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Review Article

Nanosuspensions: a promising drug delivery strategy

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Abstract

Nanosuspensions have emerged as a promising strategy for the efficient delivery of hydrophobic drugs because of their versatile features and unique advantages. Techniques such as media milling and high-pressure homogenization have been used commercially for producing nanosuspensions. Recently, the engineering of nanosuspensions employing emulsions and microemulsions as templates has been addressed in the literature. The unique features of nanosuspensions have enabled their use in various dosage forms, including specialized delivery systems such as mucoadhesive hydrogels. Rapid strides have been made in the delivery of nanosuspensions by parenteral, peroral, ocular and pulmonary routes. Currently, efforts are being directed to extending their applications in site-specific drug delivery.

Introduction

The formulation of poorly water-soluble drugs has always been a challenging problem faced by pharmaceutical scientists and it is expected to increase because approximately 40% or more of the new chemical entities being generated through drug discovery programmes are poorly water-soluble (Lipinski 2002).

The problem is even more intense for drugs such as itraconazole and carbamazepine (belonging to class III as classified by Washington 1996), as they are poorly soluble in both aqueous and organic media, and for drugs having a log P value of 2 (Pouton 2000). Such drugs often have an erratic absorption profile and highly variable bioavailability because their performance is dissolution-rate limited and is affected by the fed/fasted state of the patient.

Traditional strategies, such as micronization, solubilization using co-solvents, the use of permeation enhancers (Aungst 1993, 2000), oily solutions (Aungst 1993) and surfactant dispersions (Aungst et al 1994), which evolved earlier to tackle the formulation challenges, have limited use. Although reasonable success has been achieved in formulating water-insoluble drugs using liposomes (Schwendener & Schott 1996), emulsions (Floyd 1999; Nakano 2000), microemulsions (Lawrence & Rees 2000), solid dispersion technology (Serajuddin 1999; Leuner & Dressman 2000; Breitenbach 2002) and inclusion complexes employing cyclodextrins (Loftsson & Brewster 1996; Stella & Rajewski 1997; Akers 2002), there is no universal approach applicable to all drugs. Hence, there is a growing need for a unique strategy that can tackle the formulation-related problems associated with the delivery of hydrophobic drugs in order to improve their clinical efficacy and optimize their therapy with respect to pharmacoeconomics.

Nanosuspensions have revealed their potential to tackle the problems associated with the delivery of poorly water-soluble and poorly water- and lipid-soluble drugs, and are unique because of their simplicity and the advantages they confer over other strategies. This review focuses on the various aspects of nanosuspensions and their potential as a promising strategy in drug delivery.

Nanosuspensions can be defined as colloidal dispersions of nano-sized drug particles that are produced by a suitable method and stabilized by a suitable stabilizer.

Methods of production

Media milling (NanoCrystals)

This patent-protected technology was developed by Liversidge et al (1992). Formerly, the technology was owned by the company NanoSystems but recently it has been acquired by Elan Drug Delivery. In this method the nanosuspensions are produced

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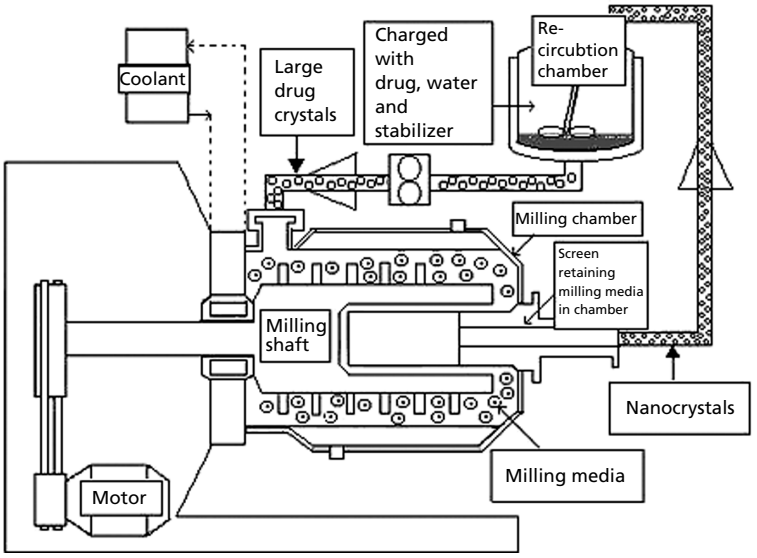

Figure 1 Schematic representation of the media milling process. The milling chamber charged with polymeric media is the active component of the mill. The mill can be operated in a batch or recirculation mode. A crude slurry consisting of drug, water and stabilizer is fed into the milling chamber and processed into a nanocrystalline dispersion. The typical residence time generated for a nanometer-sized dispersion with a mean diameter of <200 nm is 30–60 min. Reprinted from Merisko-Liversidge et al 2003 with permission from Elsevier Publications.

using high-shear media mills or pearl mills. The media mill consists of a milling chamber, a milling shaft and a recirculation chamber (Figure 1). The milling chamber is charged with the milling media, water, drug and stabilizer, as depicted in Figure 1, and the milling media or pearls are then rotated at a very high shear rate. The milling process is performed under controlled temperatures.

Principle The high energy and shear forces generated as a result of the impaction of the milling media with the drug provide the energy input to break the microparticulate drug into nano-sized particles. The milling medium is composed of glass, zirconium oxide or highly cross-linked polystyrene resin. The process can be performed in either batch or recirculation mode. In batch mode, the time required to obtain dispersions with unimodal distribution profiles and mean diameters <200 nm is 30–60 min. The media milling process can successfully process micronized and non-micronized drug crystals. Once the formulation and the process are optimized, very little batch-to-batch variation is observed in the quality of the dispersion.

Advantages

- Drugs that are poorly soluble in both aqueous and organic media can be easily formulated into nanosuspensions.
- Ease of scale-up and little batch-to-batch variation.
- Narrow size distribution of the final nano-sized product. A comparison of the size of naproxen crystals before and after media milling is given in Figure 2.
- Flexibility in handling the drug quantity, ranging from 1 to 400 mg mL^{-1}, enabling formulation of very dilute as well as highly concentrated nanosuspensions.

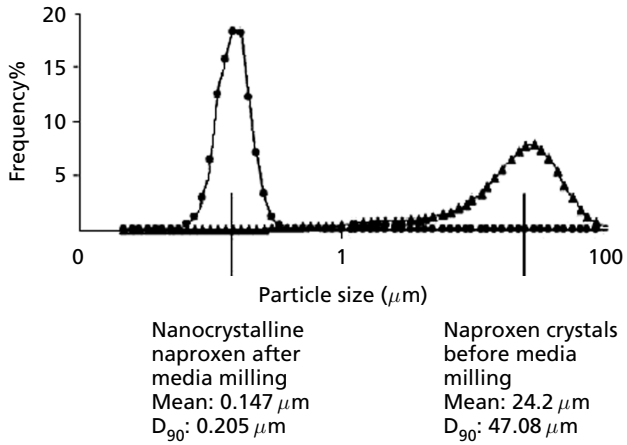

Figure 2 The particle size distribution of naproxen crystals before (▲) and after (●) milling. Before milling the drug crystals had a mean particle size of 24.2 μm. After being processed for 30 min in a media mill, the mean particle size of the nanocrystalline dispersion was 0.147 μm with $D_{90} = 0.205\,\mu$m. The particle size measurements were generated using laser light diffraction in a Horiba LA-910 using polystyrene nanospheres ranging from 0.1 to 10 μm as standards. Reprinted from Merisko-Liversidge et al 2003 with permission from Elsevier Publications.

Disadvantages

- The major concern is the generation of residues of milling media, which may be introduced in the final product as a result of erosion (Buchmann et al 1996; Müller & Böhm 1998). This could be problematic when nanosuspensions are intended to be administered

for a chronic therapy. The severity of this problem has been reduced to a great extent with the advent of polystyrene resin-based milling medium. For this medium, residual monomers are typically 50 ppb and the residuals generated during the milling processing are not more than 0.005% w/w of the final product or the resulting solid dosage form.

High-pressure homogenizers (Disso Cubes)

Disso Cubes technology was developed by R. H. Müller (Müller et al 1998). The patent rights of Disso Cubes were initially owned by DDS (Drug Delivery Services) GmbH but currently they are owned by SkyePharma plc. Disso Cubes are engineered using piston-gap-type high-pressure homogenizers. A commonly used homogenizer is the APV Micron LAB 40 (APV Deutschland GmbH, Lubeck, Germany). However, other piston-gap homogenizers from Avestin (Avestin Inc., Ottawa, Canada) and Stansted (Stansted Fluid Power Ltd, Stansted, UK) can also be used. A high-pressure homogenizer (Figure 3) consists of a high-pressure plunger pump with a subsequent relief valve (homogenizing valve). The task of the plunger pump is to provide the energy level required for the relief. The relief valve consists of a fixed valve seat and an adjustable valve. These parts form an adjustable radial precision gap. The gap conditions, the resistance and thus the homogenizing pressure vary as a function of the force acting on the valve. An external impact ring forms a defined outlet cross-section and prevents the valve casing from being damaged due to the flow (Jahnke 1998). The instrument is available in discontinuous and continuous versions. The continuous version is suitable for optimizing the various parameters of the homogenization process. Use of the discontinuous version is sensible if the drug is very costly or of limited availability. The instrument can be operated at pressures varying from 100 to 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 production). It is advisable to start with the micronized drug (particle size < 25 μm) for production of nanosuspensions in order to prevent blocking of the homogenization gap. Hence, generally a jet-milled drug is employed as the starting material for producing Disso Cubes. Before subjecting the drug to the homogenization process, it is essential to form a presuspension of the micronized drug in a surfactant solution using high-speed stirrers. During the homogenization process, the drug suspension is pressed through the homogenization gap in order to achieve nano-sizing of the drug.

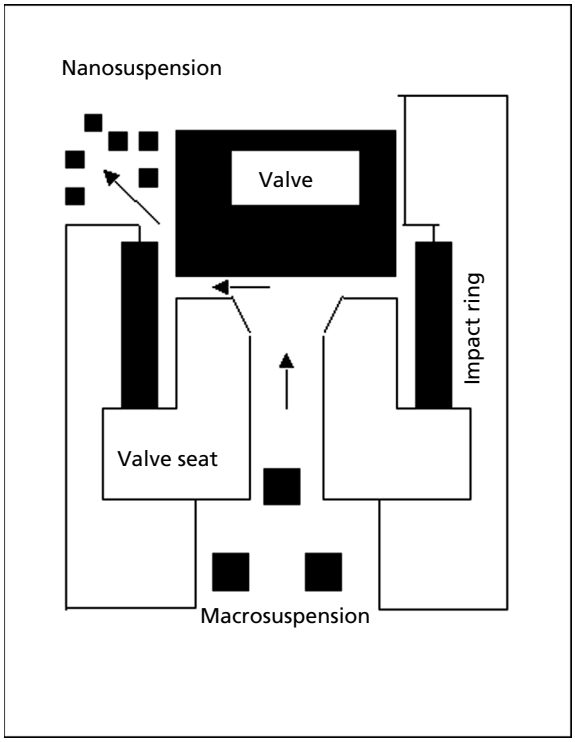

Figure 3 Schematic representation of the high-pressure homogenization process.

Principle During homogenization, the fracture of drug particles is brought about by cavitation, high-shear forces and the collision of the particles against each other. The drug suspension, contained in a cylinder of diameter about 3 mm, passes suddenly through a very narrow homogenization gap of 25 μm, which leads to a high streaming velocity.

In the homogenization gap, according to Bernoulli's equation, the dynamic pressure of the fluid increases with the simultaneous decrease in static pressure below the boiling point of water at room temperature. In consequence, water starts boiling at room temperature, leading to the formation of gas bubbles, which implode when the suspension leaves the gap (called cavitation) and normal air pressure is reached again. The implosion forces are sufficiently high to break down the drug microparticles into nanoparticles. Additionally, the collision of the particles at high speed helps to achieve the nano-sizing of the drug. To improve the efficiency of nano-sizing, the addition of viscosity enhancers is advantageous in certain cases as increasing the viscosity increases the powder density within the dispersion zone (homogenization gap).

In order to obtain an optimized formulation, the effect of the following process variables should be investigated.

- *Effect of homogenization pressure*. As the homogenizer can handle varying pressures, ranging from 100 to 1500 bars, the effect of the homogenization pressure on the particle size should be investigated in each case in order to optimize the process parameters. It is expected that the higher the homogenization pressure, the lower the particle size obtained. The studies carried out on RMKP 22, 4-[N-(2-hydroxy-2-methyl-propyl)-ethanolamino]-2,7-bis (*cis*-2,6-dimethylmorpholin-4-yl)-6-phenyl-pteridine, revealed that an inverse relationship exists between the homogenization pressure and the particle size (Müller & Böhm 1998; Müller & Peters 1998; Grau et al 2000).

- *Number of homogenization cycles*. For many drugs it is not possible to obtain the desired particle size in a single homogenization cycle. Typically, multiple cycles are required. Hence, depending on the hardness of the drug, the desired mean particle size and the required homogeneity of the product, homogenization can be carried out in three, five or 10 cycles. It is anticipated that the higher the number of homogenization cycles, the smaller the particle size obtained. The optimum number of homogenization cycles can be arrived at by analysing the particle size and polydispersity index of the drug after each cycle.

Advantages
- Drugs that are poorly soluble in both aqueous and organic media can be easily formulated into nanosuspensions.
- Ease of scale-up and little batch-to-batch variation (Grau et al 2000).
- Narrow size distribution of the nanoparticulate drug present in the final product (Müller & Böhm 1998).
- Allows aseptic production of nanosuspensions for parenteral administration.
- Flexibility in handling the drug quantity, ranging from 1 to 400 mg mL^{-1}, thus enabling formulation of very dilute as well as highly concentrated nanosuspensions (Krause & Müller 2001).

Disadvantages
- Prerequisite of micronized drug particles.
- Prerequisite of suspension formation using high-speed mixers before subjecting it to homogenization.

Emulsions as templates
Apart from the use of emulsions as a drug delivery vehicle, they can also be used as templates to produce nanosuspensions. The use of emulsions as templates is applicable for those drugs that are soluble in either volatile organic solvent or partially water-miscible solvent. Such solvents can be used as the dispersed phase of the emulsion. There are two ways of fabricating drug nanosuspensions by the emulsification method.

In the first method, an organic solvent or mixture of solvents loaded with the drug is dispersed in the aqueous phase containing suitable surfactants to form an emulsion. The organic phase is then evaporated under reduced pressure so that the drug particles precipitate instantaneously to form a nanosuspension stabilized by surfactants. Since one particle is formed in each emulsion droplet, it is possible to control the particle size of the nanosuspension by controlling the size of the emulsion. Optimizing the surfactant composition increases the intake of organic phase and ultimately the drug loading in the emulsion. Originally, organic solvents such as methylene chloride and chloroform were used (Bodmeier & McGinity 1998). However, environmental hazards and human safety concerns about residual solvents have limited their use in routine manufacturing processes. Relatively safer solvents such as ethyl acetate and ethyl formate can still be considered for use (Sah 1997, 2000).

Another method makes use of partially water-miscible solvents such as butyl lactate, benzyl alcohol and triacetin as the dispersed phase instead of hazardous solvents (Trotta et al 2001). The emulsion is formed by the conventional method and the drug nanosuspension is obtained by just diluting the emulsion. Dilution of the emulsion with water causes complete diffusion of the internal phase into the external phase, leading to instantaneous formation of a nanosuspension. The nanosuspension thus formed has to be made free of the internal phase and surfactants by means of diultrafiltration in order to make it suitable for administration. However, if all the ingredients that are used for the production of the nanosuspension are present in a concentration acceptable for the desired route of administration, then simple centrifugation or ultracentrifugation is sufficient to separate the nanosuspension.

Advantages
- Use of specialized equipment is not necessary.
- Particle size can easily be controlled by controlling the size of the emulsion droplet.
- Ease of scale-up if formulation is optimized properly.

Disadvantages
- 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.
- Need for diultrafiltration for purification of the drug nanosuspension, which may render the process costly.
- High amount of surfactant/stabilizer is required as compared to the production techniques described earlier.

The production of drug nanosuspensions from emulsion templates has been successfully applied to the poorly water-soluble and poorly bioavailable anti-cancer drug mitotane, where a significant improvement in the dissolution rate of the drug (five-fold increase) as compared to the commercial product was observed (Trotta et al 2001).

Microemulsions as templates
Microemulsions are thermodynamically stable and isotropically clear dispersions of two immiscible liquids, such as oil and water, stabilized by an interfacial film of surfactant and co-surfactant (Eccleston 1992). Their advantages, such as high drug solubilization, long shelf-life and ease of manufacture, make them an ideal drug delivery vehicle. There are several research papers available that describe the use of microemulsions as drug delivery vehicles (Constantinides et al 1994, 1995; Kim et al 1998; Park & Kim 1999; Kawakami & Yoshikawa 2002). Recently, the use of microemulsions as templates for the production of solid lipid nanoparticles (Gasco 1997) and polymeric nanoparticles (Rades et al 2002) has been described. Taking advantage of the microemulsion structure, one can use microemulsions even for the production of nanosuspensions (Trotta et al 2003). Oil-in-water microemulsions are preferred for this purpose. The internal phase of these microemulsions could be either a partially miscible liquid or a suitable organic solvent, as described earlier.

The drug can be either loaded in the internal phase or pre-formed microemulsions can be saturated with the drug by intimate mixing. The suitable dilution of the microemulsion yields the drug nanosuspension by the mechanism described earlier. The influence of the amount and ratio of surfactant to co-surfactant on the uptake of internal phase and on the globule size of the microemulsion should be investigated and optimized in order to achieve the desired drug loading. The nanosuspension thus formed has to be made free of the internal phase and surfactants by means of diultrafiltration in order to make it suitable for administration. However, if all the ingredients that are used for the production of the nanosuspension are present in a concentration acceptable for the desired route of administration, then simple centrifugation or ultracentrifugation is sufficient to separate the nanosuspension.

The advantages and disadvantages are the same as for emulsion templates. The only added advantage is the need for less energy input for the production of nanosuspensions by virtue of microemulsions.

The production of drug nanosuspensions using microemulsions as templates has been successfully applied to the poorly water-soluble and poorly bioavailable antifungal drug griseofulvin, where a significant improvement in the dissolution rate of the drug (three-fold increase) as compared to the commercial product was observed. It was found that the nature of the co-surfactant affected the dissolution rate of the drug nanosuspension, as anticipated (Trotta et al 2003). However, this technique is still in its infancy and needs more thorough investigation.

Formulation considerations

Stabilizer

Stabilizer plays an important role in the formulation of nanosuspensions. In the absence of an appropriate stabilizer, the high surface energy of nano-sized particles can induce agglomeration or aggregation of the drug crystals. The main functions of a stabilizer are to wet the drug particles thoroughly, and to prevent Ostwald's ripening (Rawlins 1982; Müller & Böhm 1998) and agglomeration of nanosuspensions in order to yield a physically stable formulation by providing steric or ionic barriers. The type and amount of stabilizer has a pronounced effect on the physical stability and in-vivo behaviour of nanosuspensions. In some cases, a mixture of stabilizers is required to obtain a stable nanosuspension.

The drug-to-stabilizer ratio in the formulation may vary from 1:20 to 20:1 and should be investigated for a specific case. Stabilizers that have been explored so far include cellulosics, poloxamers, polysorbates, lecithins and povidones (Liversidge et al 1992). Lecithin is the stabilizer of choice if one intends to develop a parenterally acceptable and autoclavable nanosuspension.

Organic solvents

Organic solvents may be required in the formulation of nanosuspensions if they are to be prepared using an emulsion or microemulsion as a template. As these techniques are still in their infancy, elaborate information on formulation considerations is not available. The acceptability of the organic solvents in the pharmaceutical arena, their toxicity potential and the ease of their removal from the formulation need to be considered when formulating nanosuspensions using emulsions or microemulsions as templates. The pharmaceutically acceptable and less hazardous water-miscible solvents, such as ethanol and isopropanol, and partially water-miscible solvents, such as ethyl acetate, ethyl formate, butyl lactate, triacetin, propylene carbonate and benzyl alcohol, are preferred in the formulation over the conventional hazardous solvents, such as dichloromethane. Additionally, partially water-miscible organic solvents can be used as the internal phase of the microemulsion when the nanosuspensions are to be produced using a microemulsion as a template.

Co-surfactants

The choice of co-surfactant is critical when using microemulsions to formulate nanosuspensions. Since co-surfactants can greatly influence phase behaviour, 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 dipotassium glycerrhizinate as co-surfactants, various solubilizers, such as Transcutol, glycofurol, ethanol and isopropanol, can be safely used as co-surfactants in the formulation of microemulsions.

Other additives

Nanosuspensions may contain additives such as buffers, salts, polyols, osmogent and cryoprotectant, depending on either the route of administration or the properties of the drug moiety.

Post-production processing

Post-production processing of nanosuspensions becomes essential when the drug candidate is highly susceptible to hydrolytic cleavage or chemical degradation. Processing may also be required when the best possible stabilizer is not able to stabilize the nanosuspension for a longer period of time or there are acceptability restrictions with respect to the desired route. Considering these aspects, techniques such as lyophillization or spray drying may be employed to produce a dry powder of nano-sized drug particles. Rational selection has to be made in these unit operations considering the drug properties and economic aspects. Generally, spray drying is more economical and convenient than lyophillization. The effect of post-production processing on the particle size of the nanosuspension and moisture content of dried nano-sized drug should be given due consideration.

Advantages of nanosuspensions

Increase in the dissolution velocity and saturation solubility of the drug

This is an important advantage that makes nanosuspensions amenable to numerous applications. The reason

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