Current Research in Drug Nanocrystals Technology

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Abstract: *Nanotechnology will affect our lives tremendously over the next decade in many diverse fields, including pharmacy and medicine. Transfer of materials to the nanodimension changes their physical properties which are used in pharmaceutics to develop a new innovative formulation principle for poorly soluble drugs: the drug nanocrystals. Development of poorly soluble and/or permeable drug molecules using nanocrystal formulations has proven to be highly successful due to the greater surface/volume ratio, ensuing in improvements in dissolution and bioavailability as well as enhanced permeability. The drug nanocrystals do not belong to the future; the first products are already on the market. The industrially relevant production techniques, pearl milling and high pressure homogenization, are reviewed and also the physics behind the drug nanocrystals and changes of their physical properties are discussed earlier. Drug nanocrystals consist of the pure poorly water-soluble drug without any matrix material means carrier free drug delivery system. This opinion focuses on recent developments in the preparation of nanocrystals and the role of surface properties on optimizing dissolution and targeted delivery.*

Keywords: *Drug nanocrystals, saturation solubility, dissolution velocity, bioavailability, enhanced permeability, drug delivery*

Introduction

Many new drug candidates exhibit poor water solubility and as a consequence exhibit very low bioavailability after oral administration. This poor solubility of drug is a major challenge for formulation scientists and the nanocrystal technology has emerged as a valuable tool to build the bridge between drug discovery and preclinical application [1-3]. Nanosuspension offers the advantages of enhancement of bioavailability, reduction in variability and diminished food effect after oral administration [2-6]. Crystalline nanosuspensions are defined as colloidal aqueous dispersions of submicron sized active pharmaceutical ingredient (API) crystals and are stabilized by electrostatic and steric stabilizers [2-4]. These submicron 'nanoparticles' have similar benefits to conventional nanoparticles which are less than 100nm but are scalable and can be applied in all existing manufacturing processes and dosage forms [7]. There are two main approaches to produce nanosized API crystals: the 'top down' and the 'bottom up' technologies. The term 'bottom up' summarizes controlled precipitation/crystallization techniques. The 'top down' approach is applied more often. API crystals are downsized by crushing and mechanical attrition process. This is realized by high-pressure homogenization (e.g. the DissoCubes® technology) or by wet media milling (e.g. the NanoCrystal® technology). Stabilizers which adsorb to the particle surface are required to prepare a stable formulation. They protect the submicron sized particles against inter-particle forces leading to aggregation. Polymers (e.g. cellulose derivatives) are used as steric stabilizers and anionic surfactants (e.g. sodium lauryl sulfate or dioctyl sulfosuccinate) typically function as electrostatic stabilizers.

The nanocrystals technology, mainly for the poorly water-soluble compounds can be incorporated into all dosage forms parenteral, solid, and liquid; fast-melt pulsed release and controlled release oral dosage forms. Oral administration is possible as a suspension and more patient convenient dosage forms can be produced by transferring the liquid nanosuspension to solid dosage forms, i.e. tablets or pellets or granules containing capsules. Apart from this, because of their small size the nanosuspension can be injected parenterally and by intravenous injection leading to a 100% bioavailability [8, 9].

It was reported that approximately 28 nano-drugs were on the market by 2009. These products include liposome based formulations, polymeric based nano-drugs, nanocrystals and albumin-bound platform [10]. With the drug nanocrystals invented at the beginning of the 1990s, drug nanocrystals have been developed in pharmaceutical industry at a very fast pace during the last two decades owing to their outstanding advantages. This review focuses on some recent nanocrystalline formulations to enhance solubility as well as dissolution and improve *in vitro* behavior.

Improved pharmacokinetic behavior and bioavailability through nanocrystals formulation

Smet *et al.* developed a nanocrystalline paclitaxel formulation by wet milling technique using Pluronic F127® as stabilizer with a high paclitaxel-to-stabilizer ratio which can be used for hyperthermic intraperitoneal chemotherapy (HIPEC). They evaluated suitability of paclitaxel nanosuspensions for HIPEC treatment by analyzing the cytotoxicity of both formulation as well as stabilizer, and by establishing the maximum tolerated dose (MTD) and bioavailability. Moreover, the effect on tumor growth was evaluated by magnetic resonance imaging (MRI) at day 7 and 14 after HIPEC treatment in rats with peritoneal carcinomatosis of ovarian origin. MRI data after HIPEC treatment with a paclitaxel nanocrystalline suspension showed a significant reduction of tumor volume compared to the non-treated group [11].

Wang *et al.* formulated and evaluated the puerarin nanocrystals *and* for the assessment of the pharmacokinetic parameters the developed formulations have been intravenous administered to beagle dogs. Administration of the puerarin nanocrystals led to a mean plasma profile with almost similarly low variations in comparison to the reference solution, nevertheless with no initial blood peak as observed with the solution formulation. The nanocrystals of puerarin exhibited a significantly ($P < 0.05$) reduced C_{max} and clearance, and a significantly ($P < 0.05$) greater mean residence time, clearance and elimination half-life compared to the puerarin solution. Results of these studies revealed the opportunity to formulate puerarin in nanocrystals for intravenous delivery with higher safety [12].

Oner *et al.* prepared ezetimibe nanocrystals to improve the solubility and dissolution rate by utilizing ball milling, high speed homogenization techniques using pluronic F127 as a surface modifier to stabilize the nanocrystal formulations. Tablets were prepared containing ezetimibe nanocrystals. Consequently, it was found that the dissolution rate of the nanocrystal formulations increased and although tablet formulations which did not contain any solubilizing agent, the dissolution profile of these formulations were found similar to the commercial product [13].

Amighi *et al.* prepared nifedipine nanocrystals to enhance solubility of BCS class II drug using high-pressure homogenization and investigated influence of nifedipine particle size on nifedipine permeation rate across intestinal cell models (Caco-2 and HT29-5M21 cultures and co-cultures). They carried out Apical to basolateral transfer studies across Caco-2 and HT29-5M21 cultures and co-cultures. Caco-2/HT29-5M21 co-cultures (seeding ratio 3:1) were evaluated to better represent *in vivo* intestinal conditions. These studies showed that nifedipine permeation rate across the different *in vitro* models evaluated can be significantly enhanced (≈ 6-fold) by formulation of nifedipine as nanoparticles [14].

Cui *et al.* developed a solid formulation containing nitrendipine nanocrystals for oral delivery using a tandem precipitation-homogenization process followed by spray drying, to convert the nanocrystals into a solid form. Both DSC and X-ray diffraction analysis indicated that nitrendipine was present in crystalline form. *In vitro* dissolution rate of the nanocrystals was significantly increased compared with the physical mixture and commercial tablet. Moreover the *in vivo* testing demonstrated that the C_{max} of the nanocrystals was approximately 15-fold and 10-fold greater than that of physical mixture and commercial tablet, respectively. In addition, the $AUC_{0\rightarrow24}$ of the nanocrystals was approximately 41-fold and 10-fold greater than that of physical mixture and commercial tablet, correspondingly [15].

Zuo *et al.* prepared nanocrystals of fenofibrate by a bead-milling method to study the critical parameters on redispersed particle size of dried nanocrystals as pretabletting material during spray drying process. They studied five types of hydrophilic excipients in combination with sodium dodecyl sulfate. Spray dried powder with a mean redispersed particle size of 699 nm was produced by using mannitol and sodium dodecyl sulfate as supporting agent. They found that the particle size of the nanocrystals strongly influenced by the weight ratio (RF/m) of fenofibrate : mannitol and inlet temperature. Dissolution profiles of tablets prepared with the spray dried powder were similar to the commercial nanocrystal formulation Lipidil™ ez, and faster than that of the micronized formulation. As well as the relative bioavailability of the spray-dried formulation was determined to be 89.6% taking Lipidil™ ez as the reference sample. There were no significant statistic differences of $AUC_{0\rightarrow72}$ and C_{max} between the two formulations [16].

Kumar *et al.* formulated and characterized lecithin complexed glibenclamide nanocrystals and analyzed the effect of PEG 20000 and lecithin on drug properties like particle size reduction and stability of nanocrystals using photon correlation spectroscopy. Studies revealed that pure glibenclamide exhibited an average particle size of 1551 nm and the average particle size of precipitated nanocrystals was between 236 - 7000 nm, while that of complexed nanocrystals was between 155 - 842 nm. Furthermore, DSC studies showed no change in crystalline structure and X-ray powder diffraction studies proved that crystallinity was maintained in nanocrystals. Finally they concluded that lecithin complexed glibenclamide nanocrystals offer enhanced surface properties as well as stability, and can be successfully used in development of various formulations due to its high stability and decreased particle size [17].

Nayak *et al.* formulated nelfinavir mesylate nanocrystals by ball milling to improve its pharmacokinetic behavior. They prepared nanocrystals by ball milling and finally nanocrystals were lyophilized using mannitol as cryoprotectant. The particle size and zeta potential of optimized formulation was found to be 740.12 ± 79.21 nm and 23.31 ± 1.10 mV respectively with polydispersity index of 0.20 ± 0.07. DSC analysis and SEM revealed that there was slight decrease in crystallinity in the nanocrystals compare to the raw crystals. Finally they concluded that nanonisation and reduction in crystallinity was observed by formulating nelfinavir mesylate nanocrystals that will help in increasing dissolution velocity and thereby bioavailability [18].

Mauludin *et al.* formulated ibuprofen nanocrystals by high pressure homogenization incorporated into effervescent and pellet formulations to accelerate the dissolution velocity of ibuprofen for a faster performance. They used Micron LAB 40 (APV Homogenizers, Unna, Germany) for the high pressure homogenization and after 40 homogenization cycle's suitable nanosuspension formulation could be found with average particle size 929 nm and a polydispersity index of 0.157, specify a narrow size distribution. They successfully produced pellets and effervescent powders of ibuprofen nanocrystals and it could be redispersed completely from both formulations [19].

Nakarani *et al.* formulated itraconazole nanosuspension by pearl milling technique using zirconium oxide beads as a milling media, glycerol as a wetting agent to increase the aqueous solubility and to improve its formulation related parameters and poloxamer 407 as a stabilizer, the saturation solubility, dissolution and hence oral bioavailability. Optimized nanosuspension of itraconazole showed spherical shape with surface oriented surfactant molecules and a mean particle diameter of 294 nm. Results revealed that itraconazole nanosuspension represent a promising new drug formulation for oral drug delivery for treatment of fungal infection [20].

Ravichandran *et al.* developed solid dosage capsule form of spray-dried curcumin nanocrystal and compared its dissolution behavior with market capsule in different media with

the aim to obtain a stable nanocrystal loaded drug capsule with an increased drug saturation solubility and dissolution velocity. Results revealed that improved dissolution behavior in nanocrystal-loaded solid dosage forms should lead to better bioavailability of poorly soluble drugs in the body [21].

Du *et al.* produced oral nanocrystal capsules formulations in order to optimize dissolution properties of poorly soluble drug glimepiride and improve its bioavailability. The i*n vitro* dissolution testing of the nanocrystal-loaded capsules of glimepiride showed an evident increase in dissolution rate compared to micronized and market capsules. *In vivo* studies demonstrated a marked enhancement of bioavailability of nanocrystal-loaded capsules, which was superior as compared to the microcrystal-loaded capsules and market formulation. This may in turn reduce the risk of side effect by allowing a reduction in either the dose or its frequency of administration [22].

Conclusion

Drug nanocrystals are considered as one of the most important formulation approaches for poorly soluble drugs at the beginning of this new century. The smartness of technology is that it can be universally applied to practically any drug. Identical to micronisation, it is a universal formulation principle, nevertheless limited to BCS class II drugs. Owing to their great formulation versatility drug nanocrystals are no longer only the last chance rescue for a small number of drugs. Numerous insoluble drug candidates are in clinical trials formulated as drug nanocrystals. Presently, attention is turned to improving the diminution performance to produce drug nanocrystals well below 100 nm, also in cases of very hard drugs. Primary approaches were already successful.

Innovative technologies are in development to produce final dosage forms with higher drug loading capacity, better redispersibility at their site of action, as well as an improved drug targeting.

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