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Nanosuspension Technology for Drug Delivery

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ABSTRACT

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 poorly 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. This review describes the methods of pharmaceutical nanosuspension production, formulations and pharmaceutical applications in drug delivery as well as the marketed products.

Keywords: Nanosuspensions, drug delivery, bioavailability, colloid

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 [1,2]. 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 [1]. 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 [3].

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 [4]. 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.

PREPARATION OF NANOSUSPENSIONS

Nanosuspension technology has been developed as a promising candidate for efficient delivery of hydrophobic drugs [1,4-6]. 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 [1,7]. 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.

Table 1 Summary of the nanosuspension formation technologies and compounds produced in nanosuspension.

Technology	Advantage	Disadvantage	Drug
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	Carbamazepine [25] Cyclosporine [24] Griseofulvin [9] Retinoic acid [11]
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	Albendazole [20] Amphotericin B [44,45,52] Aphidicolin [39] Atovaquone [42-44] Azithromycin [21] Budesonide [49] Bupravaquone [12,13,50,51] Clofazamine [7,44] Disodium cromoglycate [23] Fenofibrate [46] Glucocorticoid drugs [48] Ibuprofen [16] Itraconazole [40] Mitotane [10] Nifedipine [15] Oleanolic acid [19] Omeprazole [14] Paclitaxel [38,44] Spironolactone [18]
Emulsion/ Microemulsion template	-High drug solubilization -Long shelf life -Ease of manufacture	-Use of hazardous solvent -Use of high amount of surfactant and stabilizers	Breviscapine [58] Griseofulvin [17] Ibuprofen [16] Mitotane [10]

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	Cilostazol [59] Danazol [38] Naproxen [27,38]
Dry Co-grinding	-Easy process -No organic solvent -Require short grinding time	-Generation of residue of milling media	Clarithromycin [35] Glibenclamide [30] Glisentide [31] Griseofulvin [30] Indomethacin [36] Naproxen [32] Nifedipine [30,34] Phenytoin [33] Pranlukast [29]

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. The NANOEDGE process (is a registered trademark of Baxter International Inc. and its subsidiaries) relies on the precipitation of friable materials for subsequent fragmentation under conditions of high shear and/or thermal energy [8]. This is accomplished by a combination of rapid precipitation and high-pressure homogenization. Rapid addition of a drug solution to an antisolvent leads to sudden supersaturation of the mixed solution, and generation of fine crystalline or amorphous solids. Precipitation of an amorphous material may be favored at high supersaturation when the solubility of the amorphous state is exceeded. The success of drug nanosuspensions prepared by precipitation techniques has been reported [8-11].

II. High pressure homogenization

High pressure homogenization has been used to prepare nanosuspension of many poorly water soluble drugs [12-21]. 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 [1,17,22-26]. DissoCubes technology is an example of this technology developed by R.H. Müller using a piston-gap-type high pressure

homogenizer, which was recently released as a patent owned by SkyePharm plc [4]. Other technologies and patents which are based on the homogenization processes are shown in **Table 2** [26].

Table 2 Overview of the technologies and patents/patent applications on which the various homogenization processes are based.

Nanocrystal	Company	Patent/patent application examples
Hydrosol	Novatis (prev. Sandoz)	GB 22 69 536 GB 22 00 048
Nanomorph™	Soligs/Abbott	D 1963 7517
Nanocrystal™	Élan Nanosystems	US 5,145,684
Dissocubes®	SkyePharma	US 5,858,410
Nanopure	PharmaSol	PCT/EP00/0635
NANOEDGE™	Baxter	US 6,884,436

III. Lipid emulsion/microemulsion template

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 [4]. Moreover, microemulsions as templates can produce nanosuspensions. 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 [4]. 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 [17]. 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.

IV. Milling techniques

Media milling

Media milling is a further technique used to prepare nanosuspensions [1,4-6,27]. Nanocrystal is a patent protected technology developed by Liversidge *et al.* [28]. 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 [4].

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 [29-31]. Itoh *et al* [30] 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 [29-34]. 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 [29-36]. 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.

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. 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 [26]. 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 3** [37].

Table 3 Current marketed pharmaceutical products utilizing nanocrystalline formation.

Product	Drug compound	Indication	Company	Nanoparticle technology
RAPAMUNE®	Sirolimus	Immunosuppressant	Wyeth	Elan Drug Delivery Nanocrystals®
EMEND®	Aprepitant	Antiemetic	Merck	Elan Drug Delivery Nanocrystals®
TriCor®	Fenofibrate	Treatment of hypercholesterolemia	Abbott	Elan Drug Delivery Nanocrystals®
MEGACE® ES	Megestrol acetate	Appetite stimulant	PAR Pharmaceutical	Elan Drug Delivery Nanocrystals®
Triglide™	Fenofibrate	Treatment of hypercholesterolemia	First Horizon Pharmaceutical	SkyePharma IDD®-P technology

PHARMACEUTICAL APPLICATIONS OF NANOSUSPENSIONS IN DRUG DELIVERY

Parenteral administration

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. In this regard, liposomes are much

more tolerable and versatile in terms of parenteral delivery. However, they often suffer 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 [38]. Similarly, aphidicolin, a poorly water soluble new anti-parasitic lead molecule, when administered as a nanosuspension resulted in an improvement in EC_{50} in comparison to DMSO-dissolved drug [39]. 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 [7]. Rainbow and co-workers reported an intravenous itraconazole nanosuspension enhanced efficacy of antifungal activity relative to a solution formulation in rats [40].

Peroral administration

Nanosizing of drugs can lead to a dramatic increase in their oral absorption and subsequent bioavailability. Improved bioavailability can be 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 nanosuspensions can be used directly in a liquid dosage form and a dry dosage form such as tablet or hard gelatin capsule with pellets. Ketoprofen nanosuspensions have been successfully incorporated into pellets to release the drug over a period of 24 h [41]. The aqueous nanosuspension can be used directly in the granulation process or as a wetting agent for preparing the extrusion mass pellets. A similar process has been reported for incorporating solid lipid nanoparticles into pellets. Granulates can also be produced by spray drying of nanosuspensions. Atovaquone an antibiotic used for treating opportunistic *Pneumocystis carinii* infections for HIV patients, non-complicated *P. falciparum* malaria and leishmanial infections was also prepared in the form of a nanosuspension [42]. Administration of atovaquone as a nanosuspension resulted in an increase in oral bioavailability when compared to the commercial product Wellvone®, which contains the micronized drug [43,44]. This is because of the high adhesiveness of the drug particles sticking on biological surfaces of the epithelial gut wall. Amphotericin B, an antibiotic used for treatment of gastrointestinal mycosis and leishmaniasis lacks good oral bioavailability. However, oral administration of amphotericin B as a nanosuspension produced a substantial improvement in its oral absorption in comparison to the orally administered commercial formulations such as Fungizone, AmBisome and micronized amphotericin B [44,45]. Bupravaquone nanosuspensions have been used for the *Cryptosporidium parvum* infection, the main pathogen causing severe diarrhea in immunosuppressant HIV patients. In comparison to the micronized drug powder, the infectivity score was reduced from 2.0 to 1.47 for micronized bupravaquone and even to 1.02 for equivalent nanosuspensions [44]. In addition, oral fenofibrate nanosuspensions showed bioavailability enhancement in comparison to conventional suspensions of micronized drugs [46].

Ophthalmic drug delivery

Nanosuspensions could prove to be vital for drugs that exhibit poor solubility in lachrymal fluids. Suspensions offer advantages such as prolonged residence time in a cul-de-sac, which is desirable for most ocular diseases for effective treatment and avoidance of 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 fluids governs its release and ocular bioavailability. However, the intrinsic dissolution rate of the drug will vary because of the constant inflow and outflow of lachrymal fluids. One example of a nanosuspension intended for ophathamic controlled delivery was developed as a polymeric nanosuspension of ibuprofen [47]. This nanosuspension is successfully prepared using Eudragit RS100 by a quasi-emulsion and solvent diffusion method. Nanosuspensions of glucocorticoid drugs; hydrocortisone, prednisolone and dexamethasone enhance rate, drug absorption and increase the duration of drug action [48].

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 [49]. 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 [50].

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 [13,51]. 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 [52].

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 [53-57].

CONCLUSIONS

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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บทคัดย่อ

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เทคโนโลยีการผลิตนาโนซัสเพนชันสำหรับระบบนำส่งยา

ความสามารถในการละลายน้ำของยาน้อยเป็นอุปสรรคสำคัญในการพัฒนาตำรับยา การนำนาโนเทคโนโลยีมาประยุกต์ใช้ในการเพิ่มความสามารถในการละลายน้ำของยาได้รับความสนใจเพิ่มขึ้นในปัจจุบัน การที่อนุภาคมีขนาดเล็กในระดับนาโนเมตรจะสามารถเพิ่มอัตราการละลายของยาละลายน้ำยากได้ ซึ่งจะส่งผลต่อการเพิ่มชีวประสิทธิผลของการใช้ยา การเตรียมยาในรูปของนาโนซัสเพนชันซึ่งเป็นรูปแบบที่ให้ผลึกยาในระดับนาโนเมตรกระจายตัวในของเหลวได้อย่างคงตัว เป็นวิธีการหนึ่งที่ทำให้ยาละลายน้ำยากมีความสามารถในการละลายเพิ่มขึ้น ยาเตรียมในรูปแบบนาโนซัสเพนชันสามารถนำไปประยุกต์ใช้ทางเภสัชกรรมในการนำส่งยาทั้งในรูปแบบของยารับประทาน ในรูปยาฉีด หรือระบบนำส่งอื่นๆ ได้ ในบทความนี้ได้รวบรวมเทคโนโลยีในการผลิตยาในรูปแบบนาโนซัสเพนชัน รูปแบบเภสัชภัณฑ์และการประยุกต์ใช้ทางเภสัชกรรมสำหรับระบบนำส่งยา รวมถึงตัวอย่างยาที่วางจำหน่ายในท้องตลาดที่เตรียมในรูปแบบของนาโนซัสเพนชันไว้

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