



Nanosuspension Technology: Method and Characterisation and Techniques for Improving Stability of Nanosuspension in Drug Delivery.

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ABSTRACT :

Solubility proves to be major obstacle for the prosperous and commercialization of new drug. Nano-drug delivery system have the potential to address the challenges of delivery of drug of BCS class 2nd and 4th. Nanosuspension is growing approach for pharmaceutical product development due to unique properties applied in pharmacy. Nanosuspension have a promising approach for the systematic delivery of hydrophobic drugs because of their adaptable features and unique advantages. This review was concerned to the techniques and approach for improving nanosuspension stability in drug delivery system to recaptured the state-of-the-art nanosuspension. The main aim of the present review on nanosuspension include the approach for preparation method and guidelines for selection and optimizing stabilizers, the stability enhancement approach and other factor that influence the stability of prepared nanosuspension. For drug their was set of properties this review promote as a reference in making an educated choice of stabilizers and improving stability of nanosuspension rather than trial-and-error approach practice currently.

KEYWORD: Nanosuspension, Stability, Solubility enhancement, Surfactant

INTRODUCTION:

Pharmaceutical industries are constantly seeking new approaches in order to obtain an adequate oral bioavailability, as most of biological properties exhibiting NCEs are poorly water - soluble. The increasing frequency of poorly water soluble NCEs exhibiting therapeutic activity is of major concern to the development of new formulations in pharmaceutical industry which leads to low turnout in the development of new molecular entities as drug formulations is poor solubility and poor permeability of the lead compounds.[6] Now, more than 40% drug candidates in development and about 60% of directly synthesized drugs are poorly water soluble.[1] Low aqueous solubility is one of the major challenges during the formulation of new chemical object and generics[2] Pharmaceutical industries are constantly seeking new approaches in order to obtain an adequate oral bioavailability, as most of biological properties exhibiting NCEs are poorly water - soluble.[3] . The problem is more severe for drugs belonging to BCS class II, such as Itraconazole and carbamazepine as they are poorly soluble in both aqueous and organic media[4] There are many conventional methods for increasing the solubility of poorly soluble drugs, which include micronization, solubilisation using co-solvents, salt form, surfactant dispersions, precipitation technique, and oily solution.[5] Big thing happened in the last few years. Interested in developing new drug delivery systems using particle delivery system such as nanoparticles. Nanoparticles are a promising system for controlled drug delivery targeted released. The next development step is conversion of micronized drugs into drugs nanoparticles and nanosuspensions. Nanoparticle drug delivery system is has many advantages compared to traditional administration forms are reduced including improved toxicity ,biodistribution, and patient confidence. Nanosuspension technology provide a new solution to these difficult solubility problems of drugs. Nanosuspension consist of pure,poorly water-soluble drugs with or without a matrix. Material suspended during dispersion they can contains no surfactants, contains surfactants, stabilizers or both. One of the important issues related to poorly soluble drugs have insufficient bioavailability or irregular absorption. These techniques have been shown to improve solubility can be used to a limited extent due to some restrictions improved solubility. Thus nanosuspension solve the problems of these traditional approaches to solubility and improved bioavailability.[8]

DEFINATION:

A pharmaceutical nanosuspension is defined as "very finely dispersed solid drug particles in an aqueous vehicle, stabilized by surfactants, for either oral and topical use or parenteral and pulmonary administration, with reduced particle size, leading to an increased dissolution rate and therefore improved bioavailability"[6] The particle size distribution of the solid particles in nanosuspensions is usually less than one micron with an average particle size ranging between 200 and 600 nm. Nanosuspensions differ from nanoparticles and solid lipid nanoparticles. Nanoparticles are commonly polymeric

colloidal carriers of drugs whereas solid lipid nanoparticles are lipid carriers of drugs. Nano is a Greek word, which means 'dwarf'. Nano means it is the factor of 10⁻⁹ or one billionth. Some comparisons of nanoscale are given below,

0.1 nm = Diameter of one Hydrogen atom

2.5 nm = Width of a DNA molecule 1 micron = 1000 nm.

1 nm = 10⁻⁹m = 10⁻⁷ cm = 10⁻⁶ mm.

Micron = 10⁻⁶m = 10⁻⁴ cm = 10⁻³mm.[7]

ADVANTAGES OF NANOSUSPENSIONS:

1. Drugs with high p values are formulated as an increasing nanosuspension bioavailability of such drugs .
2. Improving biological performance due to high resolution speed , color saturation and batch variations.
3. Long -term physical stability (cause:Ostwald's lack of maturity)
4. Nanosuspensions can be incorporate into Tablets, Pellets, Hydrogels, Suppositories suitable for various routes management.
5. Increased internal amorphous content ,particles bring the possibility of change more than crystal structure solubility.
6. It can be specified with any route and reduced tissue inflammation.
7. Rapid lysis and tissue targeting capabilities can be achieve by intravenous administration.
8. Oral administration of nanosuspension ensures rapid onset of action and reduced fed/fasted doses also improve ratio and bioavailability.
9. Absorption through the absorption window this allows the dosage to be increased particle size reduction.
10. Higher bioavailability and more stable eye drop dosage can formed also enhance the inhalation delivery.[6]

LIMITATION OF NANOSUSPATION:

In addition to numerous advantages, nanosuspensions can become physically unstable during storage due to the increased sedimentation rate of dispersed nanoparticles. Although this can be a major problem in nanosuspensions, this problem can be overcome by using appropriate polymers. Pharmaceutical nanosuspension are bulky and can be subject to abrasion during handling and transportation. Therefore, great care must be taken when handling and transporting it.[10]

CRITERIA FOR SELECTION OF NANOSUSPENSION:

Nanosuspension can be prepared according to existing APIs one of following characteristics .Although insoluble in water ,soluble in oil (high log P) or API insoluble both water-based and oil-based drugs are on the decline. Resolves crystals very well regardless of solvent API with large doses.[11]

FORMULATION OF NANOSUSPENSION:

Nanosuspension formulation requires basically stabilizers ,co-surfactants ,solvents and other additives ingredients for preparation.

1. STABILIZERS

Stabilizers play an important role .This is part of the nanosuspension method. If one is missing adequate stabilizers, excessive soil strength nanoparticles can cause agglomeration or accumulation of chemical crystals. In general ,the main characteristic of stabilizers is that

are very wet. To safely remove and prevent drug particles Ostwald ripening and nanoparticles aggregation suspension for a stable body formulation using steric or ionic input barrier.[12] The type and amount of stabilizer has a noticeable effect physical stability and effects on in vivo behavior nanosuspension. Sometimes a mixture of stabilizers required to obtain a stable nanosuspension.[11] The ratio of drug to stabilizer is considered on a case -by-case basis. The mostly used stabilizers are polysorbate ,povidone ,cellulosics, poloxomers and lecithin.[12]

2. ORGANIC SOLVENTS

Organic solvents are often used in part preparations of nanosuspension emulsion or microemulsion technology was used in model making part .This solvents is very dangerous from a physiological and environmental means still, dangerous water will be slightly reduced miscible solvents such as methanol, ethanol, chloroform, isopropanol and partially water miscible solvent ethyl acetate, ethyl formate, butyl lactate, triacetin, propylene

carbonate, benzyl alcohol, used than dichloromethane which reported as hazardous solvent.[7] Solvent such as ethylene glycol can be used as internal solvents microemulsion as template. Accepted organic solvents in medicine should be removed from the model to consider when formulating nanosuspensions use of emulsion or microemulsion as samples (Table 1).

3. SURFACTANT

Selection of surfactant are important when nanosuspension are prepared using microemulsion as template. Surfactant are added to improve this dispersion due to decrease in interfacial tension. It also acts as a wetting agent or anti agglomerating agent. Example : Tween and Span –widely used surfactants.[6]

4. CO-SURFACTANT

Common interests surfactants are very important when using microemulsions preparation of nanosuspensions. Due to co-surfactants section may affect certain behaviours and interventions helps absorb microemulsion ingredients chemicals installations should be checked. Example: Transcutol, Glycerin, Ethanol and Isopropyl alcohol bile salt and Dipotassium giycyrrhizinate can be used as co-surfactant.[12]

5. MISCELLANEOUS

Water soluble polymers such as polyvinyl alcohol (PVA), polyvinylpyrrolidone and PEGylated chitosan are used as stabilizers. Bilizer has been found to significantly improve resolution speed and bioavailability of nanosuspensions. Functionalized surface coating of poorly soluble drug beclomethasone propionate was performed using hydrophobin, a protein surfactant based. Adaptability to surface modification genetic engineering makes it suitable for various pharmaceutical applications.[14] Soluplus is a new type of excipient which is made from polyvinylcaprolactam-polyvinyl acetate-PEG copolymer developed by BASF industries. Used accordingly stabilizer provides good stability in many nanosuspension. It also increased stability, improved dissolution rate and bioavailability.[13]

6. OTHER ADDITIVES

Use of other ingredients depends on the situation, route of administration or physiochemical properties of drug. This includes not only pharmaceutical but also additives such as buffers, salts, polyols, osmotic agents and a cryoprotectant is usually used. [7]

CHARACTERIZATION TECHNIQUES:

The characteristics of nanosuspension are as follows: Appearance, color, content, accompanying impurities, particle size, zeta potential, crystallinity morphological status, dissolution studies and in vivo studies. Below are the main points characterization method are discussed.

1. Zeta potential (Surface charge)

Zeta potential gives specific information about the surface charge properties and long term physical stability of nanosuspension. Zeta potential of nanosuspension is stabilizer and the drug itself. It can provide relevant information surface load characteristics and long term physical stability of nanosuspension. To achieve stable suspension, electrostatic repulsion, minimum zeta potential of +/-30 mV is required. But when electrostatics and 3 are combined the stabilizer generates a zeta potential of +/-20mV is enough.[15]

2. Mean particle size and size distribution

Many parameters of nanosuspensions like saturation solubility, dissolution rate, physical stability, biological performance depends on mean particle size and particle size distribution.

Mean particle size and particle width can be decided through Photon correlation spectroscopy, laser diffraction and colter current multi-sizer. Polydispersity index must be low to maintain long-term stability nanosuspension. Polydispersity index value of 0.1 to 0.25 is narrow size distribution. Polydispersity index value greater than 0.5 indicates a very large size distribution. Photon correlation spectroscopy (PCS) determines particle size in the following ranges (3 nm to 3 micro) this probability become difficult to judge. Contamination of nanosuspension with particulate drug (Particle size of 3 micron or more) therefore in addition to PCS, nanosuspension analysis, laser diffraction (LD) performed for both drug detection and quantification particulates that may have been generated during the process. LD determines the particle size in the following ranges 0.05-80 micron to 2000micron. Determination of 50%LD and 99% diameters value indicating that 50% or 99% of particles are affected smaller than the specified size. When used by parenteral the particle size should be the same considering that capillaries are small, less than 5 micron so larger particle sizes can cause capillary occlusion and embolism. For nanosuspension that are intended for IV administration, particle size analysis by counter technique is essential in addition to PCS and LD analysis. Since the coulter counter gives the absolute number of particles per volume unit for the different size groups.[16]

PREPARATION OF NANOSUSPENSION:

There are many methods of nanosuspensions preparation, dosage forms, components and drug delivery system are given in following chart

There are two main ways to prepare nanosuspension. Conventional precipitation method (Hydrosol) is called "bottom-up technology". Below technique dissolve the drug in a solvent and then is added to these non-solvent to precipitate crystals.[11]

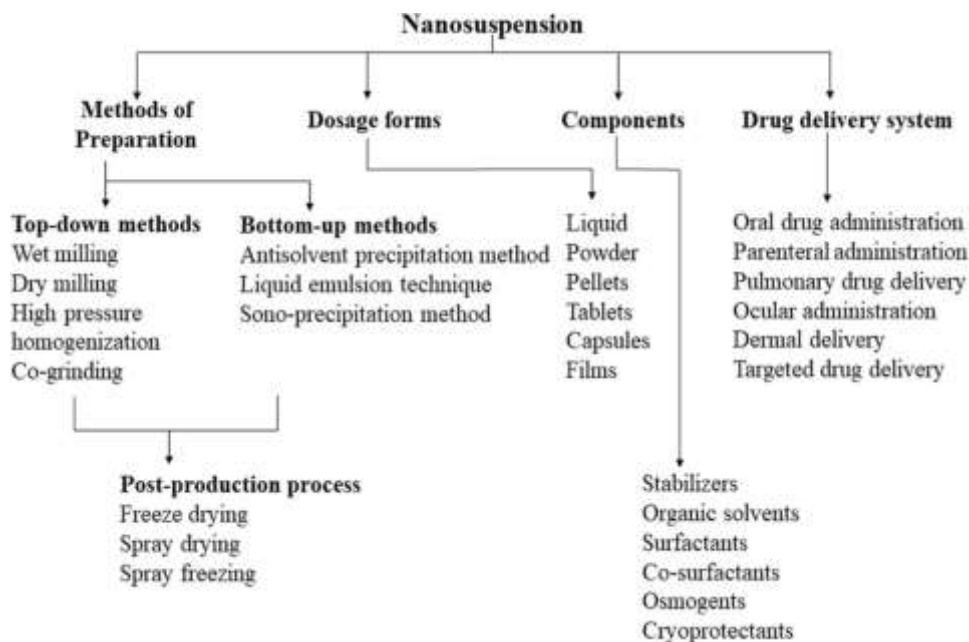


Figure1: Schematic representation of method of preparation of nanosuspension.

Homogenization in water –Disso cubes.

Homozinization in non aqueous media- Nanopure.

Nanojet Technology

Combined precipitation and homogenization -nanoedge

Emulsification solvent evaporation technique

Hydrosol method

Supercritical fluid method

Dry-co-grinding

Emulsion as template – lipid emulsion

Microemulsion as template

Nanocrystal/nanosystem (media milling)

Wet milling

Ultra assisted sonocrystallization method

Miscellaneous method

1. Homogenization in water -disso cubes

Homogenization in water -disso cubes technology is developed by R.H.Muller uses high piston clearance type pressure homogenizer in 1999. In this method, the suspension contains the drug and the surfactant is forced under pressure through a valve with a nanometer opening high pressure homogenizer. [6]

Principle

In the piston gap homogenizer, particle size is reduced based on the cavitation principle. Piston clearance Homogenizers such as APV Gaulin type were obtained clock. Particles are also reduced due to high levels shear force and particle collision This is against that. Dispersion contained within The cylinder has a diameter of 3 cm; suddenly come across one very narrow space of 25 μm . Reducing diameter from 3 cm to 25 μm leads to increase dynamic pressure and static pressure drop below the boiling temperature of room water temperature. For this reason, the water begins to boil ambient temperature and form air bubbles explodes when the suspension leaves the space (called cavitation) and normal atmospheric pressure is obtain. Size of drug nanocrystals can be achieved mainly depends on factors such as temperature, number of homogenization cycles, and the energy density of the homogenizer and uniform pressure. 2 Disso blocks technology is an example of this technology Developed by R.H. Muller in 1999, for example: Omeprazole.[17]

Advantages :

1. It does not cause erosion of processed products materials.
2. It applies to drugs that are poorly soluble in water and organic media.[7]

Limitations:

- 1.Pretreatment such as microdosing of drugs obligatory.
- 2.Need expensive tools to increases the cost of the dosage form.

1.Homozinization in non aqueous media – Nanopure

Nanopure is a homogeneous suspension in water free medium or water mixture, i.e. drug suspension in a non-aqueous medium is homogenous at 0°C or even below freezing point and is therefore called "frozen"; uniformity. The results obtained are comparable to DissoCubes and can therefore be used effective on heat labile substances at milder temperatures condition.Dispersed drug nanocrystals in polyethylene glycol (PEG) liquid or various types The oil can be administered directly as a medicinal suspension HPMC or gelatin capsules.[5]

3.Nanojet Technology

Nanojet technology is also known as reverse flow technology. In this technique suspension flows into two or more divided parts transmitted with high pressure is converted into colloid with each others,due to the high shear forces generated during the process leading to a reduction in particle size.[16]

4.Combined precipitation and homozinization - nanoedge

Nanoedge technology is a combination of both precipitation and homogenization. The basic principle is the same as that of precipitate and homogenize. [18]One Combining these techniques gives smallerresultsbetter particle size and stability in a shorter time. The maindisadvantageof precipitation techniques, such as crystal growth and longevity stability,nullcan be solved using Nanoedge technology.[19]

5. Emulsification solvent evaporation technique

This technique involves preparing a solution the drug is then emulsified in another form.The liquid is not a solvent for the medicine. Solvent evaporation leads to precipitation of medicine. Growth of crystals and particles synthesis can be controlled by creating high level shear force by high speed stirrer.[6]

6.Melt emulsification method

In this method, the drug is dispersed in an aqueous solution of the stabilizer and heated above the melting point of the drug and homogenized for an emulsion. During this process, the sample holder wrapped with heat tape equipped with a temperature controller and the emulsion temperature is maintained on the substrate point of medication. The emulsion is then cooled slowly at room temperature or in an ice bath.Main benefits of merger Emulsification technique compared to solvent diffusion method is Completely avoid organic solvents during production. Ibuprofen nanosuspension is prepared by this method46.Construction of ibuprofen nanosuspension by fusion emulsification method. This method shows a higher dissolution rate than the solvent formulation.[16]

7. Lipid emulsion/microemulsion template

This method mainly applies to drugs Soluble in volatile organic substances solvent or partially miscible with water solvent. According to this method, the medicine is Soluble in suitable organic solvents and It is then emulsified in the aqueous phase by use suitable surfactant. Then organic solvent is evaporated slowly Reduce the pressure to form drug particles precipitates in the resulting aqueous phase Aqueous suspension of clear drug required particle size.[7]

8.dry cogrinding

For many years, nanosuspensions have been prepared by a wet milling process using a granular ball mill. Nowadays, nanosuspensions can be prepared by dry milling. Stable nanosuspensionswereprepared by dry grinding of a poorly soluble drug with soluble polymers and copolymers after dispersion in a liquid medium.Itohetal.described the formation of colloidal particles of many poorly water-soluble drugs such as nifedipine, griseofulvin, and glibenclamide with sodium dodecyl sulfate and polyvinylpyrrolidone as stabilizers.[20-22]

9. Supercritical fluid method

Different methods such as rapid supercritical solution expansion (RESS) process, supercritical antisolvent process and compressed antisolvent precipitation (PCA) process are used to produce nanoparticles. In the RESS technique, the drug solution is spread through a nozzle into the supercritical fluid, resulting in precipitation of the drug as fine particles due to the loss of solvent capacity of the supercritical fluid. Using the RESS method, Young et al. The prepared cyclosporine nanoparticles have a diameter of 400-700 nm. In the PCA method, the drug solution is atomized in a compressed CO₂ chamber. When the solvent is removed, the solution becomes saturated and precipitation eventually occurs. In the supercritical antisolvent process, the drug solution is injected into the supercritical fluid and the solvent is extracted and the drug solution becomes supersaturated. [23]

Formulation components

Excipients are most frequently used in nanosuspensions are stabilizers, polymers, surfactants, penetrants or - Organic solvents, cryoprotectants, buffering agents, complexing agents, buffering agents, buffering agents, sensory agents and preservatives.

Stabilizers

Stabilizer It has been reported in the literature that API carrying high log P and high enthalpy values are abundant feasibility of developing stable nanosuspensions by Stable both spatially and electrostatically. Further, Physical properties such as molecular weight are absent demonstrated that it has a direct effect on the grain pruning or stabilization phase. Measured zeta potential (ζ) at the shear plane determines the level of thrust between neighboring particles of similar charge in the system. [24]

Characteristics technologies for nanosuspension

These techniques are useful for comparing effectiveness between formulations and for developing an optimized product. Since each technique has its own strengths and limitations, choosing appropriate characterization methods is a confusing issue for researchers and technologists. To overcome these challenges, some reliable techniques with sufficient reproducibility are needed. This review article describes various evaluation techniques that can be used effectively to produce products of optimal quality.

1. Energy Dispersive X-Ray Spectroscopy (EDX)
2. Particle Size Analyzer
3. Scanning Electron Microscopy (SEM)
4. transmission electron microscope (tem)
5. X-Ray Diffraction (XRD)
6. Thermogravimetric Analysis (TGA)
7. Ultraviolet (UV) Spectroscopy
8. Zeta Potential
9. Dynamic Light Scattering (DLS)
10. Atomic Force Microscopy (AFM)
11. Fourier Transform Infrared Spectroscopy (FTIR)

PROBLEMS IN MANUFACTURING AND SCALABILITY OF NANOSUSPENSION

Besides the many advantages of nanosuspensions, nanosuspensions also have some disadvantages, such as manufacturing complexity, stability issues, and nanotoxicity. Stability is an important aspect of product safety and effectiveness. Particle agglomeration can be a serious problem during intrapulmonary injection of drugs because it affects the effectiveness of the drug. Similarly, if the pharmaceutical nanosuspension has a particle size greater than 5 μm , it can impede blood flow due to capillary blockage. Therefore, under storage conditions, particle size should be carefully monitored. Stability issues sometimes arise during nanosuspension fabrication because high pressure and temperature can induce changes in the crystal structure of the drug particles. The various common stability problems associated with nanosuspension are particle sedimentation, crystal formation and change in crystalline state, agglomeration and agglomeration. [9]

The problem associated with nanosuspensions is the change in crystalline state of the active pharmaceutical ingredient (API). This problem affects the solubility, stability and efficacy of the drug. This problem is related to amorphous drug formation or API conversion caused by high shear forces. Different top-down nanosuspension production methods involve grinding of materials, etc. applies high shear forces to the formulation, while some bottom-up methods can also convert drug particles to an amorphous state. Various technologies can be used to determine the state of the API, such as solid-state nuclear magnetic resonance, infrared (IR) spectrometer, X-ray diffraction, differential scanning calorimetry. [25]

These issues directly or indirectly affect the manufacturing process and scalability of nanosuspensions. These issues can be controlled by controlling various factors that influence formulation development and scalability, such as process factors and formulation factors.

CURRENT AND FUTURE DEVELOPMENT

In recent years, the nanosuspension method has been used in an additional way to solve problems arising from poor drug solubility. Nanosuspensions with improved solubility or redispersibility in aqueous media have attracted the attention of formulators due to their unique properties. Choosing a stabilizer is very complicated and difficult because it requires too much time and effort. Indeed, in the pharmaceutical field, well-stabilized nanosuspensions without any stabilizers are fashionable. Therefore, nanosuspensions are more compatible with the human body and also reduce complications associated with the use of stabilizers. To do this, some scientists are studying the concept of self-stabilization. However, this field is quite difficult and has many complexities. Therefore, considerable research is required to develop nanosuspensions without stabilizers. By focusing on nanosuspension technology, human society will benefit from improved simplicity, profitability, solubility and solubility.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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