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Nanosuspensions: Advantages and disadvantages

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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. The poor water solubility of drugs is major problem for drug formulation. To date, nanoscale systems for drug delivery have gained much interest as a way to improve the solubility problems. The reduction of drug particles into the sub-micron range leads to a significant increase in the dissolution rate and therefore enhances bioavailability. Nanosuspensions are promising candidates that can be used for enhancing the dissolution of poor water soluble drugs. Nanosuspensions contain submicron colloidal dispersion of pharmaceutical active ingredient particles in a liquid phase stabilized by surfactants. Production of drugs as nanosuspensions has been developed for drug delivery systems as an oral formulation and non-oral administration. Currently, efforts are being directed to extending their applications in site-specific drug delivery.This review describes the methods of pharmaceutical nanosuspension production, formulations and pharmaceutical applications in drug delivery as well as the marketed products.

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INTRODUCTION

A nanosuspension is a submicron colloidal dispersion of drug particles which are stabilized by surfactants. A pharmaceutical nanosuspension is defined as very finely dispersed solid drug particles in an aqueous vehicle for either oral and topical use or parenteral and pulmonary administration. 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. Nanoparticles are commonly polymeric colloidal carriers of drugs whereas solid lipid nanoparticles are lipidic carriers of drugs. In nanosuspension technology, the drug is maintained in the required crystalline state with reduced particle size, leading to an increased dissolution rate and therefore improved bioavailability. An increase in the dissolution rate of micronized particles (particle size < 10 μm) is related to an increase in the surface area and consequently the dissolution velocity. Nanosized particles can increase solution velocity and saturation solubility because of the vapor pressure effect.

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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. Furthermore, the saturation solubility is increased as well. Another possible explanation for the increased saturation solubility is the creation of high energy surfaces when disrupting the more or less ideal drug microcrystals to nanoparticles. Dissolution experiments can be performed to quantify the increase in the saturation solubility of a drug when formulated into a nanosuspension[1-4].

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 Oswald 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[5,6].

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.The problem is even more intense for drugs such as itraconazole and carbamazepine as they are poorly soluble in both aqueous and organic media, and for drugs having a log P value of 2. 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[4,5].

Traditional strategies, such as micronization, solubilization using co-solvents, the use of permeation enhancers, oily solutions and surfactant dispersions, which evolved earlier to tackle the formulation challenges, have limited use. Although reasonable success has been achieved in formulating water-insoluble drugs using liposomes, emulsions, microemulsions, solid dispersion technology and inclusion complexes employing cyclodextrins 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[7,8].

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[9,10].

PREPARATION OF NANOSUSPENSIONS

Nanosuspension technology has been developed as a promising candidate for efficient delivery of hydrophobic drugs. This technology is applied to poorly soluble drugs that are insoluble in both water and oils. Preparation of nanosuspensions were reported to be a more cost effective and technically more simple alternative, particularly for poorly soluble drugs and yield a physically more stable product than liposomes; conventional colloidal drug carriers. Nanosuspension engineering processes currently used are preparation by precipitation, high pressure homogenization,emulsion and milling techniques. These techniques and the obtained compounds are summarized in Table 1 and are briefly described in the following sections[11].

I. Precipitation

Using a precipitation technique, the drug is dissolved in an organic solvent and this solution is mixed with a miscible antisolvent. In the water-solvent mixture the solubility is low and the drug precipitates. Mixing processes vary considerably.

Precipitation has also been coupled with high shear processing. Precipitation of an amorphous material may be favored at high supersaturation when the solubility of the amorphous state is exceeded[11,12].

II. High pressure homogenization

High pressure homogenization has been used to prepare nanosuspension of many poorly water soluble drugs. In the high pressure homogenization method, the suspension of a drug and surfactant is forced under pressure through a nanosized aperture valve of a high pressure homogenizer. The principle of this method is based on cavitation in the aqueous phase. The particles cavitations forces are sufficiently high to convert the drug microparticles into nanoparticles. The concern with this method is the need for small sample particles before loading and the fact that many cycles of homogenization are required[13,14].

III. Lipid emulsion/microemulsion

Lipid emulsions as templates are applicable for drugs that are soluble in either volatile organic solvents or partially water miscible solvents. This technique follows an organic solvent or mixture solvent loaded with the drug dispersed in an aqueous phase containing suitable surfactants to form an emulsion. The organic

phase is then evaporated under reduced pressure to make drug particles precipitate instantaneously to form the nanosuspension which is stabilized by surfactants. Another way to produce nanosuspensions is to use an emulsion which is formed by the conventional method using a partially water miscible solvent as the dispersed phase. Nanosuspensions are obtained by just diluting the emulsion. Moreover, microemulsions as templates can produce nanosuspensions[15,16].

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. The drug can be either loaded into the internal phase or the pre-formed microemulsion can be saturated with the drug by intimate mixing. Suitable dilution of the microemulsion yields the drug nanosuspension. An example of this technique is the griseofulvin nanosuspension which is prepared by the microemulsion technique using water, butyl lactate, lecithin and the sodium salt of taurodeoxycholate. The advantages of lipid emulsions as templates for nanosuspension formation are that they easy to produce by controlling the emulsion droplet and easy for scale-up. However, the use of organic solvents affects the environment and large amounts of surfactant or stabilizer are required[17].

IV. Media milling

Media milling is a further technique used to prepare nanosuspensions. Nanocrystal is a patent protected technology developed by Liversidge *et al.*. In this technique, the drug nanoparticles are obtained by subjecting the drug to media milling. High energy and shear forces generated as a result of impaction of the milling media with the drug provide the necessary energy input to disintegrate the microparticulate drug into nanosized particles. In the media milling process, the milling chamber is charged with the milling media, water or suitable buffer, drug and stabilizer. Then the milling media or pearls are rotated at a very high shear rate. The major concern with this method is the residues of milling media remaining in the finished product could be problematic for administration[18,19].

V. Dry co-grinding

Nanosuspensions prepared by high pressure homogenization and media milling using pearl-ball mill are wet–grinding processes. Recently, nanosuspensions can be obtained by dry milling techniques. Successful work in preparing stable nanosuspensions using dry-grinding of poorly soluble drugs with soluble polymers and copolymers after dispersing in a liquid media has been reported. Itoh *et al* reported the colloidal particles formation of many poorly water soluble drugs; griseofulvin, glibenclamide and nifedipine obtained by grinding with polyvinylpyrrolidone (PVP) and sodium dodecylsulfate (SDS). Many soluble polymers and co-polymers such as PVP, polyethylene glycol (PEG), hydroxypropyl methylcellulose (HPMC) and cyclodextrin derivatives have been used.

Physicochemical properties and dissolution of poorly water soluble drugs were improved by co-grinding because of an improvement in the surface polarity and transformation from a crystalline to an amorphous drug. Dry co-grinding can be carried out easily and economically and can be conducted without organic solvents. The co-grinding technique can reduce particles to the submicron level and a stable amorphous solid can be obtained[19-21].

FORMULATIONS OF DRUG NANOSUSPENSIONS

Aqueous or non-aqueous drug nanosuspensions exhibiting a physical long-term stability should be sufficient to place them on the market as liquid products. In general, a dry oral dosage form as tablet or capsule is preferred. In the case of drug nanosuspensions in pure water or in water containing mixtures, they can be used as granulation fluid in the granulation process for the production of tablets or alternatively as wetting agents for the extrusion mass to produce pellets. Spray-drying of the nanosuspension is also possible. The produced powders can then be used again for tablet or pellet production or alternatively be filled in hard gelatin or HPMC capsules[22,23].

The drug nanocrystals produced in non-aqueous media such as oils or liquid/solid PEG can be used directly for filling in capsules. Production of drug nanosuspensions in melted PEG which is solid at room temperature opens further perspectives. Direct filling of capsules with the hot nanosuspension is possible. Alternatively after solidification of the PEG, the drug nanocrystal containing mass can be ground and filled as a powder into the capsules. To summarize, there are different ways to transfer the drug nanocrystals to a final dry oral dosage form for the patient. With regard to parenteral

products, the drug nanosuspensions can be used as they are, a shelf life of up to three years was shown for selected nanosuspensions. Alternatively, lyophilized products can be offered to be reconstituted prior to administration. The current marketed pharmaceutical products utilizing nanosuspensions is presented in Table 2.

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 behind the increase in the dissolution velocity and saturation solubility of the nanosuspensions can be given as follows. According to the Nernst–Brunner and Levich modification of the Noyes Whitney dissolution model equation, the dissolution velocity of the nanosuspension increases due to a dramatic increase in the surface area of the drug particles from microns to particles of nanometer size:

$$\frac{dX}{dt} = \frac{(D\text{-}A)}{h} \times \frac{(C_s\text{-}X)}{V}$$

Where dX/dt is the dissolution velocity, D is the diffusion coefficient, A is the surface area of the particle, h is the diffusional distance, Cs is the saturation solubility of the drug, X is the concentration in the surrounding liquid and V is the volume of the dissolution medium[25-27].

Improved biological performance an increase in the dissolution velocity and saturation solubility of a drug leads to an improvement in the invivo performance of the drug irrespective of the routeUsed[28].

Long-term physical stability

Another special feature of nanosuspensions is the absence of Ostwald ripening, which is suggestive of their long-term physical stability (Peters & Mu¨ ller 1996). Ostwald ripening has been described for ultrafine dispersed systems and is responsible for crystal growth and subsequently formation of microparticles. Ostwald ripening is caused by the differences in dissolution pressure/saturation solubility between small and large particles[29,30].

It is in practice an effect based on the higher saturation solubility of very small particles as compared to larger ones. 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 complete disappearance of the small particles[31,32].

The lack of Ostwald ripening in nanosuspensions 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 the different saturation solubilities and concentration gradients in the vicinity of differently sized particles, which in turn prevents the Ostwald ripening effect[33,34].

Versatility

The flexibility offered in the modification of surface properties and particle size, and ease of post-production processing of nanosuspensions enables them to be incorporated in various dosage forms, such as tablets, pellets, suppositories and hydrogels, for various routes of administration, thus proving their versatility[35].

Characterization of nanosuspensions:

The essential characterization parameters for nanosuspensions are as follows:

Mean particle size and particle size distribution.

The mean particle size and the width of particle size distribution are important characterization parameters as they govern the saturation solubility, dissolution velocity, physical stability and even biological performance of nanosuspensions[36].

Crystalline state and particle morphology.

The assessment of the crystalline state and particle morphology together helps in understanding the polymorphic or morphological changes that a drug might undergo when subjected to nanosizing. Additionally, when nanosuspensions are prepared drug particles in an amorphous state are likely to be generated. Hence, it is essential to investigate the extent of amorphous drug

nanoparticles generated during the production of nanosuspensions. The changes in the physical state of the drug particles as well as the extent of the amorphous fraction can be determined by X-ray diffraction analysis and can be supplemented by differential scanning calorimetry. In order to get an actual idea of particle morphology, scanning electron microscopy is preferred[37,38].

Particle charge (zeta potential).

The determination of the zeta potential of a nanosuspension is essential as it gives an idea about the physical stability of the nanosuspension. The zeta potential of a nanosuspension is governed by both the stabilizer and the drug itself. In order to obtain a nanosuspension exhibiting good stability, for an electrostatically stabilized nanosuspension a minimum zeta potential of _30mV is required whereas in the case of a combined electrostatic and steric stabilization, a minimum zeta potential of _20mV is desirable[39-41].

Saturation solubility and dissolution velocity.

The determination of the saturation solubility and dissolution velocity is very important as these two parameters together help to anticipate any change in the in-vivo performance (blood profiles, plasma peaks and bioavailability) of the drug. As nanosuspensions are known to improve the saturation solubility of the drug, the determination of the saturation solubility rather than an increase in saturation solubility remains an important investigational parameter. The saturation solubility of the drug in different physiological buffers as well as at different temperatures should be assessed using methods described in the literature. The investigation of the dissolution velocity of nanosuspensions reflects the advantages that can be achieved over conventional formulations, especially when designing the sustained-release dosage forms based on nanoparticulate drugs. The dissolution velocity of drug nanosuspensions in various physiological buffers should be determined according to methods reported in the pharmacopoeia[42-44].

In-vivo biological performance

The establishment of an in-vitro/in-vivo correlation and the monitoring of the in-vivo performance of the drug is an essential part of the study, irrespective of the route and the delivery system employed. It is of the utmost importance in the case of intravenously injected nanosuspensions since the in-vivo behaviour of the drug depends on the organ distribution, which in turn depends on its surface properties, such as surface hydrophobicity and interactions with plasma proteins[45,46].

Applications of nanosuspensions in drug Delivery Target drug delivery

Nanosuspensions can also be used for targeted delivery as their surface properties and *in vivo* behavior can easily be altered by changing either the stabilizer or the milieu. Their versatility, ease of scale up and commercial product enable the development of commercial viable nanosuspensions for targeted delivery. The engineering of stealth nanosuspensions by using various surface coatings for active or passive targeting of the desired site is the future of targeted drug delivery systems. Targeting of *Cryptosporidium parvum*, the organism responsible for cryptosporidiosis, was achieved by using surface modified mucoadhesive nanosuspensions of bupravaquone. Similarly, conditions such as pulmonary aspergillosis can easily be targeted by using suitable drug candidates, such as amphotericin B, in the form of pulmonary nanosuspensions instead of using stealth liposomes[47,48].

Oral drug delivery

The oral route is the preferred route for drug delivery because of its numerous well-known advantages. The efficacy or performance of the orally administered drug generally depends on its solubility and absorption through the gastrointestinal tract. Hence, a drug candidate that exhibits poor aqueous solubility and/or dissolution-rate limited absorption is believed to possess low and/or highly variable oral bioavailability. Owing to low oral bioavailability, such a drug candidate would have to be administered in a larger excess than actually required if it were completely bioavailable in order to achieve a therapeutically active concentration, thus making the therapy costly. Orally administered antibiotics such as atovaquone and bupravaquone reflect this problemvery well.Nanosizing of such drugs can lead to a dramatic increase in their oral absorption and subsequently bioavailability[49,50].

Parenteral drug delivery

Nanosuspensions can be administered via different parenteral administration routes ranging from intra-articular via intraperitonal to intravenous injection. For administration by the parenteral route, the drug either has to be

solubilized or has particle/globule size below 5 µm to avoid capillary blockage. The current approaches for parenteral delivery include salt formation, solubilization using co-solvents, micellar solutions, complexation with cyclodextrin and recently liposomes. However, there are limitations on the use of these approaches because of the limitations on their solubilization capacity and parenteral acceptability[51-53].

In this regard, liposomes are much from problems such as physical instability, high manufacturing cost and difficulties in scale-up. Nanosuspensions would be able to solve the problems mentioned above. In addition, nanosuspensions have been found to increase the efficacy of parenterally administered drugs. Paclitaxel nanosuspensions revealed their superiority over taxol in reducing the median tumour burden. Clofazimine nanosuspension, a poorly water-soluble anti-leprotic drug, revealed an improvement in stability and efficacy over the liposomal clofazimine in *M. avium*-infected female mice. Rainbow and co-workers reported an intravenous itraconazole nanosuspension enhanced efficacy of antifungal activity relative to a solution formulation in rats[54-56].

The parenteral route is an invasive route. Parenteral administration of drugs is critical and often associated with the problems such as the limited number of acceptable excipients, restrictions on the quantities of excipients approved for parenteral use, the stringent requirements of the aseptic production process, safety issues, patient noncompliance and biological problems such as allergic reactions and thrombophlebitis. Despite all these limitations, the parenteral route still retains its value because of its special advantages, such as quick onset of action in case of emergency, reduction in dose of the drug and the ability to target the drug quickly to the desired site of action, especially in the case of severe infections. The parenteral route is often employed as an alternative when the drug is either not absorbed through the gastrointestinal tract or undergoes extensive first-pass metabolism[57-59].

Ocular drug delivery

Nanosuspensions can prove to be a boon for drugs that exhibit poor solubility in lachrymal fluids. For delivery of such drugs, approaches such as suspensions and ointments have been recommended. Although suspensions offer advantages such as prolonged residence time in a cul-desac (which is desirable for most ocular diseases for effective treatment) and avoidance of the high tonicity created by water-soluble drugs, their actual performance depends on the intrinsic solubility of the drug in lachrymal fluids. Thus, the intrinsic dissolution rate of the drug in lachrymal fluid governs its release and ocular bioavailability[60,61].

However, the intrinsic dissolution rate of the drug will vary because of the constant inflow and outflow of lachrymal fluids. Hence, suspensions may fail to give consistent performance. However, nanosuspensions, by their inherent ability to improve the saturation solubility of the drug, represent an ideal approach for ocular delivery of hydrophobic drugs. Moreover, the nanoparticulate nature of the drug allows its prolonged residence in the cul-de-sac, giving sustained release of the drug. To achieve sustained release of the drug for a stipulated time period, nanosuspensions can be incorporated in a suitable hydrogel base or mucoadhesive base or even in ocular inserts. An approach that has recently been investigated to achieve the desired duration of action of the drug is the formulation of polymeric nanosuspensions loaded with the drug[62,63].

Pulmonary drug delivery

Aqueous nanosuspensions can be nebulized using mechanical or ultrasonic nebulizers for lung delivery. Basically the nanosuspensions can be used in all nebulizers.The dispersions can be relatively high concentrated. Due to the presence of many small particles instead of a few large microparticles, all aerosol droplets are likely to contain drug nanoparticles. Budesonide, a poorly water-soluble corticosteroid, has been successfully prepared as a nanosuspension for pulmonary delivery. A good relationship was obtained between increasing the drug concentration in the formulation and the number of micrograms of drug delivered per actuation. In addition, bupravaquone nanosuspensions were formulated for treatment of lung infections by using nebulization[63].

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 the drug into the skin[64].

Table 1: Summary of the nanosuspension formation technologies and compounds produced in nanosuspension[9,10].

Technology	Advantage	Disadvantage
Precipitation	-Simple process -Low cost equipment -Ease of scale up	-Drug has to soluble at least in one solvent and that this solvent needs to be miscible with a non-solvent -Growing of drug crystals needs to be limit by surfactant addition
High pressure Homogenization	-General applicability to most drugs -Useful for formation of very dilute as well as highly concentrate nanosuspension -Simple technique -Aseptic production possible -Low risk of product contamination	-High number of homogenization cycles -Prerequisite for drug to be in micronized state and suspension formation before homogenization -Possible contamination of product could occur from metal ions coming off from the wall of the homogenizer
Emulsion/ Microemulsion	-High drug solubilization -Long shelf life -Ease of manufacture	-Use of hazardous solvent -Use of high amount of surfactant and stabilizers
Media milling	-Ease of scale up -Little batch to batch variation -High flexibility in handling large quantities of drugs	-Generation of residue of milling media -Require milling process for hours to days -Prolonged milling may induce the formation of amorphous lead to instability
Dry Co-grinding	-Easy process -No organic solvent -Require short grinding time	-Generation of residue of milling media

Table 2: Current marketed pharmaceutical products utilizing nanocrystalline formation[23,24].

Product	Active Salt	Category	Company
RAPAMUNE	Sirolimus	Immunosuppressant	Wyeth
EMEND	Aprepitant	Antiemetic	Merck
TriCor	Fenofibrate	Treatment of hypercholesterolemia	Abbott
MEGACE	Megestrol acetate	Appetite stimulant	PAR Pharmaceutical
Triglide	Fenofibrate	Treatment of hypercholesterolemia	First Horizon Pharmaceutical

CONCLUSION

Nanosuspensions appear to be a unique and yet commercially viable approach to combating problems such as poor bioavailability that are associated with the delivery of hydrophobic drugs, including those that are poorly soluble in aqueous as well as organic media. The dissolution problems of poorly water soluble drugs have been largely solved to improve drug absorption and bioavailability. Nanosuspension formulations are promising candidates for enhancing the solubility of poorly water soluble drugs. Nanosuspension technology can be combined with traditional dosage forms: tablets, capsules, pellets, and can be used for parenteral products. To take advantage of nanosuspension drug delivery, simple formation technologies and variety applications, nanosuspensions will continue to be of interest as oral formulations and non-oral administration develop in the future.

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