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NANOSUSPENSION: AN PROMISING APPROACH TO ENHANCE SOLUBILITY OF POORLY SOLUBLE DRUGS

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ABSTRACT

Solubility is a vital factor for developing drug delivery systems for poorly water soluble drugs. One of the major problems associated with poorly soluble drugs is very low bioavailability. The problem is even more complex for drugs like itraconazole, simvastatin and carbamazepine which are poorly soluble in aqueous and non aqueous media, belonging to BCS class II as classified by the biopharmaceutical classification system. Recently, nanoscale systems have received much interest as a way to resolve solubility issues because of their cost effectiveness and technical simplicity compared to liposomes and other colloidal drug carriers. Nanosuspensions have proven to be a better alternatives over other approaches currently available for improving bioavailability of number of drugs with low bioavailability. Formulation as nanosuspension is an attractive and promising alternatives to solve these problems. this review describes the preparation methods, formulation aspect, characterization, and applications of the nanosuspensions.

KEYWORDS: Nanosuspension, Solubility, Bioavailability, Saturation solubility, Dissolution.

INTRODUCTION[1,2,3,4,5]

A nanosuspension is a submicron colloidal dispersion of nanosized drug particles which are stabilized by surfactants and polymers. A pharmaceutical nanosuspension is defined as very finely, biphasic, dispersed solid drug particles in an aqueous vehicle. The particle size

distribution of the solid particles in nanosuspension is usually less than 1µm with an average particle size ranging between 200-600 nm. A nanosuspension not only solve the problems of poor solubility and bioavailability but also alters the pharmacokinetics of drugs and that improves safety and efficacy. Reduction of particle size leads to an increase surface area and consequently in the rate of dissolution as described by the Nernst-Brunner & Levich modification of the Noyes- Whitney equation. Nanosized particles can increase solution velocity and saturation solubility because of the vapor pressure effect. In addition, the diffusional distance on the surface of drug nanoparticles is decreased, thus leading to an increased concentration gradient. The increases in surface area and concentration gradient lead to a much more pronounced increase in the dissolution velocity as compared to a micronized product. In nanosuspension technology, the drug is maintained in the required crystalline state with reduced particle size, leading to an increased in dissolution rate and therefore improved bioavailability.

Nanosuspensions differs from the nanoparticles. Nanoparticles are commonly polymeric colloidal carrier of drugs whereas solid lipid nanoparticles are lipidic carriers of drugs. The stability of the particles obtained in the nanosuspension is attributed to their uniform particle size which is created by various manufacturing processes. The absence of particles with large differences in their size in nanosuspensions prevents the existence of different saturation solubilities and concentration gradients, consequently preventing the Ostwald ripening effect. Ostwald ripening is responsible for crystal growth and subsequently formation of microparticles. It is caused by a difference in dissolution pressure/saturation solubility between small and large particles. Molecules diffuse from the higher concentration area around small particles which have higher saturation solubility to an area around larger particles possessing a lower drug concentration. This leads to the formation of a supersaturated solution around the large particles and consequently to drug crystallization and growth of the large particles. Nanosuspensions can successfully formulate the brick dust molecules for improved dissolution and good absorption.

NEED OF NANOSUSPENSION[6,7]

More than 40% of drugs are poorly soluble in water, so they show problems in formulating them in conventional dosage forms. Also, for class II drugs which are poorly soluble in aqueous and organic media, the problem is more complex. Preparing nanosuspension is preferred for such compounds that are insoluble in water (but are soluble in oil) with high log

P value. Various approaches to resolve problems of low solubility and low bioavailability. In these cases, nanosuspensions are preferred. In case of drugs that are insoluble in both water and in inorganic media instead of using lipidic systems, nanosuspensions are used as a formulation approach. It is most suitable for the compounds with high log P value, high melting point, and high dose. Nanosuspensions can be used to enhance the solubility of drugs that are poorly soluble in aqueous as well as lipid media. As per Noyes–Whitney equation, drugs with smaller particle size have enlarged surface areas which lead to increase dissolution velocity and faster dissolution rate together with the resulting higher concentration gradient between gastrointestinal lumen and systemic circulation thus increasing the oral bioavailability of drugs.

Table 1: Potential Benefits of Nanosuspension.[8,16,17]

Route of Administration	Potential Benefits
Oral	- Rapid dissolution and higher bioavailability - Reduced fed / fasted ratio
Intravenous (IV)	- Tissue targeting - Rapid dissolution - Longer duration of retention in systemic circulation
Ocular	- Higher bioavailability - Less irritation - More consistent dosing
Inhalation	- Higher bioavailability - More consistent dosing
Subcutaneous / Intramuscular	- Higher bioavailability - Rapid onset - Reduced tissue irritation

SELECTION CRITERIA OF DRUG FOR NANOSUSPENSION[9,10]

Nanosuspension can be prepared for the API that is having either of following characteristics:

- Water insoluble but which are soluble in oil (high log P) or API are insoluble in both water and oils
- drugs with a reduced tendency of the crystals to dissolve ,regardless of the solvent
- API with a very large dose

PROPERTIES OF NANOSUSPENSION[7,9,11]

1. Physical long term stability: Nanosuspensions is a highly dispersed systems; therefore physical instability due to Ostwald ripening would be expected according to the Ostwald Freundlich equation, the saturation solubility increases with decreasing particle size. Ostwald ripening is caused by the differences in dissolution pressure/saturation solubility between

small and large particles. Molecules diffuse from the higher concentrated area around small particles (higher saturation solubility) to areas around larger particles possessing a lower drug concentration. This leads to the formation of a supersaturated solution around the large particles and consequently to drug crystallization and growth of the large particles. The diffusion process of the drug from the small particles to the large particles leaves an area around the small particles that is not saturated any more, consequently leading to dissolution of the drug from the small particles and finally completes disappearance of the small particles.

2. Internal structure of nanosuspension: The high energy input during the disintegration process causes structural changes inside the drug particles. When the drug Particles are exposed to high pressure homogenization, the particles are transformed from crystalline state to amorphous state. The change in the state depends upon the hardness of drug, number of homogenization cycles chemical nature of drug and power density applied by homogenizer.

3. Adhesiveness: As the particle size decreases the adhesive properties of the particles will be improved and thus improved oral delivery of poorly soluble drug. There is a distinct increase in adhesiveness of ultra-fine powders compared to coarse powders. A drastically remarkable report is that of the increase in bioavailability for danazol from 5 % (as macrosuspension) to 82% (as nanosuspension).

4. Increased in Saturation solubility and dissolution velocity of drug: Dissolution of the drug is increased due to an increased surface area of the drug particles from micrometers to the nanometer size. According to Noyes-Whitney equation dissolution velocity increases due to increase in the surface area from micron size to particles of nanometer size.

$dx/dt = [(D \times A)/ h] [Cs-X/V]$

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

5. Crystalline state and morphology: A potential change in the crystalline structure of nanosuspensions saying increasing the amorphous fraction in the particle or even creating completely amorphous particles is a characteristic of consideration. The application of high pressures during the production of nanosuspensions was found to promote the amorphous state.

TECHNIQUES OF PREPARATION OF NANOSUSPENSIONS[9,10,12,13,14,15]

In current scenario, Bottom-up technology and Top-down technology are two approaches are used for preparation of nanosuspensions.

A) Bottom up technology

As the name suggests, this approach starts from the bottom i.e start from molecular level and lastly goes to molecular association for the formulation of small solid particles. This means it is novel precipitation technique in which the solvent quantity should be reduced.

1. Nanoprecipitation technique (Antisolvent method)

The most common method of precipitation used in anti-solvent addition method in which drug is dissolved in suitable organic solvent and this solution mixed with a miscible anti-solvent. Rapid addition of drug solution in to the anti-solvent leads to the sudden supersaturation of drug in the mixed solution forms ultrafine drug solids. Precipitation method involves two phases-nuclei formation & crystal growth. When preparing a stable suspension with the minimum particle size, a high nucleation rate and but low growth rate is necessary. Both rates are depending on temperature. In this technique the drug needs to be soluble in at least one solvent which is miscible with non-solvent.

B) Top down technology

Top down technology is the disintegration method. The top down technologies include media milling, high pressure homogenization, emulsion diffusion method, supercritical fluid method and this are preferred over the precipitation method.

1. Media milling techniques

The method is first developed by Liversidge et al. Nanosuspensions is produced by high shear media mills or pearl mills. It consist of milling chamber, recirculation chamber and milling shaft. Milling media consist of balls or pearls which are made up of ceramic sintered aluminium oxide and zirconium oxide with high abrasion resistance. The milling chamber charged with milling media, water, drug and stabilizer. Balls rotated at high shear rate under controlled temperature the balls have an impact on the sample. Due to the both forces of fraction and impact particle size reduction occurs and nanosized particles will obtained. A nanosuspension of naproxen with a mean particle size of 300-600 nm was prepared using pearl milling technique.

2. High pressure homogenization

It is used for preparing poorly water soluble drugs. Homogenization involves the forcing of the suspension under pressure through the valve having a narrow aperture. In this method ,the surfactant and drug is focussed under pressure and its through nanosized aperture value of high pressure homogenization. Principal is based on cavitations in aqueous phase. The particle cavitations force is sufficiently high to convert the drug microparticles into nanoparticles. The concern with this method is needed to small sample particle before loading and fact that many cycles of homogenization required. The instrument can be operated at pressures varying from 100-1500 bars. In some instruments, a maximum pressure of 2000 bars can be reached. High pressure homogenizers are available with different capacities ranging from 40 ml (for laboratory purposes) to a few thousand litres (for large scale productions). Before subjecting the drug to the homogenization process, it is essential to form a presuspension of micronized drug in a surfactant solution using high speed stirrers.

2.1 Types of pressure homogenization

2.1.1 Nanopure (homogenization in non aqueous media)

This is another type of preparation technique of nanosuspension which involves homogenization in water mixtures or water free media and it is prepared for the thermolabile compounds. Temperature will be 0 degree or even at freezing point. So it is known as deep freez homogenization.

2.1.2 Dissocubes (homogenization in aqueous media)

This technique is developed by Muller et al. in 1999. In this technique suspension is forced by a pressure plunger pump through a narrow valve under high pressure. When the suspension is allowed to pass through the orifice the static pressure will be reduced below the boiling pressure of water which results in the boiling of water and formation of gas bubbles. When it leaves the orifice pressure will be normal and bubbles will implode. So surrounding particles will rush into the surface which causes the size reduction.

2.1.3 Nanoedge (combined precipitation and homogenization)

As the name indicate both precipitation and homogenization are carried out at same time. In which drug mixed in an organic solvent and then the solution is also mixed with a miscible antisolvent for precipitation. In this technique, the precipitated suspension is further homogenized to get smaller particle size and avoid crystal growth.It produces nanosized stable dispersion with short period of time.

2.1.4 Nanojet

Nanojet is mostly used technology, in which high pressure of force is applied to passes the suspension which is separated into at least two sections and that are impact with each other due to high shear forces produced all through the process it marks to reduce of particle size.

3. Emulsification solvent evaporation technique

This technique involves preparing a solution of drug followed by its emulsification in another liquid that is a non-solvent for the drug. Evaporation of the solvent leads to precipitation of the drug. Crystal growth and particle aggregation can be controlled by creating high shear forces using a high-speed stirrer.

4. Supercritical fluid method

Novel nanosizing and solubilising technology whose application is increased. Particle size reduces via supercritical fluid process. It can be defined as dense non condensable fluid. This fluid is whose temp. and pressure is greater than its critical temperature and critical pressure. Its processes allow micronization of drug particle within narrow range of particle size, often submicron level. Current SCF process has demonstrated the ability to create nanoparticulate. Nanosuspension occurs particle size between 5 to 2000nm in a diameter. Poorly soluble drug and surfactant in supercritical CO2 and high pressure requires for these processes, restrict the utility of technology in industry.

5. Dry co grinding

Preparing a stable nanosuspension using dry grinding of poorly soluble drug with soluble polymer and copolymer after dispersing in liquid media has been reported. Many soluble polymers and co-polymers such as PVP, PEG, HPMC used. Physicochemical property and dissolution of poorly soluble drug were improved by co-grinding because of an enhancement in surface polarity and transformation from crystalline to an amorphous drug. Dry co-grinding can be carried out easily and carried out without organic solvent. It reduces the particle size.

Table 2: Summary of Nanosuspension Formation Technology and Compound Produced in Nanotechnology.[13]

Technology	Advantage	Disadvantages	Drug
Precipitation	-Simple process -Low cost equipment -Easy to scale up	-Drug has to soluble in at least one solvent and that is need to be miscible with a non solvent.	- Carbamazepine -Cyclosporine - Retinoic acid
High pressure homogenization	-General applicability to most drugs. -Used for formation of very dilute as well as highly con. Nanosuspension -Low risk of product contamination	-High number of homogenization cycles. -Possible contamination occur from metal ion coming off from the wall of the homogenizer.	- Albendazole - Amphotericin B - Clofazamine - Azithromycin - Fenofibrate
Emulsion template	-High drug solubilization -Long shelf life -Ease of manufacture	-Use of hazardous solvent -Use of high amount of surfactant and stabilizers.	- Ibuprofen - Mitotane
Media milling	-Easy to scale up -Little batch to batch variation -High flexibility to handling large quantities of drug	-Generation of residue of media milling -Require milling process to hour to days -Prolong milling may induce the formation of amorphous leads to instability	- Cilostazole - Naproxen
Dry co -grinding	-Easy process -No organic solvent -Required short grinding time	- Generation of residue of media milling	- Clarithromycin - Glibenclamide - Naproxen - Phenytoin

POST PRODUCTION PROCESSING[18]

Nanosuspensions are thermodynamically unstable. Solidification techniques transform nanosuspensions into solid dosage forms such as tablets, capsules and pellets. Solid dosage forms increased the storage stability of nanosuspensions. It is convenient from marketing perspective and is practically important for patient convenience. Pelletization, granulation, spray drying, and lyophilization are the unit operations of the solidification techniques. Matrix former (e.g mannitol, cellulose derivative) are usually added the to nanosuspension before solidification to prevent destabilisation of particles due to creating additional thermal stresses such as heating during spray drying or freezing during lyophilization. For example, microcrystalline cellulose was used by bernard et al. as a matrix former during the freez drying of itraconazole nanosuspension.

FORMULATION ASPECTS OF NANOSUSPENSION[13,19,20,21]

Stabilizers

Stabilizers plays an important role in the formulation of nanosuspension. In the absence of the appropriate stabilizers, the high surface energy of the nanosized particles can induced agglomeration or aggregation of the drug crystals. The main functions of stabilizers is to wet the drug particles through and prevent Ostwald ripening. In some cases, mixture of stabilizer is required to obtain a stable nanosuspension. The type and amount of stabilizers has a pronounced effect on the physical stability and in vivo behaviour of nanosuspension.

Example- SLS, PVPK30, Poloxamer, cellulosic and Povidone, Lecithin.

Surfactants

Surfactants is used to improve the dispersion by reducing the interfacial tension. They act as wetting or foaming agent.

Example – Tween 80 or span

Co surfactants

It is used for influence phase behaviour when microemulsion is used to formulate the nanosuspension. Since co- surfactant can greatly influence phase behaviour, the effect of cosurfactant on uptake of the internal phase for selected microemulsion composition and on drug loading should be investigated.

Example - Ethanol, glycofurol, bile salts, Transcutol.

Organic solvents

Pharmaceutically less hazardous solvent used for nanosuspension formulation.

Example- Ethanol, Methanol, Isopropanol, Ethyl acetate etc.

Other additives

According to need of required route or the property of drug.

Example- Buffer, bile salt, Osmogen, polyols etc.

CHARACTERIZATION OF NANOSUSPENSION[6,21,22,23,24]

1. Mean particle size and particle size distribution

Particle size and particle size distribution are two important parameters since it will affect the saturation solubility, dissolution rate, stability and in vivo behaviour of nanosuspensions. Any change in particle size will leads to change in solubility and dissolution. Particle size

determines physicochemical behaviour of the drug. The mean particle size and width of the particle size distribution called polydispersity index (PI) governs the saturation solubility, dissolution velocity and biological performance. Polydispersity index and particle size can be determined by photon correlation spectroscopy (PCS). A PI value of 0.1- 0.25 indicates a fairly narrow size distribution, If PI value greater than 0.5 indicates a very broad distribution. The particle size can also be determined by laser diffraction (LD) and coulter counter multisizer. the coulter counter gives absolute no. of particles per volume unit for the different size classes and it is more efficient and appropriate technique than LD for quantifying the contamination of nanosuspension by microparticulate drugs. Laser diffractometry (LD) measures volume size distribution And measures particle ranging from 0.05-80µm upto 2000µm. Atomic force microscope is used for visualization of particle shape.

2. Surface charge (Zeta potential)

Zeta potential determines the physical stability of nanosuspension. Zeta potential is indirect measurement of the thickness of the diffusion layer, i.e can be used to predict the long term stability. for electrostatically stabilized nanosuspension a minimum zeta potential of ±30 mv and for combined steric and electrostatic stabilization it should be a minimum of ±20mv.

3. Crystalline state and particle morphology

Differential scanning colorimeter (DSC) determines the crystalline structure. When nanosuspensions are prepared drug particles get converted to amorphous form hence it is essential to measure the extent of amorphous drug generated during the production of nanosuspensions. The x-ray diffraction is also used for determining change in physical state and extent of amorphous drug. high pressure homogenization nanosuspensions can undergo a change in crystalline structure, which may be to an amorphous form or to other polymorphic form because of high pressure of homogenization.

4. Saturation solubility and dissolution velocity

Nanosuspension increases the dissolution velocity and saturation solubility. Size reduction leads to increase in the dissolution pressure. An increase in solubility that occurs with relatively low particle size reduction may be mainly due to a change in surface tension leading to increased saturation solubility. The investigation of the dissolution velocity of nanosuspensions reflects the advantages that can be achieved over convectional formulations, especially when designing the sustained-release dosage forms based on nanoparticulate drugs.

5. Drug content

Drug content of nanosuspension formulation was carried out by taking lyophilized powder (weigh equivalent to 5mg of drug) 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.

Total volume of nanosuspension = total volume of nanosuspension x amount of drug in Aliquot / Volume of Aliquot.

6. Stability

Stability of nanosuspensions depends on the particle size of the suspended particles. Decrease in the particle size to the n increases the surface energy of the particles and the tendency of particles to agglomerate increases. Therefore the stabilizers are used to decrease the chances of Ostwald ripening and to improved the stability of the suspension by providing a steric or ionic barrier. Stability of optimized nanosuspension formulation was evaluated by determining change in particle size during storage at 2-8°C. Any change in particle size of nanosuspension formulation was observed using Malvern Zetasizer 2000 at periodic time intervals. Nanosuspensions can be store at different stress conditions like temperature (15, 25, 35, 45°C), thermal cycling, and mechanical shaking and change in their mean particle size can be followed for three months.

APPLICATIONS OF NANOSUSPENSIONS[15,16,25,26,27,28]

Nanosuspensions have a wide range of applications especially in the case of low solubility and low bioavailability drugs. They are mentioned below.

1. Oral drug delivery

Negative solubility, incomplete solvency, deficient disintegration and inadequate adequacy are the fundamental obstacle of oral medication organization. Nanosizing of drugs can leads to a dramatic increase in their oral absorption and subsequent bioavailability. Improved bioavailability can explained by the adhesiveness of drug nanoparticles to the mucosa, the increased saturation solubility leading to an increased concentration gradient between gastrointestinal tract lumen and blood and the increased dissolution velocity of the drug. Aqueous nanosuspension can be used to directly in a liquid dosage form and dry dosage form

such as tablet or hard gelatin capsules. Granulates can also be produced by spray drying of nanosuspension.

2. Parenteral drug delivery

One of the important applications of nanosuspension technology is the formulation of intravenously administered products. IV administration results in several advantages, such as administration of poorly soluble drugs without using a higher concentration of toxic cosolvent, improving the therapeutic effect of the drug available as conventional oral formulations, and targeting the drug to macrophages and the pathogenic microorganisms residing in the macrophages. Injectable nanosuspensions of poorly soluble drug tarazepide have been prepared to overcome the limited success achieved using conventional solubilization techniques, such as use of surfactants and cyclodextrins to improve bioavailability.

3. Ocular drug delivery

The ocular bioavailability of nanosuspensions depends on the dissolution rate of the drug in the lacrimal fluid. However, the inflow and outflow of the lacrimal fluid causes variation in the dissolution rate of the drug .nanosuspensions attain saturation solubility in the lacrimal fluid, representing an ideal approach for the ocular delivery of hydrophobic drugs . the nanosized drug particles had shown a prolong residual time in cul-de-sac , giving sustained release of drug. The best example of nanosuspension is ibuprofen. The anti-inflammatory activity of ibuprofen increased compared with the aqueous preparation.

4. Pulmonary drug delivery

Nanosuspensions may prove to be an ideal approach for delivering drugs that exhibit poor solubility in pulmonary secretions. Currently, such drugs are delivered as suspension aerosols or as dry powders by means of dry powder inhalers. For pulmonary delivery, nanosuspensions can be nebulized through mechanical or ultrasonic nebulizers. Due to the presence of many small particles, all aerosol droplets contain drug nanoparticles. Budesonide corticosteroid has been successfully prepared in the form of nanosuspension for pulmonary delivery.

5. Targeted drug delivery

Nanosuspensions are suitable for targeting particular organs because of their surface properties. Along with this, it is easy to alter in vivo behaviour by changing the stabilizers.

the drug will be taken up by the mononuclear phagocytic system which allows region specific delivery. This can be used for targeting antimycobacterial, fungal, or leishmanial drugs to the macrophages if the infectious pathogen is persisting intracellularly. the further plan of action for targeted drug delivery system is by using various surface coatings for active or passive targeting. Atovaquone is used as targeting nanosuspension to the brain.

6. Mucoadhesion of the nanoparticles

A nanoparticle has an ability to adhere to the mucosa surface due to small particles. The adhesion of the nanoparticles is the first step before particle absorption. To further increased the adhesive time nanosuspensions are formulated hydrogels made from mucoadhesive polymers, e.g different types carbapol and chitosan. The adhesiveness of the nanosuspensions not only helps to improve bioavailability but also improves targeting of the parasites persisting in the GIT.

7. Bioavailability enhancement

A drug with poor solubility and permeability in the gastrointestinal tract leads to poor oral bioavailability. Nanosuspension resolves the problem of poor bioavailability by solving the problem of poor solubility, and poor permeability across the membranes.

8. Topical formulations

Drug nanoparticles can be incorporated into creams and water free ointments. the nanocrystalline form leads to an increased saturation solubility of the drug in the topical dosage form, thus enhancing the diffusion of drug into the skin.

CONCLUSION

Nanosuspension solve problem of poor bioavailability problem of hydrophobic drugs and drugs which are poorly soluble in aqueous and organic solutions. Production techniques such as media milling and high pressure homogenization are used for large scale production of nanosuspensions. nanosuspensions can be administered through oral, parenteral, pulmonary, ocular and topical routes. Since nanotechnique is simple, less requirements of excipients, increased dissolution velocity and saturation solubility many poor bioavailability of drugs are formulated in nanosuspension forms.

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