometres in size.[2]

By reducing the drug particles size to such a small extent, the dissolution rate of the drug can be improved because of the increased surface area and saturation solubility. Nanosuspensions are found effective in overcoming the problems which are associated with conventional drug formulations. Nano suspensions are found effective in the delivery of poorly soluble drug. These suspensions contain solid nanoparticles which are dispersed in a liquid phase, mostly water or a water-based solution. For the stability of particles in nanosuspensions it is important that the particle size should be uniform. The problem of low solubility and bioavailability in drugs can be addressed using nanosuspensions, which makes them more efficient and safer. It is especially suitable for medicines that are not soluble in water or organic solvents. They are appropriate for formulations of drugs with high lipophilicity, high melting point and high dosages. Nanotechnology application to the production of poorly water-soluble drugs as nanosuspensions presents a chance to rectify the weaknesses inherent in this class of medications. [3]

The intravenous administration of poorly soluble drugs become possible with the nanosuspension technology, without the risk of blockage of blood capillaries. Additionally, lyophilization and spray drying of nanosuspensions is possible, and the nanoparticles within the

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nanosuspension can also be incorporated into a solid matrix. And also, liquid dosage forms have many advantages over solid dosage forms. This review focuses on the different methods that are used for preparation of nanosuspensions, the evaluation parameters of nanosuspension and the different applications of nanosuspension.[4]

Nano-suspensions have gained significant attention in various industries due to their unique properties and potential applications. Some common uses of nano-suspensions include-

1. Pharmaceutical Industry
2. Cosmetic Industry
3. Food Industry

Advantages of Nanosuspension:[5]

Nano-suspensions providevarious advantages over Traditional dosage form, due to these nanosuspensions have various application in pharma and other Industries. Some of the key advantages include:

1. Nano-suspensions can improve the solubility of poorly soluble drugs or compounds to a significant extent by reducing particle size to the nanometre range. Decreasing size to nanometer range leads to increased surface which allows better interaction with the solvent, leading to enhanced dissolution rates and bioavailability.
2. Due to the small size of the particle of nanosuspensions the absorption and bioavailability of drug enhanced which leads to more predictable and consistent pharmacological effects. This is a particularly advantage for drugs with low oral bioavailability
3. Nano-suspensions helps in targeted delivery of drugs or active ingredients to specific cells, tissues, or organs. The modification in the surface morphology of nano suspensionhelps in site-specific drug release, reduction in systemic side effects and improved therapeutic outcomes
4. Nano-suspensions shows improved stability in comparison to conventional formulations due to reduced particle size and increased surface area. This increased stability minimizes aggregation, sedimentation, etc.which leads to longer shelf-life and improved product efficacy.
5. Nano-suspensions helps in controlled and sustained release of drugs results in prolonged therapeutic effects. By modulating nanoparticle properties and formulation parameters, release kinetics can be altered to meet desired therapeutic profile.
6. Nano-suspensions can reduce the toxicity of certain drugs or compounds by improving their pharmacokinetic profiles and reducing systemic exposure. Targeted delivery to specific sites can minimize off-target effects and mitigate adverse reactions.
7. In topical formulations, nano-suspensions can improve the penetration of active ingredients through the skin or mucosal membranes, improving efficacy and onset of action.[6,7]

Disadvantages of Nanosuspension:

Although nano-suspensions have a number of advantages, but they also have some disadvantages which are needed to be kept in consideration while formulation. Some common disadvantages of nano-suspensions are-

1. Particle aggregation or Ostwald ripening may occur in nano-suspensions over time, which lead to the instability and increase in particle size. Stabilization techniques like use of stabilizing agents are needed to eliminate this issue.
2. Nanosuspension manufacturing involves complex processes like high-pressure homogenization, wet milling, or precipitation methods which require specialized equipment and expertise, resulting high production cost.
3. Achieving narrow particle size distribution in nano-suspensions can be difficult, leading to variations in drug release kinetics and pharmacokinetics.
4. Special storage and handling conditions are required for nano-suspensions may to maintain stability and prevent degradation. Factors like temperature, light exposure, and pH can affect the stability of nanosuspension.
5. Nano-suspensions shows different pharmacokinetic and biodistribution profiles compared to conventional formulations, which make it necessary to evaluate safety and risk management.
6. Nano-suspensions may involve higher production costs compared to conventional formulations due to the need for specialized equipment, raw materials, and quality control measures.
7. Compatibility testing is necessary because nano-suspensions may exhibit compatibility issues with other excipients or formulation components, affecting stability, efficacy, or safety.[6,8]

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SELECTION OF DRUG TO BE FORMULATED AS NANO SUSPENSION

For selecting drug to be formulation as nanosuspension, there are several points which one should kept in consideration to ensure the successful development of a stable and effective product. These include:

1. Poor Solubility
2. High Permeability
3. Therapeutic Importance
4. Target Site
5. Stability
6. Biocompatibility
7. Manufacturability
8. Regulatory Considerations

FORMULATION OF NANOSUSPENSION

The component which are essential for the formulation of nanosuspension are-

Stabilizer:

Stabilizers helps in prevention of formation of agglomeratein the pharmaceutical formulation and prevent aggregation of particles which in turn provide physical stability to the pharmaceutical formulation. The type and amount of stabilizer usedin nanosuspension formulation has effect on in-vivo performance of nanosuspensions. If more than onestabilizeris used then they should be in proper ratioto obtain a stable formulation. Various types of stabilizers like poloxamers, cellulosic, polysorbates, povidones, lecithins, Vitamins, PGS, etc can be used which depends on the other ingredients.In nanosuspension formulation thedrug-stabilizer ratio of can be varied from 1:20 to 20:1. Lecithin is the best stabilizer for the formulation of parenteral nanosuspension.[9]

Organic Solvent:

The organic solvent which is going to be used in the formulation of nanosuspension should be stable and non-hazardous. Organic solvents are used if we use emulsion as mediumin the development of nanosuspension. Solvents which aremiscible in watersuch as ethanol, methanol, chloroform,isopropanol etc are mostly usedin nanosuspension preparation. Othersolvents which are partially miscible in water like ethyl formate, butyl lactate, propylene carbonate, ethyl acetate, and benzyl alcohol etc are also used. Othersolvents which are harmfulsuch as dichloromethane are not usedin formulationof nanosuspension as they are hazardous.[10]

Surfactants:

In the formulation of nanosuspensions surfactants has a major role as they provide stability to the drug particles and prevent their agglomeration. Surfactants have amphiphilicnature, which means they have both hydrophobic and hydrophilic properties. This helps the surfactant to get adsorbed on thedrug particles surface results information a protective film, which preventsinteraction between particles. Interfacial tension between drug particles and mediumof dispersion is reduced by this layer, enhancing their stability. Different surfactants like poloxamers, polysorbates, lecithins, and pluronicsare used for the formulation of nanosuspensions. The selection of surfactant depends on different physical and chemical properties of the drug and theroute by which the is to be administered.[11]

Co-Surfactant:

Co-surfactants are used with surfactants to enhance the property of surfactantused in formulation development of nanosuspensions. The solubilization capacity of the surfactant can be improved by addition of co-surfactants which in turn enhancethe stability of the nanosuspension. Glycols, alcohols, and polyethylene glycols are Some commonly used co-surfactants in nanosuspensions. The selection of co-surfactant depends on surfactant used. The stability of nanosuspension is directly affected by the ratio between surfactant and co-surfactant. The use of appropriate co-surfactants in nanosuspension formulation can help in improving drug delivery results in increased efficacy of drug.[2,11]

Other additives:

In addition to the above components,salts, buffers, polyols, osmotic agents, and cryoprotectants are some other additives which areused in nanosuspensions. These additives are used on the basis of route by which nanosuspension is to be administred and the physical and chemical properties of the drug. Salts and buffers can be used to adjust the pH of the nanosuspension and maintain its stability. Polyols and osmotic agents can be added for enhancement of stability of the formulation and prevent aggregation of the drug particles. Cryoprotectants like sucrose and trehalose can be added to protect the nanosuspension from freeze-thaw cycles and maintain its stability during storage.[12]

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PREPERATION OF NANOSUSPENSION

The "top-down" and "bottom-up" technologies are two main methods used for manufacturing nanosuspensions. The conventional precipitation methods were called "bottom-up technology," whereas the disintegration methods were termed as "top-down technologies" and these are preferred over precipitation approaches. Top-down technologies involves different techniques such as media milling, high-pressure homogenizationand dry co-grinding. In addition, emulsion as templates and microemulsion as templates can be employed to prepare nanosuspensions. [6,13,14,]

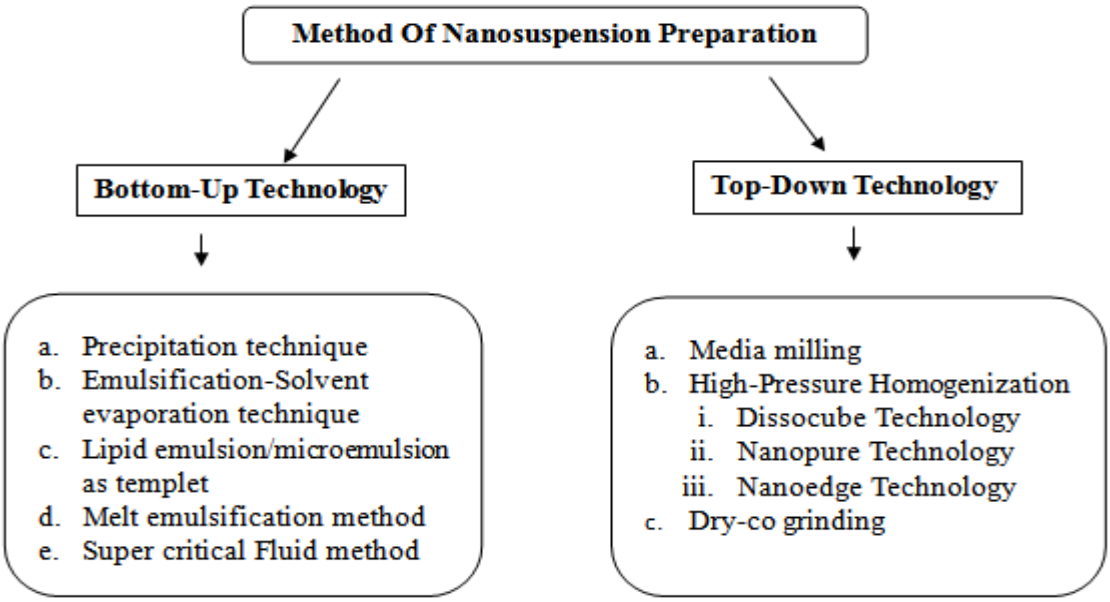

Figure 1: Nanosuspension Preparation Techniques

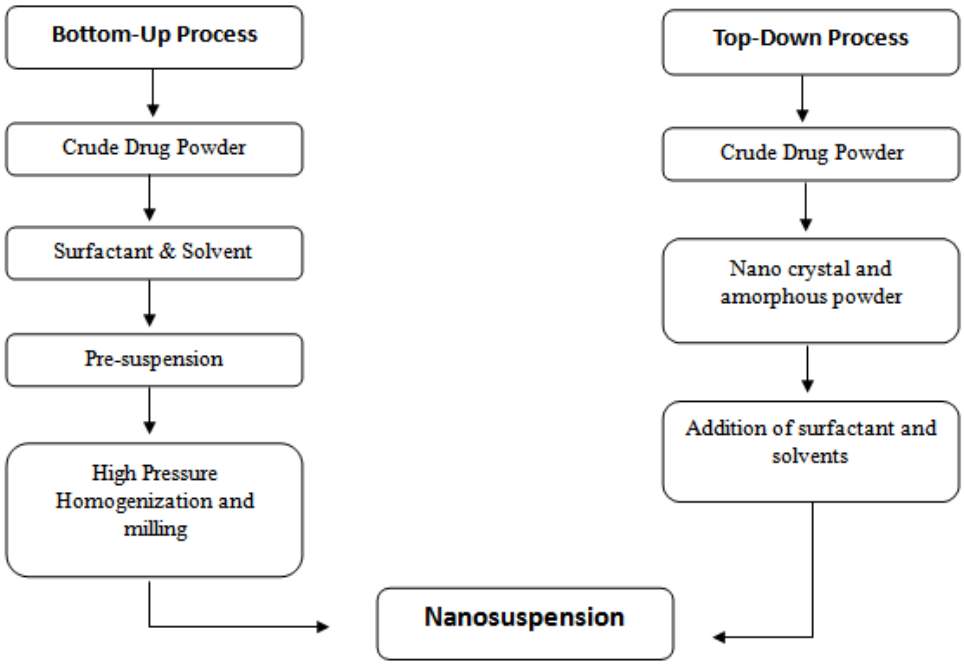

Figure 2: Nanosuspension Preparation Techniques

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TOP-DOWN TECHNOLOGY[14]

This process involves breaking down larger and smaller particles into much smaller nanosized particles, known as top-down techniques. There are several approaches used in this method, which are described below.

a. Media milling
b. High-Pressure Homogenization
   i. Dissocube Technology
   ii. Nanopure Technology
   iii. Nanoedge Technology
   iv. Nanojet technology
c. Dry-co grinding

Media Milling:

Media milling technology, was invented by Liversidge et al. in 1992. It is also known as nano-crystals technique. High shear mills like media mills or pearl mills are utilized in this technique to produce nanosuspensions. Milling chamber, a milling shaft, and a recirculation chamber are main components of a media mills. Drugalong with milling medium, anti-solvent, and stabilizers are introducedin milling chamber, followed by the operation of milling medium. Due to a high-speed rotation a high shear force is produced between the milling media and drug due to the impaction. This results in the size reduction of microsized drug particles into nanosized particulates, producing nanoparticles of drug substance. Zirconium oxide, glass, and highly cross-linked polystyrene resin are some common milling media. For getting nanoparticle of size range 0.1 μmor less Planetary ball mills is best.Niwa T et al. hadprepared nanosuspension using media milling technique.[15]

Advantages:

1. Variation betweenbatches is very small
2. Scale up this method is quite easy.
3. There is flexibility in drug quantity.

Disadvantages:

1. Finished product may be contaminated if the balls or pearls material erodes during production.
2. It is not suitable for thermolabile drugs due to production of heat during process.
3. Due to longer milling time there is a chance of microbial growth in water.
4. Time consuming.
5. The process by which nanoparticles are separated from milling material is time consuming and very costly.

High Pressure Homogenization:[16]

High-pressure homogenization involves different techniqueswhich are-

i. **Dissocube Technology:** This technique wasinvented by R. H. Muller et al. in 1998. In this method, pre-suspension under high pressure is passed through a valve of very small aperture. The most common homogenizer used for this purpose is the APV micron LAB 40, although other homogenizers such as the Stansted and piston-gap homogenizers can also be used. Firstly,conventional method is used to prepare micro size drug suspension. According to Bernoulli's equation the static pressure of water can be reduces below its boiling point if it issubjected to pressure and passes through the small orifice. This causes water to boil and gas bubbles to form.

The operational pressure of homogenizer rangesbetween 100 to 1500 bars, although some homogenizers can handle pressures up to 2000 bars. On the basis of required size of particle, hardness of drug particle, and the required homogeneity, it is necessary to repeat cycle. A phenomenon called cavitation in which gas bubble goes off takes places when the suspension passes orifice. Thereafter, air pressure backs to normal, and the particles of drug moves faster towardscentre, where bi-colloidal processes reduce them into nano-sized particles via the implosion process. Kayser O et al. had developed nanosuspension containing amphotericin with the help of this method.[17]

Advantages

1. Suitable for heat sensitive material.
2. Forms nano suspensions with very fine particle

Disadvantages

1. This technique is costly.
2. For hard material it is needed to repeat the cycle of homogenization several times.

ii. Nanopore Technology: The homogenization technique in which nanosuspensions are preparedwith the help of a media that is water-free, the technique is known as nanopore. This technique was first developed by Pharmasol GmbH/Berlin. Nanopure technology is particularly useful fordrugs whichdegrades or are sensitive to water and heat. Non-aqueous phases like alcohol or water-alcohol mixtures are commonly used in nanopure technology,

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which is beneficial when tablets are to be prepared from nanosuspensions. This method requires low heating temperature for solvent removal, making it "deep freeze" homogenization method. The drug is dispersed in a non-aqueous medium, and the formed suspension is homogenized using a piston-gap homogenizer at 0°C or below the freezing point, such as -20°C. This process is more effective at lower temperatures, where cavitation in the gap is low or non-existent due to the low vapor pressure of the dispersion medium being used. This means that the desired nanosized can still be obtained even if cavitation is not present. Lower energy is required to evaporate the solvent due to the reduced water content, which makesnanopure homogenization technology a cost-effective method.[4]

Advantages
1. Low energy is required.
2. Useful for heat sensitive material

iii. Nanoedge Technology: This technique is a combination of two different technique i.e. precipitation and homogenization technique, which have similarity in their mechanisms. Nanoedge technology is considered superior as it produces smaller particle sizes in a short time frame. The two main disadvantages of precipitation method are low crystal growth and enhanced stability of nanosuspension. In Nanoedge technology, firstly a drug solution is prepared which is then rapidly added into an anti-solvent solutionwhich results information of super-saturated solution generating fine particles, to avoidcrystal growth in solution homogenization process is employed by whichparticle of smaller sizes are obtained.[18]

Advantages
1. Low energy is required.

iv. Nanojet Technology: The another name of nanojet technology is opposite stream technology, is another technique which is used for producing drug particle of smaller size. This method involves formation of more than onestream of suspension whichare made to collide with each otherwith high pressure. This generates high shear forces, which reduces the size of drugparticle. The nanojet technology is particularly useful because it does not involves the use of stabilizers or surfactants for producing nanosuspensions.[19]

Advantages
1. Do not require stabilizer or surfactant.

Disadvantages
1. Not suitable for heat sensitive material.

Dry-co Grinding:

Dry-co-grinding methodis used for preparing nanosuspensions andthis technique does notrequireorganic solvents. The dissolution ofpoorly water-soluble drugs can be enhanced with the help of this method. In this method the phase transition of drug from crystalline to amorphous form takes place. This method also enhances the surface polarity of drug. A stable nanosuspensions of drug which arepoorly soluble in water can be prepared using dry-co-grinding method. This technique can reduce particle size to the extent of submicron level. Nano suspension of drugslikeglibenclamide, griseofulvin, and nifedipine which are poorly soluble in watercan formulated usingthis technique.Some common polymers which are used in this technique are PEG, PVP, HPMC,etc.[20]

Advantages
1. The process of nanosuspension formation by this method is easy.
2. The organic solvents are not required in thisprocess.

Disadvantages
1. The final product may contain residue of milling.

BOTTOM-UP TECHNOLOGY[21]

Different method of bottom-up technology are-
a. Precipitation technique
b. Emulsification-Solvent evaporation technique
c. Lipid emulsion/microemulsion as templet
d. Melt emulsification method
e. Super critical Fluid method

Precipitation Technique:

This method is primarilyused for drugs which are poorly soluble in water and iscontinuously used for over years to develop nanoparticles. In this method, anti-solvent is added to the solution of drug which results in the precipitation of drug from its solution. This method is helpful in preparingnano-suspensions of several drugs. Particles morphology ofthe final product is controllable by using precipitation technique. This

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method involves dissolution of drug in appropriate solvent. Surfactant and stabilizer are dissolved in another solvent which is called anti-solvent,that is typically water. Then the drug solution is added dropwise into the anti-solvent containing stabilizer, which results indiffusion of solvent into anti-solvent, and formation of nanoparticle of drug.

"Ostwald ripening" may occur during this process which can be prevented by using suitable stabilizers and additives. Ultrafine solid drug particles ranging in nanometre range are formed with the help of this method.[21,22]

Advantages

1. This is easy and cheaper method.
2. Scale-up is possible.

Disadvantages

1. The solvent and antisolvent selected has direct effect on particle size.

Emulsification-solvent Evaporation technique:

In Emulsification-solvent Evaporation technique, firstlya solution of drug is prepared by dissolving drug in solvent, then an emulsion is prepared by adding liquid in which drug is not soluble in previously prepared solution. Then the drug solvent is made to evaporate from emulsion, causing the drug to precipitate out. To ensure that the particles do not aggregate or grow too large during this process, high-speed stirrers are used.Aceclofenac nanosuspension was developed by Patel HM et alwith the help of this method this method using acetone as the solvent and, Tween-80 as surfactant informulation. [23,24]

Lipid Emulsion/Microemulsion as template:

Nano suspension of drugs which are soluble in solvents that are partially water miscible or volatile in nature is prepared using this method. Firstly, a solution of drug is prepared, an aqueous phase containing surfactant is than added to the solution resulting in formation of emulsion. Then solvent is evaporated, causing the drug particles to precipitate in the aqueous phase. To produce nanosuspensionsby this method microemulsions can be used. Nanosuspensions are obtained by diluting the resulting suspension or microemulsion.[25]

Advantage

1. Method is easy

Disadvantage

1. Employed harmful solvents.
2. Surfactants required in large amount.

Melt Emulsification Method:

Melt Emulsification Method is an approach for producing nano-suspensions. In this method firstly an aqueous suspension of the drug is prepared. This suspension then heated above its melting point;this leads to the formation of an emulsion which is of oil-in-water type. Then small droplets of this emulsion are formed using different techniques such as homogenization, ultra-sonication, magnetic stirring, etc. On coolingthe drug droplets solidify and recrystallize into nanosized particles. This method of preparing nanosuspension is used only for those drugs which have melting point lower thanboiling point of water. The size of nanoparticle is affected by various aspects such as coolingrate, sonication energy, and stabilizers used.[26]

Advantages

1. This method is superior than other methods.

Disadvantage

1. It is difficult to control formation of larger particles.

Super critical fluid method:

Supercritical fluid technique is gaining popularity these days.This methodemployed CO2 and a solvent to solubilize drug. When the solvent is removed the drug precipitate out as fine particles. In the RESS method drug solution is expanding through a nozzle, while in PCA method the solution is introduced into a chamber which contains compressed CO2. In the SAS process, the solution of drug is introduced into a supercritical fluid with the help of injection, which extracts the solvent and results in precipitation of the drug as fine crystals.[27]

Advantages

1. Fast and convenient method

EVALUATION OF NANOSUSPENSION[28]

Evaluating nano suspensions involves several key aspects to ensure their stability, efficacy, safety, and applicability for intended purposes. Here's an evaluation framework:

Particle Size Analysis:

The size of particle in nanosuspension is the main factor which determines the efficacy and safety of nanosuspensions. The smaller the particle size, the better the dissolution velocity, physical stability, saturation solubility, and physiological performance of the nanosuspension. Nanosuspension with narrow particle size distribution are stable over long time. PCS is the

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most common technique used to measure the mean particle diameter and polydispersity Index (PI) of nanosuspensions, while for the detection of nanoparticulate drugs Laser Diffractometry (LD) is used. For ensuring the safety and efficacy of nanosuspension particle size analysis is important.[29]

Zeta Potential:

Zeta potential measurement is required for the determination of the physical stability of the nanosuspension. The electric charges on the particle surface stop nanoparticles in suspension from aggregating and precipitating because they have charges on them. A diffusion layer of oppositely charged ions and a stern layer make up the electric double layer encircling the particles. Zeta potential is the name given to the electric potential at a shear plane. For electrostatic stabilisation to be successful, the zeta potential must be at least ±30 mV. A zeta potential of at least ±20 mV is adequate when stearic stabilisation is paired with electrostatic stabilisation. The hydrated and adsorbed polymer layers on the dispersed particle inhibit precipitation and aggregation at this zeta potential. In short zeta potential measurement is essential for ensuring the physical stability of nanosuspension during storage.[30]

Physical Stability:

Physical stability is important to increase shelf-life of nano suspensions. Stability studies are performed to assess the physical integrity of nano suspensions over time. This includes monitoring changes in particle size, aggregation, sedimentation, and creaming. Accelerated stability tests under different storage conditions (temperature, pH, light exposure) are conducted to predict shelf-life and storage conditions.[31]

Chemical Stability:

Chemical stability is important for maintaining efficacy of API. Chemical stability evaluates the integrity of active pharmaceutical ingredients (APIs) or other compounds within the nano suspension. Techniques such as high-performance liquid chromatography (HPLC) or spectroscopic methods are used to analyse chemical degradation or changes in composition.[32]

Drug Release Profile:

The evaluation of release kinetics of the active compound from the nano suspension is important. Dissolution studies or in vitro release assays help understand the release profile under different conditions, guiding dosage form optimization and formulation adjustments.

Drug Content:

Spectrophotometric analysis can be used to ascertain the drug content of a nanosuspension. The solidified nanosuspension is filtered, diluted in an appropriate solvent, and examined using a UV spectrophotometer. Magnetic stirring can also be substituted with centrifugation.

pH:

To determine the pH of a nano-suspension, use a pH metre. The pH of the nanosuspension is measured in a 10-milliliter beaker.

Osmolarity:

The osmolarity of a nanosuspension can be determined using an osmometer. This measurement is essential for figuring out how well the nanosuspension functions physiologically.[33]

APPLICATION OF NANOSUSPENSION

Applications of nanosuspension is not only limited to pharma industry but is spread to other industries also. Some of the major applications of nanosuspensions are discussed below-

Oral Drug Delivery:

Shah Ripal Kumar et al 2021 had developed lumefantrine nanosuspension for oral administration. The aim of the study was to enhance the solubility of drug which in tern enhance oral bioavailability resulting in improved antimalarial activity of drug. The polymer used for the preparation of nano suspension was polysorbate 80.[34]

Liu Qiang et al 2020 had prepared Cilnidipine nanosuspension for oral delivery. The aim of the study was to enhance the rate of dissolution and improve the oral bioavailability of the drug. In the preparation of nano suspension wet milling method was employed and PVP VA64 and SLS were used as stabilizer.[35]

Sun Min et al 2010 had prepared Quercetin nanosuspension with the aim to improve the rate of dissolution and enhanced oral bioavailability and for this purpose they employed the high-pressure homogenization method.[36]

Intravenous Drug Delivery:

Wang Yonglu et al 2011 had formulated paclitaxel nanosuspension for intravenous administration of drug. The aim of the study was to

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remove problems associated with the solubility of paclitaxel for this the develop nanosuspension of paclitaxel using high pressure homogenization.[37]

Xiong Ruolan et al 2008 had developed and characterize the nimodipine intravenous injection. High pressure homogenization method was used to prepare nano suspension.[38]

Rabinow Barrett et al 2007 had prepared Itraconazole nano suspension for intravenous administration. Homogenization method was used for preparation of nanosuspension.[39]

Nasal Drug Delivery:

Aref Zaki F et al 2021 had prepared intranasal nanosuspension spray of Ivermectin for COVID-19 treatment. The aim of the study was to analyse the efficacy of ivermectin in patient with mild COVID-19 infection. The result shows that the nanosuspension is effective in treatment of patient with COVID-19.[40]

Brain Targeting:

Bhavna et al 2014 had worked on the development of nanosuspension intended for the brain targeting of drug Donepezile. For the preparation of nanosuspension Ionic-crosslinking method was used. For brain targeting the drug was administered as a nasal spray.[41]

Transdermal Drug Delivery:

Lai Francesco et al 2013 had developed tretinoin nanosuspension for the transdermal delivery. The aim of the study was to improve photostability of tretinoin and its permeation to the skin. Precipitation method was used for the preparation of nanosuspension. Different evaluation parameters like morphological studies, mean size and size distribution were evaluated.[42]

Pulmonary Drug Delivery:

Jacobs Claudia et al 2001 had developed Budesonide nanosuspension for administration by pulmonary route. The aim of the study was to prepare a stable nanosuspension formulation that can be nebulized. For the preparation of nanosuspension high pressure homogenization technique was used.[43]

Mucoadhesive Drug delivery:

Muller R.H. et al 2001 had prepared and optimized Buparvaquone mucoadhesive nanosuspension. The aim of the study was to increase bioavailability of the drug Buparvaquone. The method high pressure homogenization was used for the preparation of nanosuspension.[44]

Ocular Drug delivery:

Das Swarnali et al 2011 had developed a nanosuspension for improved delivery of Amphotericin B to ocular delivery. The aim of the study was to prolong the action time of drug on ocular surface. Polymer used for preparation of nanosuspension was Eudragit RS100.[45]

Kassem M.A. et al 2007 had formulated nanosuspension for ophthalmic delivery of glucocorticoid drug. The aim of the study was to improve water solubility of drug. High-pressure Homogenization technique was used for preparation of nanosuspension.[46]

Anti-cancer activity:

Wang Yancai et al 2011 had prepared mycoepoxydiene nanosuspension for anti-cancer activity. The drug had poor solubility and dissolution profile; the aim of the study was to improve these properties of drug. High pressure homogenization technique was used for preparation of nano suspension.[47]

II. CONCLUSION

Nanosuspensions are a good choice for developing drugs with poor solubility and increasing their bioavailability. This method has various formulations and therapeutic benefits, including easy way of preparing them, limited number of the excipients, faster dissolution rate, saturation solubility; improved adhesion leading to reduced bioavailability requiring less doses and fasted-fed variability; ease in scale up. Such nanosuspension can be manufactured for different routes such as oral, parenteral, ocular, topical or pulmonary administration. The technology is increasingly important due to the rising numbers of molecules with solubility and bioavailability issues every day. Hence nanotechnology may play a vital role in drug discovery programs aimed at enhancing the poorly soluble drugs' aqueous solubility and bioavailability.

Nanosuspensions attracts researchers not just for their ability to enhance solubility and bioavailability but also cause alteration of drug pharmacokinetics thereby making it safer and more effective. In addition, nanosuspension technology can be combined with traditional oral dosage forms such as tablets, capsules and pellets as well as being used for parenteral products. Simple manufacturing techniques and vast application fields will continue to make nanosuspensions still interesting in the future because of improving oral formulation or non-oral routes of administration.

REFERENCE

[1]. Zuccari G, Alfei S. Development of phytochemical delivery systems by nano-suspension and nano-emulsion techniques. International Journal of Molecular Sciences. 2023 Jun 6;24(12):9824

[2]. Chinthaginjala H, Abdul H, Reddy AP, Kodi K, Manchikanti SP, Pasam D. Nanosuspension as Promising and Potential Drug Delivery: A Review. 2020. Int J Life Sci. Pharm Res. 2020;11(1):P59-66

[3]. Sutradhar KB, Khatun S, Luna IP. Increasing possibilities of nanosuspension. Journal of nanotechnology. 2013 Jan 1;2013

[4]. Patel VR, Agrawal YK. Nanosuspension: An approach to enhance solubility of drugs. Journal of advanced pharmaceutical technology & research. 2011 Apr 1;2(2):81-7

[5]. Patel M, Shah A, Patel NM, Patel MR, Patel KR. Nanosuspension: A novel approach for drug delivery system. Jpsbr. 2011 Jul;1(1):1-10

[6]. Arunkumar N, Deecaraman M, Rani C. Nanosuspension technology and its applications in drug delivery. Asian Journal of Pharmaceutics (AJP). 2009;3(3).

[7]. Chingunpituk J. Nanosuspension technology for drug delivery. Walailak Journal of Science and Technology (WJST). 2007;4(2):139-53.

[8]. Thattil JG, Kumar KK, and Kumar BD (2018). Nanosuspension technology in pharmaceuticals. J Bio Innov 7: 660-677.

[9]. Ghosh I, Bose S, Vippagunta R, Harmon F. Nanosuspension for improving the bioavailability of a poorly soluble drug and screening of stabilizing agents to inhibit crystal growth. International journal of pharmaceutics. 2011 May 16;409(1-2):260-8.

[10]. Singare DS, Marella S, Gowthamrajan K, Kulkarni GT, Vooturi R, Rao PS. Optimization of formulation and process variable of nanosuspension: An industrial perspective. International journal of pharmaceutics. 2010 Dec 15;402(1-2):213-20.

[11]. Gao L, Liu G, Wang X, Liu F, Xu Y, Ma J. Preparation of a chemically stable quercetin formulation using nanosuspension technology. International Journal of Pharmaceutics. 2011 Feb 14;404(1-2):231-7.

[12]. Godge GR, Garje MA, Dode AB, Tarkase KN. Nanosuspension Technology for Delivery of Poorly Soluble Drugs and Its Applications: A Review. International Journal of Pharmaceutical Sciences and Nanotechnology (IJPSN). 2020 Jul 11;13(4):4965-78.

[13]. Geetha, G., U. Poojitha, and K. Arshad Ahmed Khan. "Various techniques for preparation of nanosuspension-a review." International Journal of Pharma Research & Review 3.9 (2014): 30-37.

[14]. Agarwal V, Bajpai M., "Preparation and Optimization of Esomeprazole Nanosuspension using Evaporative Precipitation– Ultrasonication", Tropical Journal of Pharmaceutical Research, no (2014):497-503.

[15]. Van Eerdenbrugh B, Van den Mooter G, Augustijns P. Top-down production of drug nanocrystals: nanosuspension stabilization, miniaturization and transformation into solid products. International journal of pharmaceutics. 2008 Nov 19;364(1):64-75.

[16]. Lakshmi P, Kumar GA. Nanosuspension technology: A review. Int J Pharm Pharm Sci. 2010 Aug;2(4):35-40.

[17]. Kayser O, Olbrich C, and Yardley V (2003). Formulation of amphotericin B as nanosuspension for oral administration. Int J Pharm, 254: 73-75

[18]. Nayak BS and Roy H (2018). Nanosuspension: Bioavailability enhancing novel approach. Int J Pharm Biol Sci, 8: 540-554.

[19]. Malakar J, Basu A, and Ghosh A (2012). Nanosuspension: A Nano-Heterogeneous Carrier for Drug Delivery System. Int J Pharm Biol Sci Arch, 3: 4-13

[20]. Gupta MK, Sreedharan SK, Sajeeth CI. Design development and characterization of omeprazole loaded nanosuspension. Journal of Pharmaceutical Negative Results. 2022 Nov 5:1195-208.

[21]. Junyaprasert VB, Morakul B. Nanocrystals for enhancement of oral bioavailability of poorly water soluble drugs. Asian journal of pharmaceutical sciences. 2015 Feb 1;10(1):13-23..

[22]. Kamala Kumari PV and Srinivasa Rao Y. Nanosuspensions: A review. International

journal of pharmacy 2017 Jan 21;7(2):77-89.

[23]. Patel HM, Patel UB, Shah C, and Akbari B (2018). Formulation and Development of Nanosuspension as an Alternative Approach for Solubility and Dissolution Enhancement of Aceclofenac. Int J Adv Pharm 7: 33-47.

[24]. Mathew M, Krishnakumar K, Dineshkumar B, and Nair SK (2017). Antibiotics Nanosuspension: A Review. J Drug Del Ther, 7: 128-131

[25]. Iqubal MK, Hamdard J, and Shukla VK (2014). Review Article on Microemulsions: Current Trends in Novel Drug Delivery System. J Pharm Chem Biol Sci, 1: 39-51.

[26]. Bhakay A, Rahman M, Dave RN, and Bilgili E (2018). Bioavailability Enhancement of Poorly Water-Soluble Drugs via Nanocomposites : Formulation – Processing Aspects and Challenges. Pharmaceutics, 10: 1-62.

[27]. Sunder S, and Nair R (2016). Methods of Nanonization of Drugs for Enhancing their Dissolution. Euro J Adv Engg Tech, 3: 101-110

[28]. Guo JJ, Yue PF, Lv JL, Han J, Fu SS, Jin SX, Jin SY, Yuan HL. Development and in vivo/in vitro evaluation of novel herpetrione nanosuspension. International journal of pharmaceutics. 2013 Jan 30;441(1-2):227-33.

[29]. Li W, Yang Y, Tian Y, Xu X, Chen Y, Mu L, Zhang Y, Fang L. Preparation and in vitro/in vivo evaluation of revaprazan hydrochloride nanosuspension. International journal of pharmaceutics. 2011 Apr 15;408(1-2):157-62.

[30]. Bose S, Sharma P, Mishra V, Patial S, Saraogi GK, Tambuwala MM, Dua K. Comparative in vitro evaluation of glimepiride containing nanosuspension drug delivery system developed by different techniques. Journal of Molecular Structure. 2021 May 5;1231:129927.

[31]. Eltaib L, Mujtaba MA. Stability Testing of Amoxicillin Nano-suspension as Promising Tool for Drug Delivery System. Journal of Pharmaceutical Research International. 2021 Dec 26;33(60B):2481-8.

[32]. Patel VR, Agrawal YK. Nanosuspension: An approach to enhance solubility of drugs. Journal of advanced pharmaceutical technology & research. 2011 Apr 1;2(2):81-7.

[33]. Kayser O, Olbrich C, Yardley V, Kiderlen AF, Croft SL. Formulation of amphotericin B as nanosuspension for oral administration. International journal of pharmaceutics. 2003 Mar 18;254(1):73-5.

[34]. Shah R, Soni T, Shah U, Suhagia BN, Patel MN, Patel T, Gabr GA, Gorain B, Kesharwani P. Formulation development and characterization of lumefantrine nanosuspension for enhanced antimalarial activity. Journal of Biomaterials Science, Polymer Edition. 2021 May 3;32(7):833-57.

[35]. Liu Q, Mai Y, Gu X, Zhao Y, Di X, Ma X, Yang J. A wet-milling method for the preparation of cilnidipine nanosuspension with enhanced dissolution and oral bioavailability. Journal of Drug Delivery Science and Technology. 2020 Feb 1;55:101371..

[36]. Sun M, Gao Y, Pei Y, Guo C, Li H, Cao F, Yu A, Zhai G. Development of nanosuspension formulation for oral delivery of quercetin. Journal of biomedical nanotechnology. 2010 Aug 1;6(4):325-32

[37]. Wang Y, Li X, Wang L, Xu Y, Cheng X, Wei P. Formulation and pharmacokinetic evaluation of a paclitaxel nanosuspension for intravenous delivery. International journal of nanomedicine. 2011 Jul 13:1497-507.

[38]. Xiong R, Lu W, Li J, Wang P, Xu R, Chen T. Preparation and characterization of intravenously injectable nimodipine nanosuspension. International Journal of Pharmaceutics. 2008 Feb 28;350(1-2):338-43

[39]. Rabinow B, Kipp J, Papadopoulos P, Wong J, Glosson J, Gass J, Sun CS, Wielgos T, White R, Cook C, Barker K. Itraconazole IV nanosuspension enhances efficacy through altered pharmacokinetics in the rat. International journal of pharmaceutics. 2007 Jul 18;339(1-2):251-60.

[40]. Aref ZF, Bazeed SE, Hassan MH, Hassan AS, Rashad A, Hassan RG, Abdelmaksoud AA. Clinical, biochemical and molecular evaluations of ivermectin mucoadhesive nanosuspension nasal spray in reducing upper respiratory symptoms of mild

COVID-19. International journal of nanomedicine. 2021 Jun 15:4063-72.

[41]. Md S, Ali M, Ali R, Bhatnagar A, Baboota S, Ali J. Donepezil nanosuspension intended for nose to brain targeting: in vitro and in vivo safety evaluation. International journal of biological macromolecules. 2014 Jun 1;67:418-25.

[42]. Lai F, Pireddu R, Corrias F, Fadda AM, Valenti D, Pini E, Sinico C. Nanosuspension improves tretinoin photostability and delivery to the skin. International journal of pharmaceutics. 2013 Dec 15;458(1):104-9.

[43]. Jacobs C, Müller RH. Production and characterization of a budesonide nanosuspension for pulmonary administration. Pharmaceutical research. 2002 Feb;19:189-94

[44]. Müller RH, Jacobs C. Buparvaquone mucoadhesive nanosuspension: preparation, optimisation and long-term stability. International journal of pharmaceutics. 2002 Apr 26;237(1-2):151-61.

[45]. Das S, Suresh PK. Nanosuspension: a new vehicle for the improvement of the delivery of drugs to the ocular surface. Application to amphotericin B. Nanomedicine: Nanotechnology, Biology and Medicine. 2011 Apr 1;7(2):242-7.

[46]. Kassem MA, Rahman AA, Ghorab MM, Ahmed MB, Khalil RM. Nanosuspension as an ophthalmic delivery system for certain glucocorticoid drugs. International journal of pharmaceutics. 2007 Aug 1;340(1-2):126-33

[47]. Wang Y, Liu Z, Zhang D, Gao X, Zhang X, Duan C, Jia L, Feng F, Huang Y, Shen Y, Zhang Q. Development and in vitro evaluation of deacetymycoepoxydiene nanosuspension. Colloids and surfaces B: biointerfaces. 2011 Apr 1;83(2):189-97.

[48]. Ali HS, York P, Blagden N. Preparation of hydrocortisone nanosuspension through a bottom-up nanoprecipitation technique using microfluidic reactors. International journal of pharmaceutics. 2009 Jun 22;375(1-2):107-13.

[49]. Diefenthaelera SH, Bianchinb MD, Marquesc MS, Nonnenmacherd JL, Benderd ET, Benderd JG, Neryd SF, Cichotad LC, Külkamp-Guerreiro I., **"**Omeprazole nanoparticles suspension: Development of a stable liquid formulation with a view to paediatric administration", International Journal of Pharmaceutics, no (2020):589-599

[50]. Carvalho DD, Takeuchi KP, Geraldine RM, Moura CJ, Torres MC. Production, solubility and antioxidant activity of curcumin nanosuspension. Food Science and Technology. 2015 Jan;35:115-9.

[51]. Dubey R. Impact of nanosuspension technology on drug discovery and development. Name: Drug Deliv Technol. 2006;6(6).

[52]. Liu X, Fan H, Meng Z, Wu Z, Gu R, Zhu X, Gan H, Dou G. Combined silver sulfadiazine nanosuspension with thermosensitive hydrogel: an effective antibacterial treatment for wound healing in an animal model. International Journal of Nanomedicine. 2023 Dec 31:679-91.

[53]. Lee MK, Kim MY, Kim S, Lee J. Cryoprotectants for freeze drying of drug nano-suspensions: effect of freezing rate. Journal of pharmaceutical sciences. 2009 Dec 1;98(12):4808-17.

[54]. Mathew M, Krishnakumar K, Dineshkumar B, and Nair SK (2017). Antibiotics Nanosuspension: A Review. J Drug Del Ther, 7: 128-131

[55]. Bhakay A, Rahman M, Dave RN, and Bilgili E (2018). Bioavailability Enhancement of Poorly Water-Soluble Drugs via Nanocomposites : Formulation – Processing Aspects and Challenges. Pharmaceutics, 10: 1-62.

[56]. Malakar J, Basu A, and Ghosh A (2012). Nanosuspension: A Nano-Heterogeneous Carrier for Drug Delivery System. Int J Pharm Biol Sci Arch, 3: 4-13.