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REVIEW ARTICLE

DRUG NANONIZATION: AN OVERVIEW OF INDUSTRIALLY FEASIBLE TOP-DOWN TECHNOLOGIES FOR NANOCRYSTAL PRODUCTION

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Many drugs are associated with one or more problems in their delivery including, poor bioavailability, *in vivo* stability, solubility, intestinal absorption, sustained and targeted delivery to site of action, therapeutic effectiveness, side effects and plasma fluctuations of drugs which either fall below the minimum effective concentrations or exceed the safe therapeutic concentrations. Extensive research efforts have been reported including micronization, salt formation, pH modification, solid dispersions, complexation, solubilization, hydrotropy etc for addressing one or more of these challenges in order to achieve desired formulation performance. Many of these techniques have been commercialized and still under continuous research. In spite of their potential for improved drug delivery, they suffer from one or more limitations and could not be exploited fully. Recently, various nanonization strategies have emerged to increase the dissolution rates and bioavailability of numerous drugs that are poorly soluble in water. These technologies have been proved to be highly effective not only for improving poor aqueous solubility and bioavailability problems but also in dealing with other formulation challenges. This article overviews the potential of nanonization to overcome many problems associated with modern drug delivery and addresses the salient features of the industrially feasible top-down technologies involved in production of nanocrystals.

Key words: Nanocrystal, Nanosizing, Top-down techniques, Nanonization, Nanoparticles.

INTRODUCTION

Poorly-water soluble compounds comprise a significant and growing percentage of the industries' drug development pipeline and are viewed as highly challenging development candidates. To address this issue, formulation strategies for molecules which belong to BCS class II (poorly soluble and permeable) and Class IV (poorly soluble and impermeable), have been of greatest interest to the formulation scientists. The use of particle size reduction approaches to form stable nanometer size drug nanosuspensions or nanoparticles is a relatively newer formulation strategy (Dahiya *et al* 2007). A number of methodologies can be adapted to improve solubility of poor water soluble drug and further to improve its bioavailability. The techniques generally employed for solubilization of drug includes micronization, salt formation, chemical modification, pH adjustment, solid dispersion, complexation, co-solvency, micellar solubilization, hydrotropy, self-emulsifying drug delivery, microemulsions etc. In past, various research efforts have been reported with potential results employing solid dispersion and

cyclodextrin technology (Dahiya, 2017; 2010; Radhika *et al* 2015; Patel *et al* 2015; Dahiya and Onker, 2015; Dahiya *et al* 2015; Prusty, 2014; Dahiya and Tayde, 2013; Pabreja and Dua , 2011; Dahiya and Kaushik, 2010; Pathak *et al* 2008; Dahiya *et al* 2008; Dahiya and Pathak, 2007, 2006a; 2006b). In spite of potential results achieved, these techniques are associated with one or more limitations which led to their limited commercialization.

Some of the challenges of most drug delivery systems include problems such as poor bioavailability, *in vivo* stability, solubility, intestinal absorption, sustained and targeted delivery to site of action, therapeutic effectiveness, side effects and plasma fluctuations of drugs which either fall below the minimum effective concentrations or exceed the safe therapeutic concentrations (Khanbabaie and Jahanshahi, 2012). Nanotechnology in drug delivery is an approach designed to overcome these problems due to the development and fabrication of nanostructures at submicron scale and nanoscale which are mainly polymeric and have multiple advantages. Nanostructures have the ability to protect drugs encapsulated within them from hydrolytic and enzymatic degradation in the gastrointestinal tract; target the delivery of a wide range of drugs to various areas of the body for sustained release and thus are able to deliver drugs, proteins and genes through the peroral route of administration. They deliver drugs that are highly water insoluble; can bypass the liver, thereby preventing the first pass metabolism of the incorporated drug. They increase oral bioavailability of drugs due to their specialized uptake mechanisms such as absorptive endocytosis and are able to remain in the blood circulation for a longer time, releasing the incorporated drug in a sustained and continuous manner leading to less plasma fluctuations thereby minimizing side-effects caused by drugs. Due to the size of nanostructures, they are able to penetrate into tissues and are taken up by cells, allowing efficient delivery of drugs to sites of action. The uptake of nanostructures was found to be 15-250 times greater than that of microparticles in the 1-10 μm range. Literature has reports indicating that delivered drugs that are highly water insoluble; can bypass the liver, thereby preventing the first pass metabolism of the incorporated drug (Ochekpe *et al* 2009).

At the beginning of the 1990s, the drug nanocrystals were developed as more efficient approach to increase drug solubility and dissolution velocity. Instead of micronizing the drug powder, it is nanonized leading to nanocrystals with a typical size of about 200 nm up to approximately 600 nm. The success of this approach is clearly documented by the short time between invention and the first product on the market in the year 2000 (Rapamune®, Wyeth). With continuation, many products are on the market as well as in various clinical phases. Until now, abundant work has been done in developing production technologies for the nanocrystals. The state of the art first generation technologies such as bottom up (precipitation) and top down (comminution), to the second, improved and smarter drug nanocrystal generation known as second generation technology (SmartCrystals). The review focuses on nanonization concept with special emphasis on industrially feasible top-down Nanocrystals production technologies.

Concept of nano, nanosizing and nanonization

Nanonization is a term for reducing particle size to the nanometer range and brings about several advantages. It further increases the surface area of active pharmaceutical ingredient (API) which could result in enhanced solubility and drug bioavailability. Reducing the particle size of an API possessing poor solubility characteristics can lead to higher specific surface area, thereby increasing bioavailability and dissolution rate. Due to the increased bioavailability a lower amount of API is required which in turn leads to a more cost-efficient product with less risks and side effects for the patient. The term 'nanosizing' is used to reference particle sizes in the sub-micron range, typically 100-200 nm (nanometers, or $1/1000^{th}$ of a micrometer) in size. Nanosizing is typically accomplished by milling the compound in a stabilized solution to the targeted size, which can be further processed into the final dosage form. The process of converting particles to nanosize is known as nanonization. Recently, various nanonization strategies have emerged to increase the dissolution rates and bioavailability of numerous drugs that are poorly soluble in water. These strategies include increasing the surface area to volume ratios of drug powders, changing the crystalline forms and designing novel nanomaterials that can act as carriers for controlled release (Junghanns and Muller, 2008). Nanonization can result in improved drug

solubility and pharmacokinetics, and it might also decrease systemic side-effects (Riehemann *et al* 2009). Nanonization of hydrophobic drugs generally involves the production of drug nanocrystals through either chemical precipitation or disintegration (Junghanns and Muller, 2008). Alternatively, nanotechnology-based drug delivery systems such as nanoemulsions and polymeric micelles can be used. During the past decade, several drug nanoformulations have been clinically approved or are under clinical investigation (Junghanns and Muller, 2008).

Distinct features of nanosized drugs

Drug nanoparticles are a formulation principle for all poorly soluble drugs for which the dissolution velocity is the rate limiting step for absorption and thus the reason for a too low oral bioavailability. This means nanocrystals are made essentially from poorly soluble drugs; water soluble drugs cannot be formulated as nanocrystals at least in aqueous dispersion medium. The increase in surface area leads to an increase in the dissolution velocity according the Noyes-Whitney equation. A fact in the past often overlooked is the increase in the saturation solubility of nanonized compounds compared to micrometer particles, precisely the kinetic saturation solubility increases. The basis for this is the Kelvin equation describing the vapour pressure as a function of the curvature of liquid droplets in a gas phase. Compared to micrometer crystals the nanocrystals lead to a supersaturated solution. This situation is metastable, that means as a function of time crystallisation will be initiated, large crystals will precipitate and the system returns to the thermodynamically stable state of the saturation solubility of micrometer crystals. However, in general duration of this supersaturated state is sufficient for oral absorption. The excellent advantages offered by nanonized drug is possible due to its distinct features *i.e.* increased saturation solubility, increased dissolution velocity and increased adhesiveness to surfaces/cell membranes.

Nanocrystalline particles vs NanoCrystal

Drug nanocrystals are nanoparticles with a crystalline character. The size of a particle to be classified as a nanoparticle, depending on the discipline, *e.g.* in colloid chemistry particles are only considered as nanoparticles when they are in size below 100 nm or even below 20 nm. Based on the size unit, in the pharmaceutical area nanoparticles should be defined as having a size between a few nanometers and 1000 nm (= 1 μm). Drug nanocrystals are particles made from 100% drug; typically they are stabilized by surfactants or polymeric steric stabilizers. Drug nanocrystals do not possess any carrier material as in matrix nanoparticles consisting *e.g.* of a polymeric matrix (polymeric nanoparticles), or a lipidic matrix (nanoemulsions, liposomes and lipid nanoparticles). The nanocrystals are typically produced in a liquid dispersion medium, *i.e.* the nanocrystals are suspended in the liquid. Dispersion of drug nanocrystals in liquid media leads to so called "nanosuspensions" in contrast to the "microsuspensions" or "macrosuspensions". The dispersed particles need to be stabilized, such as by surfactants or polymeric stabilizers. Dispersion media can be water, aqueous solutions or nonaqueous media (*e.g.* liquid polyethylene glycol (PEG), oils). Depending on the production technology, processing of drug microcrystals to drug nanoparticles can lead to an either crystalline or to an amorphous product, especially when applying precipitation.

NanoCrystal is a patent protected technology (Liversidge *et al* 1992) in which the drug nanoparticles are obtained by subjecting the drug to media milling (*e.g.* water, stabilizer solution or buffer). High energy and shear forces generated as a result of impaction of the milling media or beads with the drug providing necessary energy input to disintegrate the microparticle drug into nanonized particles. This technique provides advantage of producing very viscous suspensions with 20-30% higher solid content that cannot be produced with HPH, which can be further diluted with stabilizer solution to produce desired concentration of nanosuspension. The major concern with this method is the residues of milling media remaining in the finished product could be problematic for administration. This technology was extended further by Muller group where nanosuspension prepared by combination technology (CT) process, milling followed by HPH, to get more stable nanosuspension.

The pharmaceutical benefits of nanocrystals include improvement in formulation performance, such as enhanced dissolution velocity and saturation solubility, reproducibility of oral absorption, improved dose-bioavailability, proportionality and increased patient compliance *via* reduction of number of

oral units to be taken. Nanocrystal serves as ideal delivery system for oral drugs having the dissolution velocity as rate limiting step for absorption, *i.e.* drugs of the biopharmaceutical classification system (BCS) class II and IV. In addition, nanocrystals can be injected intravenously as aqueous nanosuspensions. The first product Emend® was on the market in 2000. Nanocrystals, a new carrier-free colloidal drug delivery system with a particle size ranging from 100 to 1000 nm, is thought as a viable drug delivery strategy to develop the poorly soluble drugs, because of their simplicity in preparation and general applicability.

Nanocrystals fundamentally possess two most important properties; increase in dissolution velocity and increase in saturation solubility, which are considered to be the main reasons for the increased dissolution velocity and thus increased bioavailability.

Nanocrystal production technologies

There are several production techniques to produce drug nanocrystals. Two basic approaches are involved in production of nanocrystals,

- the top–down technologies (comminution)
- the bottom-up technologies (controlled precipitation/crystallization) and
- combination technologies

The industrially relevant methods are the top down technologies starting from a large-size drug powder to be reduced in size. The bottom up technologies (starting from a dissolved molecule, precipitation) include the need for solvent removal, the difficulty in controlling the process, and the fact that many poorly soluble drugs are poorly soluble not only in aqueous, but also organic media. The drug is dissolved in a solvent and subsequently added to a nonsolvent, leading to the precipitation of finely dispersed drug nanocrystals. Typically, the drug nanocrystals are generated in a liquid dispersion medium (*e.g.* by precipitation or a disintegration process). The obtained product from this process is a suspension of drug nanocrystals in a liquid stabilized by a surfactant or polymer (so-called 'nanosuspension'). The drug nanocrystals can be administered using very different administration routes. Oral administration is possible as a suspension. More patient convenient dosage forms can be produced by transferring the liquid nanosuspensions to solid dosage forms, *i.e.* tablets or pellets or granulate containing capsules. In addition, because of their small size, the nanosuspensions can be injected parenterally, especially intravenously. The schematic of basic nanocrystal production technology is depicted in **Figure 1** (Srivalli and Mishra, 2016).

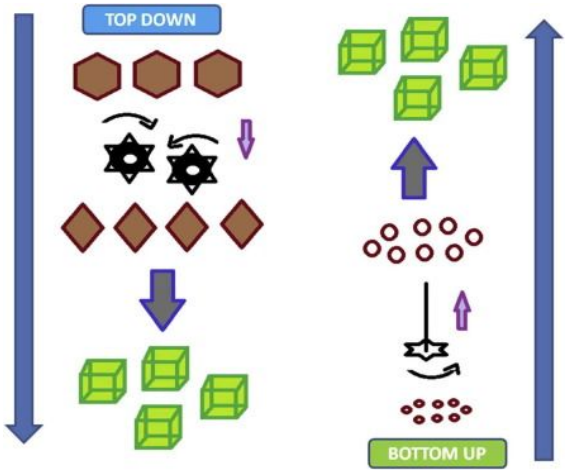

Figure 1. Basic approaches for nanocrystal production technology (NPT)

First generation top down technologies for nanocrystal production

In the top down technologies, one starts from large crystals in the micron range and goes down to the nanodimension by diminuting the crystals, *i.e.* performing a milling process. Many techniques including dry milling, wet milling, media milling (pearl/bead milling), high pressure homogenization, and cryogenic milling have been attempted and investigated for various drugs. Among these, two major processes extensively used are pearl milling and high pressure homogenization. All the aforementioned technologies allow nanocrystals production in the size range of about 200 nm to 1000 nm. When moving toward or below 100 nm, the processes become more tedious. Even running up to 20 passages changes very little in the size of the bulk population after about 10 passages. With small milling beads of 50 μm, there is a lack of large-scale production lines using such small beads, thereby developing and building them would be relatively costly. This means that larger quantities of ultra-fine drug nanoparticles cannot be produced with reasonable efforts. High pressure homogenization (HPH) is limited by the pressure applicable in production lines under industrial conditions. For many drugs, it was observed that the smallest achievable size was in the range 150-200 nm when applying high pressure

homogenization. The 'standard' production conditions that are often applied are 1500 bar and 20 homogenization cycles, sometimes even 40 homogenization cycles.

Increasing the homogenization pressure from 1500 to 3000 bar and above had very little effect on further reducing the size. Therefore, there is a need for process modifications available making ultra-fine drug nanoparticles more accessible. A brief overview of first generation top-down techniques is summarized in **Table 1**.

Table 1. Summary of top down techniques

Technique	Remarks
Dry milling (*e.g.* jet milling)	Nanosuspensions in this case are prepared by dry grinding of poorly soluble drugs with soluble polymers and copolymers. Polymers and co-polymers like polyvinylpyrrolidone (PVP), sodium dodecylsulfate (SDS), polyethylene glycol (PEG), hydroxypropyl methylcellulose (HPMC), and cyclodextrin derivatives are used in dry co-grinding techniques for preparation of nanosuspensions.
Wet milling	Wet milling involves size reduction of drug particles suspended in a liquid medium that may be aqueous or non-aqueous in nature. Wet milling is particularly suited for potent drugs and drugs which possess high residual moisture contents (>50% moisture) because dry milling may be problematic for drugs of this nature Drug particles are dispersed in surfactant/stabilizer solution to obtain macrosuspension which is further subjected to milling energy.
Media milling	Media milling can be considered a modernized version of the ball mill. In media milling, mechanical attrition and impaction of the suspended drug particles are brought about by grinding balls, often termed as the milling media, constructed out of a variety of material such as glass (yttrium-stabilized), zirconium oxide, ceramics or highly cross-linked polystyrene resins [
Pearl mill/bead mill	In media milling, when Pearl balls and beads are used, the techniques are termed pearl and bead milling respectively. A low energy milling process using milling pearls of 0.2 mm to 0.6 mm size moved by agitator. The crystals are ground between the moving pearls and the resulting product is nanosuspensions. Commercially, this is the most successful technique
High pressure homogenization	The drug powder is first dispersed into an aqueous surfactant solution and passed through a homogenizer to obtain a desired size range. The process uses a jet stream homogenizer that is Microfluidizer. The high energy fluid stream of suspension collides; in the collision zone, the crystals are diminuted by collision and cavitation. The pressures, number of cycles, and concentration of drug are the factors that dictate the final product. The advantages include homogenous particle size distribution, reproducibility, lower production time, and continuous production. Technology is called IDD technology.

Piston-gap homogenizer	An alternative to high energy method. The suspension passes with a high velocity (*e.g.* 500 m/s) a small gap, *e.g.* 10 microns in height. In the gap, the crystals are diminuted by cavitation, collision of crystals with each other, the steel wall and the shear forces of the liquid. Trade name of this technology is DissoCubes®. Typical production conditions are 1500 bar and up to 20 passes through the high pressure homogenizer. All homogenization processes are performed with water suspension.
Cryogenic milling	Size reduction begins when the externally-applied stress induces sufficient strain within the particles and causes the formation of cracks. The cracks are then propagated through lines of weaknesses in the material, with new cracks being initiated and perpetuated along the way at other discontinuities. Cryogenic milling or cryomilling in short, is a size reduction method specially catered to soft, elastic/plastic, nonbrittle and thermolabile materials. Cryomilling enables the production of both micron and nano-sized particles but it has not been widely adopted in the pharmaceutical industry for the milling of drugs.

The known limitations of the first generation/ standard standard processes (WBM, HPH) for the production of drug nanocrystals are the necessity of a micronized drug as the starting material and the long runtimes for the top-down equipment. The combinative particle size reduction techniques have been developed to overcome these drawbacks and to improve the particle size reduction effectiveness of the standard processes.

Second generation/combinative nanocrystal production technologies

Second generation technologies employ combination technologies and have been developed to obtain nanocrystals with improved properties. The SmartCrystal approach or technology is a toolbox of different combination processes for the production of nanocrystals. Within SmartCrystal toolbox, process variations can be chosen *e.g.* homogenization in water-ethanol mixtures or addition of additives which promote crystal dilution (Keck *et al* 2008). Nanocrystals of the second generation can be produced using modifications of the basic production technologies. These are, in general, combination technologies. Nowadays, five combinative methods are known: NANOEDGE (microprecipitation followed by a high-energy step such as HPH), H69 (microprecipitation immediately followed by HPH, also called "cavi-precipitation"), H42 (spray-drying followed by HPH), H96 (freeze-drying followed by HPH), and the CT combinative technology (media milling followed by HPH) (Shegokar and Muller, 2010). The approach of the SmartCrystal process is to modify the starting material in such a way that it can be better broken down by high pressure homogenization. This means that the SmartCrystal technology is basically a combination technology, a first pre-treatment step is combined with a second high pressure homogenization step (**Table 2**). The improvements achieved through these technologies mainly include faster production of nanocrystal, higher physical stability, improved *in vivo* performance of smartcrystals. Combinative processes such as the H42, H96, H69, and the NANOEDGE technologies enable the direct processing of a drug solution after synthesis without previously performing a crystallization step. However, as the H69 and NANOEDGE technologies involve the precipitation of particles in liquid media that usually contain organic solvents, these nanosuspensions are not ready to be used further. Extra drying steps need to be performed to eliminate the organic solvent content, which makes the process longer, more expensive, and more complicated regarding regulatory aspects (Shegokar and Muller, 2010; Teagarden and Baker, 2002).

Table 2. Some SmartCrystal processes

Process	Pre-treatment	Main treatment
H42	Spray-drying	High pressure homogenization
H69	Precipitation	High pressure homogenization
H96	Lyophilization	High pressure homogenization
Combination Technology (CT)	Bead milling	High pressure homogenization
NANOEDGE	Microprecipitation	High pressure homogenization

On the contrary, when employing the H42 and H96 technologies, the organic solvent necessary to dissolve the poorly soluble drugs is eliminated during the bottom-up step. In this manner, the nanosuspensions produced with the dried intermediates can be directly used or down-streamed for the production of solid dosage forms (Amidon *et al* 1995; Keck, 2009). In general, the combinative particle size reduction processes perform faster than the standard methods to produce nanosuspensions and achieve smaller final mean particle sizes.

CONCLUSION

Drug nanocrystals are considered as one of the most important formulation approaches for poorly soluble drugs when simple approaches such as solubilization, self-emulsifying drug delivery systems (SEDDS) and micro-emulsions, do not work. As the optimized nanocrystals formulations, this approach can reduce distinctly the side effects, and therefore, they might also replace existing products. First generation standard top down technologies produce nanocrystals in the size range of 200-1000 nm. These processes become more tedious when moving towards and going below 100 nm. However, ultra-fine drug nanocrystals with a size below 100 nm are clearly superior to the larger nanocrystals of the first generation and offer many potential advantages. In this context, second generation combinative technologies such as H42, H69 and H96 production, processes have been developed to provide ultra-fine nanocrystals on the lab scale. However, these processes still need to be established on a larger scale. Although the costs for these technologies is a considerable parameter; if these technologies enable highly promising new chemical entity to be put as product on market covering a real therapeutic need, the cost factor could be neglected.

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