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The impact of Critical Variables on properties of Nanosuspension: A Review

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Abstract:
Solubility is a major problem for the successful development and commercialization of new drug products. At present about 40% of drugs in the development pipelines and approximately 70% of drugs coming from synthesis are poorly soluble. Number of approaches are available for addressing the issues of low aqueous solubility. Among them nanosuspension has gain popularity in pharmaceutical industry in the last 10 years, because of their unique advantages. Nanosuspensions are defined as sub-micron colloidal dispersions of nanosized pure drug particles that are stabilized by a suitable polymer and/or surfactant and have a particle size of 1–1000 nm. Top-down and bottom-up technologies are the two primary approaches for nanosuspension production. This review article focus on different top-down and bottom-up technologies for the production of nanosuspension. The core objective of this review article is to focus on different critical variables affecting functional properties of nanosuspension.

Keywords: dissolution enhancement, Nanosuspension, bottom up, top down

1. Introduction

The poor solubility of drug is a major problem which limits the development of highly potent pharmaceutics[1]. At present about 40% of drugs in the development pipelines and approximately 70% of drugs coming from synthesis or high throughput screening are poorly soluble. Poor solubility leads to low oral bioavailability and erratic absorption[2]. Thus high doses of such drugs are often require to reach therapeutic plasma concentrations after oral administration. Improvement in the extent and rate of dissolution is highly desirable for such compounds, as this can lead to an increased and more reproducible oral bioavailability and subsequently to clinically relevant dose reduction and more reliable therapy[3]. Number of approaches are available for addressing the issues of low aqueous solubility.These approaches involves physical and chemical modification. Physical modification includes techniques like particle size reduction, complexation with cyclodextrine[4, 5], preparation of polymorphs/pseudopolymorphs, solubilizing the drugs in co-solvent, drug dispersion incarrier[6-8] while chemical modification involves techniques like salt formation[9, 10] and prodrugs etc. success of any technique dependents upon physicochemical nature of the molecules. Amongst them particle size reduction technique is the classical approach that can be applied to nonspecific formulation for many years. Reduction in the particle size to micrometer range leads to

an increase in their surface area which proportionally increases in rate of dissolution and rate of diffusion (absorption). But micronization does not improve saturation solubility of very low soluble compounds. Therefore further reduction in the particle size to nanometer size is require to improve the dissolution rate and the saturation solubility, subsequently improve the bioavailability of poorly water-soluble drugs[1].

Nanosuspensions are defined as unique liquid sub-micron colloidal dispersions of nanosized pure drug particles that are stabilized by a suitable polymer and/or surfactant and have a particle size of 1–1000 nm[11].Formulating nanosuspension of poorly water soluble drugs has gain popularity in pharmaceutical industry in the last 10 years [12].

2. PRODUCTION OF NANOSUSPENSION

Two basic approaches are involved in production of nanosuspension, the bottom–up technologies and the top–down technologies[13-15]. However, the combination techniques, combining a pre-treatment with a subsequent size reduction step are also being employed. Bottom up technology involves assembling method to form nanoparticles like precipitation, Supercritical fluid processes,Lipid emulsion/microemulsion template method and top down technology involves reduction of larger particles into nanoparticles, like high-pressure homogenization and milling methods. The principles of these methods are described in detail alone with merits and demerits of each and critical variables affecting functional properties of nanosuspension.

2.1 BOTTOM UP TECHNOLOGY

In the bottom up processes, one starts from the molecule in solution, the molecules are aggregated to from particles, being crystalline or amorphous.In1980 Sucker developed "hydrosols" (solid particles have diameters in the nanometer range) through this process and the intellectual property was acquired by Sandoz (nowadays Novartis)[16, 17]. This precipitation method involves the formation of crystalline or semicrystalline drug nanoparticles by nucleation and thegrowth of drug crystals. Drug molecules arefirst dissolved in an appropriate organic solvent at a supersaturation concentration to allow for the nucleation of drug seeds. Drug nanoparticles are then formed by adding the organic mixture to an antisolvent in the presence of stabilizers[18]. This hydrosol technique was modified in 1990s by Sandoz, which include charged glyceryl esters, such as lecithin, as an electrostatic stabilizer. The stabilizer adsorb onto the surface of drug nanoparticles and prevent agglomeration.

2.1.1 Precipitation by liquid solvent–antisolvent addition

2.1.1.1 Introduction

Among the various precipitation technique liquid antisolvent precipitation technique is the most commonly used technique for the preparation of nanosuspension. In this technique drug molecules are first dissolved in an appropriate organic solvent at a supersaturation concentration to allow for the nucleation of drug seeds.Drug nanoparticles are then formed by adding the organic mixture to an antisolvent in the presence of stabilizers[18].Characteristic of the nanosuspension is affected by the several factors like drug concentration, Solvent to Anti-solvent ratio, Flow rate of the solvent and the antisolvent, Temperature, Effect of the stirring speed and stabilizer type etc.

Mixing solvent and antisolvent is the simplest method which is carried out by only simple mixture or a modified method to facilitate mixing.

Modified methods include sonoprecipitation, high gravity precipitation, and evaporative precipitation technique.

2.1.1.2 Merits and demerits

Merits

- Simple process
- Low cost equipment
- Ease of scale up

Demerits

- Special facility and equipment is require for the proper handling of flammable and/or explosive solvents [19].
- Bottom-up approach involves the use of solvents, which are usually difficult to remove completely, any residual solvent can cause physical and chemical instabilities of the formulation[20].
- The bottom-up approach usually results in needle-shaped particles due to the rapid growth in one direction, which affect the physical stability of the nanosuspension [21].

2.1.1.3 Important Variables

1. Effect of the drug concentration

Optimum drug concentration is required to achieve smaller particle size. Concentration above the optimum level lead to generation of lager size particles. Higher drug concentration generates higher super saturation which results in a faster nucleation rate and thereby smaller particles but, at the same time, the growth of nuclei is also increased due to the higher super saturation. Second, on increasing drug concentration, viscosity is also increases, which will hinder the diffusion between solvent and anti-solvent, leading to non-uniform super saturation, slower nucleation rates and increased particle agglomeration, and hence, larger particles[22-24].

2. Solvent to Anti-solvent ratio

The relative amount of solvent and anti-solvent have major impact on the particle property of nanosuspension. Various studies have been carried out to find out the effect of amount of anti-solvent on the particle size of nanosuspension and this study shows that particle size can be decrease with increasing the amount of anti-solvent. Several reasons were drawn from such observation. If the ratio of antisolvent to solvent is increased, the degree of super saturation ratio is increased which increases the nucleation rate and decreases the particle size. Once the nuclei are formed, particle growth occurswhich is partially hindered at higher anti-solvent volumesas the diffusion distance for the growing species increases and the process becomes diffusion limited [22-25].

3. Flow rate of the solvent and the antisolvent

Flow rate of the solvent and the antisolvent also have impact on particle size. Particle size was decreased with a gradual increase of the flow rate up to a certain level, above which, the marginal change in the particle size was observed. As the flow rate increase Reynolds number is increase which reduces the mixing time of the solvent with the antisolvent and leads to a reduction of particle size[24, 25].

4. Temperature

Temperature is the important parameter in controlling the particle size in precipitation method. Temperature affects in number of parameters like saturation and supersaturation concentration, the diffusion rate, and the viscosity of the system. Reduction in the temperature, reduce the equilibrium solubility and thus degree of supersaturation increases which increases the nucleation rate and decreases the particle size. Second, on decreasing the temperature, viscosity increases which decreases the mobility of the

particle in the liquid phase. At law mobility the collision of the particle is reduces and thus the aggregation of the particle is also reduce.

5. Effect of the stirring speed

Stirring speed is the important parameter that affect the particle size. Literature survey shows that particle size decreased with increased the stirring speed. Which may be due to intensification of micro mixing. High micromixing increased the rate of diffusion and mass transfer between the multiphase and thus high homogenous supersaturation in short time is achieved which cause rapid nucleation and generates smaller particles. Moreover the growth of the particle is also prevented at high stirring speed. Thus smaller particle with narrow particle size distribution is achieved at higher stirring speed[22].

6. Stabilizer

Key challenge in the Antisolvent precipitation process is to retain the nanosize of the fresh particles. As smaller particles are more soluble than large ones, material transfer occurs from the fines to the coarse particles this phenomena is called "Ostwald ripening" whereby coarse particles grow at the expense of fine particles re-dissolving. Moreover during the antisolvent precipitation, surface Gibbs free energy of the newly formed nanoparticles have increased and thus particle undergoes aggregation in order to reduce Gibbs free energy which compromise the advantage of higher saturation solubility and bioavailability, and faster dissolution rate. Stabilizers by means of absorbing on the surface of the newly formed particle prevent Ostwald's ripening and agglomeration of nano suspension and yield a physically stable formulation by providing steric or ionic barrier. The type and amount of stabilize has a pronounced effect on the physical stability and in vivo behavior of nano suspension. Electrostatic and/or steric techniques are the most common approaches for stabilization. In electrostatic stabilization ionic surfactants (such as soya lecithin and sodium lauryl sulfate (SLS)) adsorbed on the particle surface and this surface charge and electrostatic repulsion prevents the aggregation of Nano sized particles. Steric stabilization is achieved by adsorbing polymers (suchas hydroxypropyl methyl cellulose (HPMC), D-a-tocopherolpolyethylene glycol 400 succinate (TPGS), and hydroxypropylb-cyclodextrin (HP-b-CD)) or nonionic surfactants (such asPoloxamer 188) onto the surfaces of drug nanoparticles to form adynamically rough surface to prevent coalescence by repulsiveentropic forces[25-27].

2.1.2 Supercritical fluid processes

2.1.2.1 Introduction

Various methods like RESS (rapid expansion of supercritical solution), RESOLV (rapid expansion of a supercritical solution into a liquid solvent) and SAS (supercritical antisolvent) are used for preparation of nanoparticles. In the RESS process, the solution of drug in supercritical fluid (SCF)is prepared and the solution is than passed through a narrow nozzle. The immediate reduction in pressure changes the density of the fluid and the rapid expansion of the supercritical fluid causes super saturation and the solute nucleates and precipitates. But the limitation of this technique is polar drugs are not soluble in the supercritical fluid which can be overcome by adding solid co solvent such as menthol to increase the solubility of the polar compounds[22].

Modification in RESS process leads to the development of newer process called rapid expansion of a supercritical solution into a liquid solvent (RESOLV). In this technique expansion

nozzle of RESS process was kept inside a solvent phase instead of air or gas phase.

In the SAS method, the drug is dissolved in an organic solvent, which must be miscible with the supercritical antisolvent. This drug solution is than added to the supercritical antisolvent. The solvent rapidly diffuses in the antisolvent phase and the drug precipitates due to low solubility in the antisolvent [22, 28].

2.1.2.2Merits and demerits[29]

Merits

- Minimizes the use of organic solvent and reuses the SCF in continuous process.

Demerits

- Very expensive method
- poor solubility of most of the pharmaceutical material in SCF-CO2, which, in turn require large amount of fluid
- Difficulty of scaling up the process because of particle aggregation and nozzle blockage caused by cooling due to the rapid expansion of the supercritical solution
- poor control over particle size distribution

2.1.2.3 Important Variables

1. Temperature

It has been reported that up to a point increasing the temperature led to smaller particles but further increase of temperature showed the opposite effect[30, 31]. Mean particle size was decreased by increasing the temperature and this increase was more considerable at lower pressures. This may be due to an increase in the temperature causes decrease in the density of super critical fluid solvent which results in lower drug solubility. On the other hand, the volatility of the substance increases as the temperature rises and leads to a higher solubility [32].

2. Pressure

The smaller particles were formed at optimum pressure and increasing the pressure more than that, formed larger particles[30, 31]. The decrease in particle size with increasing pressure at constant temperature leads to increase in solubility of drug in CO_2 and the supersaturation rise nucleation rate and decrease particle size [30].

3. Co solvent

The amount and nature of co-solvent affects the degree to which the polarity of supercritical fluid phase is modified[33]. When suitable co-solvent is added, the drug solubility in CO2 increases. Particle collision rate is directly proportional to the square of particle concentration, so higher solubility may cause coagulation and result in larger particles[31]. Another effect of adding co-solvent is hindering particle growth in expansion zone by surrounding the drug and preventing surface to surface interaction between drug particles[34].

4. Liquid flow rate

As the liquid flow rate increased, the average particle sizes increased [35].According to Randolph et al [35],as the flow rate increased the mass transfer rates decreased leads to decrease in the supersaturation ratio which then caused a decrease in the nucleation rate. A decrease in the nucleation rate would then lead to larger particles. It is also reported that the degree of mixing may be improved at higher liquid flow rates under miscible conditions (two phases are fully miscible) resulting in a higher supersaturation and thus, smaller particles are expected [36].

5. Drug concentration

It has two opposing effects on the one hand, with a higher concentration, it is possible to achieve higher supersaturation, which tend to diminish the particle size; and on the other hand,

condensation is directly proportional to the concentration of solute, and the increase of the condensation rate with higher concentrations tends to increase the particle size [36, 37].

6. Nozzle internal diameter

The narrower the nozzle internal diameter, the finer the particles will be.

2.1.3 Lipid emulsion/microemulsion template

2.1.3.1 Introduction

Nanosuspensions are also obtained by using Lipid emulsion/microemulsion template. In this method volatile organicsolvent or partially water-miscible solvent are use as dispersed phase. The drug is dissolve in the organic phase and this organic solution of the drug is than added to the aqueous phase contain surfactant to form an emulsion. From this emulsion drug nanosuspension can be prepare by two method. In first method organic phase of the emulsion is evaporated to precipitate the drug as nanosuspension which is stabilized by surfactant. In second method the emulsion is diluted with water which causes complete diffusion of the internal phase into the external phase, leading to immediate formation of a nanosuspension.In the case of microemulsion, oil in water type microemulsion is used for the preparation of nanosuspension and dilution of this microemulsion with water leads to the formation nanosuspension [38, 39].

2.1.3.2 Merits and demerits

Merits

- Specialized equipment is not necessary.
- It is possible to controlled Particle size by controlling the size of the emulsion droplet.
- Ease of scale-up.

Demerits

- Drugs that are poorly soluble in both aqueous and organic media cannot be formulated by this technique.
- Safety concerns because of the use of hazardous solvents in the process.
- High amount of surfactant/stabilizer is required.

2.1.3.3 Important Variables

1. Stabilizer

Stabilizer plays an important role in the formulation of nanosuspensions. Because of the high surface energy of nano-sized particles, agglomeration or aggregation of the drug crystals can be occurs in the absence of stabilizer. Stabilizer prevents Ostwald's ripening and agglomeration of nanosuspensions by providing steric or ionic barriers. The typeand amount of stabilizer has a pronounced effect on the physical stability and in-vivo behavior of nanosuspensions.In some cases, a mixture of a mixture of stabilizers is required to obtain a stable nanosuspension[39].

2. Co-surfactant

The selection of co-surfactant is critical when using microemulsionsto formulate nanosuspensions. Co-surfactantscan affect the phase behavior, the effect of co-surfactant on uptake of the internal phase for selected microemulsion composition and on drug loading should be investigated. Although the literature describes the use of bile salts and dipotassiumglycerrhizinate as co-surfactants, various solubilizers, such as Transcutol, glycofurol, ethanol and isopropanol, can be safely used as co-surfactants in the formulation of microemulsions[39].

2.2 TOP–DOWN TECHNOLOGY

2.2.1 Milling

2.2.1.1 Introduction

This is the basic technology developed by G. Liversidge and coworkers. In this technique milling media, dispersion medium (generally water) containing stabilizer along with drug are charged into a milling chamber and milling operation is

carried out for several hours to prepare nanosuspension. Collision between the milling media and drug generates Shear forces which leads to particle size reduction. Smaller or larger coated milling pearls of ceramics (cerium or yttrium stabilized zirconium dioxide), stainless steel, glass or highly cross linked polystyrene resin-coated beads can be used as a milling media.Irrespective to the type of milling media, its size is also important for effective conversion of course drug in to nanosuspension. Milling media having size of 1mm or less is generally used and depending of the type of particle size distribution profile being targeted, larger or smaller size milling media can be employed. Characteristics of resulting Nanosuspension depends on the several factors like amount and size of milling media, the amount of drug, milling time and speed [40, 41].

2.2.1.2 Merits and demerits

Merits[42, 43]

- Media milling is applicable to the drugs that are poorly soluble in both aqueous and organic media.
- low energy technique

Demerits[18]

- residual from the milling media
- loss of drug owing to adhesion to the inner surface of the milling chamber

2.2.1.3Important Parameters

1. Amount of milling media

The efficiency of the milling depends on the intensity of the grinding energy. Amount of the milling media is the important factor to control the efficiency of the milling process. Various studies have been carried out to find out the effect of amount of milling media on the particle size of nanosuspension and this study shows that particle size is decreases with increasing the amountmilling media. This could be due to increased contact point between drug and milling media which enhance the collision and thus reduced the particle size. But further increasing the milling media above optimum level, lead to inefficient milling which might be due to the overfilling of milling chamber and thud reduces the free space required for the collisions between drug particles and milling agents[44].

2. Size of milling media

Size of the milling media is also an important factor to control the milling efficiency. Reduction in particle size values is observed with reduction in size of milling media. This might be due to an increase in number of contact points between drugparticles and milling agents at lower sized milling agents[45].

3. Milling time and milling speed

Efficiency of the milling operation is also affected by milling time and milling speed. Data from the literature survey suggest that particle size decreased with increasing the milling time and milling speed which might be due to the high energy and shear forces generated as a result of the impaction of the milling media with the drug which provides the energyinput to break the microparticulate drug into nanosized particlesbut further increasing the milling time above certain limits leads to increase Particle size because the input of additional mechanical energy destabilized the particle by breaking repulsive force between the particle[44, 46, 47].

4. Effect of drug content

Concentration of the drug also affect the particle size of the nanosuspension. From the literature review it was found that particle size decreased with increasing the concentration of drug due to the effect of a higher solid content in the suspension, which produced additional attrition between the solid particles [48].

2.2.2 High pressure homogenization[49]

2.2.2.1 Introduction

The second most frequently used top down method is milling by high pressure homogenization. The two homogenization principles/homogeniser types applied are:

1. Microfluidisation
2. Piston-gap homogenization either in water (Dissocubes® technology,

SkyePharma) or alternatively in water-reduced/non-aqueous media (Nanopure® technology)

Microfluidisation

The Microfluidizer technology is based on the jet stream principle and can generate small particles. In this technique the suspension is passed through a chamber which is specially design either z type or y type. In a z type chamber direction of the suspension is change several time which lids to particle collision and shear. Whilein the case of y type chamber the suspension stream is divided in to two stream and the frontal collision of two fluid streams leads to particle size reduction. Under pressures up to 1700 bar. The jet streams lead to particle collision, shear forces and cavitation forces (Microfluidizer®, Microfluidics Inc.).

Piston-gap homogenization

Another homogenization principle that is Piston-gap homogenization was developed in the middle of the 1990s.Dissocubes® and Nanopure®are two technologies which utilized Piston-gap homogenization.

The Dissocubes® technology was developed by Müller and co-workers by employing piston-gap homogenizers (e.g. APV Gaulin/Rannie homogenizers). The technology was acquired by SkyePharma PLC in 1999. In this technology drug dispersed in an aqueous surfactant solution (macrosuspension) is forced by a piston under pressure (up to 4000 bar, typically 1500–2000 bar) through a tiny gap (e.g. 5–20_m). The resulting high streaming velocity of the suspension causes an increase in the dynamic pressure. This is compensated by a reduction in the static pressure below the vapor pressure of the aqueous phase; hence, water starts boiling forming gas bubbles. These gas bubbles collapse immediately when the liquid leaves the homogenization gap (=cavitation). The drug particles are reduced in size due the high power of the shockwaves caused by cavitation. The mean size of suspension obtained by the high pressure homogenization process depends on several factors like the power density of the homogenizer (homogenizer pressure) and number of homogenization cycles The Nanopure® technology is another approach using the piston-gap homogenizer (prev. PharmaSol GmbH, now Abbott). This technology uses non-aqueous dispersion medium e.g. Liquids (like oils, liquid and solid/melted PEG,) or water reduced media (e.g. glycerol–water, ethanol–water mixtures). These media have lowvapor pressure, cavitation takes place very limited or not at all.Even without cavitation,the size diminution is sufficient because of shear forces, particlecollisions and turbulences.

2.2.2.2 Merits and demerits

Merits

- Simple technique
- Easy to scale up
- Applicable to most of the drug

Demerits

- Multiple homogenization cycles are required to achieve desire size of the particle which increased the processing time
- The drug must also be prehomogenized(at low pressure) or milled before HPH

- Contamination by metal ion from homogenizer wall

2.2.2.3 Important Parameters

1. Effect of homogenization pressure.

In the milling process, particle breaks at a weak point i.e imperfections. As the particle size decrease the number of imperfection also decreases which means the remaining crystals becoming more and more perfect. Thus with decreasing particle size force require to break the particle size is increases. Therefore to achieve smaller size particle, the homogenizer pressure needs to be increased[39].

2. Number of homogenisation cycles

As the number of hominization cycle increases, the particle size decreases. For many drug, a single homogenization cycle is not sufficient to obtaineddesired particle size. Depending upon the hardness of the drug, multiple homogenization cycles are required to achieve desire particle size [39, 50, 51].

3. Conclusion

The formulation of poorly soluble drugs has always been a challenging problem faced by pharmaceutical industry. Nanosuspensions have appeared as a promising strategy for the efficient delivery of hydrophobic drugsbecause of the versatile features and unique advantages. Production techniques such as bottom up technique and top down technique have been successfully employed for large-scale production of nanosuspensions. Moreover By emphasizing important variables affecting nanosuspension formulation, it is possible to control the property of the nanosuspension.

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