SMART CRYSTALS TECHNOLOGY: A REVIEW
Amol D. Gholap*1, Santosh S. Borude1, Anand M. Mahajan1

1- Department of Pharmaceutics, Sharadchandra Pawar College of Pharmacy, Otur, MS, India-412409

*Address for correspondence
Mr. Amol Dilip Gholap
Department of Pharmaceutics, Sharadchandra Pawar College of Pharmacy, Otur, Tal-Junner, Dist- Pune, MS, India-413706.
Mob. No: +91-9766867053
E-mail- amolgholap16@gmail.com

Summary
Drug nanocrystals are a formulation approach for poorly soluble drugs and cosmetic actives invented at the beginning of the 1990s and having the first pharmaceutical product in 2000. The nanocrystal technology of the first generation is briefly reviewed, i.e. mainly ball milling and high pressure homogenisation (HPH) in water. SmartCrystals as second generation of the drug nanocrystals differ in their physicochemical properties. The production has been optimised by introducing modifications to the HPH process. This leads to faster production, smaller nanocrystals and an improved physical stability. This has also implications for improved in vivo performance after dermal application and oral or intravenous administration.

Keywords: Nanocrystals, Smart crystals, Technology, Solubility.

Introduction
The number of poorly soluble drugs and drug candidates (new chemical entities) is steadily increasing. About 40 % of the drugs in the pipeline and e.g. up to 70 % of molecules coming from synthesis have solubility problems and consequently poor oral bioavailability and delivery problems. The term “poor solubility” of a drug does not relate to a certain solubility concentration. It is compound-specific, that means a compound is poorly soluble in case its oral single dose does not dissolve in 250 ml gastric/intestinal fluid or a compound cannot be injected intravenously in an acceptable injection volume for a single dose. Since many years the approaches to increase drug solubility are solubilisation by surfactants, complex formation (e.g. cyclodextrins, macromolecules) self-emulsifying drug delivery systems (SEDDS), microemulsions and especially for oral administration micronisation of drug powders. At the beginning of the 1990s the drug nanocrystals were developed as more efficient approach to increase drug solubility and dissolution velocity. Instead of micronising the drug powder, it is nanonised 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. Meanwhile five products are on the market; about 20 products are estimated to be in the various clinical phases. These nanocrystals represent the first generation. This article focuses on the second, improved and smarter drug nanocrystals
Drug nanocrystals can be produced by bottom up technologies (precipitation methods) or alternatively by top down technologies (size reduction methods). The present most industrially feasible methods are the top down technologies, all products on the market are made by size reduction. The major two processes are ball milling (NanoSystems/élan technology) and high pressure homogenisation, either in water or in nonaqueous water-reduced media. Disadvantages of the ball milling process are the relatively long milling times in case of hard drug material, the limited scaling up ability (the weight of the ball mill and the milling material limit maximum size), and potential contamination of the milling material by erosion from the milling pearls. Nanocrystal production by high pressure homogenisation (HPH) requires typically 10–20 homogenisation cycles at pressures of e. g. 1000–1500 bar. Metal contamination from the homogeniser is obviously not a problem. However, despite when using a high capacity homogeniser with one ton product per hour, acceleration of production by reduction of the homogenisation cycle number would be desirable. An interesting drug nanoparticle product is Nanomorph®, amorphous drug nanoparticles. They are produced by a controlled precipitation process yielding spherical, amorphous nanoparticles (Soliqs/Germany). From the theoretical point of view they are the best formulation principle because amorphous materials possess in general higher kinetic saturation solubility compared to crystalline materials.

**Special properties of nanonised 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. 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 nanonised 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. In general amorphous material possesses a higher saturation solubility compared to crystalline material; e. g. itraconazole amorphous has a 60 times higher solubility than in the crystalline state. Therefore, to achieve highest supersaturation, the ideal drug nanoparticles should not be crystalline (drug nanocrystals) but amorphous (Nanomorph technology). The prerequisite for using this approach is that the amorphous state can be preserved. However, it has been shown that preservation of amorphous conditions or solid solutions for the shelf-life of pharmaceutical products is possible e. g. the SDD technology by Pfizer, spray-dried dispersions.

**Improvements by second generation technology**

Faster production of nanocrystals to obtain nanocrystals of the second generation with improved properties, combination technologies has been developed for their production. The smartCrystal technology is a tool box of different combination processes for the production of nanocrystals. In addition, within the smartCrystal tool box additionally process variations can be chosen, e. g. homogenisation in water-ethanol mixtures or the addition of additives which promote crystal diminution. The process H42 is a combination of spray drying with subsequent high pressure
homogenisation. At the end of the synthesis of the drug, in the final step no crystallisation is performed but spray-drying of the drug solution. The obtained micrometer size spray-dried product is then dispersed under stirring in a surfactant solution and this suspension passed through a homogeniser. Nanocrystal suspensions can be obtained in one to a few homogenisation cycles. Without having too much additional effort in the drug synthesis step, drug nanocrystal production is much faster. \(^{10,11,12}\)

**Smaller nanocrystals**

The lower size limit achievable under industrially applicable conditions of large-scale production is about 200 nm for ball milling and for HPH. Applying special running parameters and very small sized milling balls, a size of around 100 nm is also feasible with ball milling. However, this is a rather tedious process. The H96 process is a combination of lyophilisation and HPH. Again, in the last step of drug synthesis no crystallisation of the drug is performed, but the drug solution is lyophilised. In the next step the lyophilised product is dispersed in a surfactant solution which is immediately passed through a homogeniser. This yields nanocrystals with a size of about 50 nm, as shown e. g. for Amphotericin B. Such small nanocrystals are interesting for certain applications. \(^{13,14,15}\)

Higher physical stability another process variant of smartCrystal technology is the combination of ball milling and subsequent HPH (process CT). It is not meaningful to perform a size reduction in the low micrometer range by HPH in case simpler, more economic milling techniques can be used. Therefore also for the first drug nanocrystal generation it was recommended to micronise the drug powder by e.g. jet milling before homogenizing it. In the process CT the macrosuspension is premilled using a ball mill. Pre-milling is performed until a mean diameter somewhere in the range 600 nm to 1.5 µm is obtained. In the subsequent HPH process a further reduction is achieved and at the same time the nanocrystals get more uniform, an important parameter to avoid Ostwald ripening. In addition it was found when comparing nanocrystals of similar size produced either with a ball mill or by combination of ball mill and HPH, the latter product showed an increased stability against electrolytes. In addition these nanosuspensions showed an increased physical long-term stability during storage, e. g. hesperidin. \(^{16,17,18}\)

**Improved in vivo performance of smart crystals dermal application**

Surprisingly the pharmaceutical interest in nanocrystals focussed only on oral administration and intravenous injections. Completely forgotten was the dermal application. Normally cosmetic industry watches closely pharmaceutical developments to exploit them for cosmetic products (e. g. liposomes). Also cosmetic industry forgott the nanocrystals. Nanocrystals can increase the penetration of poorly soluble cosmetic and pharmaceutical actives into the skin. The increased saturation solubility leads to an increased concentration ingredient, thus promoting passive penetration. Molecules penetrated into the skin are very fast replaced by new molecules dissolving from the nanocrystal depot in the cream. The first four cosmetic nanocrystal products were launched by Juvena. \(^{19,20}\)

**Oral administration of smart crystals**

Oral bioavailability enhancement when administering poorly soluble drugs as nanocrystals is well documented in the literature, also by the five pharmaceutical products being placed on the market since 2000. The fast dissolution of nanocrystals allows to optimally exploiting an absorption window in the gut. The difference between fed and non-fed state is distinctly reduced. Compared to macrosuspensions, not only the bioavailability is enhanced, but also often
nanosuspensions can be made more concentrated (less application volume) and be formulated less viscous (easier to swallow) (e.g. product Megace® ES). One problem drug nanocrystals are facing in the gut is the presence of electrolytes. The electrolytes reduce the nanocrystal zeta potential leading to nanocrystal aggregation. In case of pronounced aggregation, the aggregates dissolve much slower and the formulation looses the advantages of nanocrystals. Therefore the enhanced physical stability (long-term, but also against electrolytes) of smartCrystals is beneficial for oral products.\textsuperscript{21, 22}

**Intravenous injection of nanosuspensions**

In principle aqueous nanosuspensions are an ideal formulation approach to overcome side effects of i. v. formulations due to not very well tolerated excipients (example: Paclitaxel formulated with Cremophor EL in the product Taxol®; Itraconazole formulated with cyclodextrine in the product Sporanox®). However, injection of the first generation of nanosuspensions leads to a different pharmacokinetics compared to injecting the drug solutions. Nanocrystals above 200 nm do not dissolve fast enough; they are taken up by the macrophages of the liver, potentially targeting toxicity to the liver. In case nanosuspensions of very small nanocrystals (smartCrystals) are injected, they dissolve much faster due to their nanocrystals size well below 100 nm. Therefore they are considered to be better suited to minimize/avoid uptake by the liver and to mimic intravenously injected solutions.\textsuperscript{23, 24}

**Conclusions**

Drug nanocrystals are considered as one of the most important formulation approaches for poorly soluble drugs at the beginning of this new century. Of course each formulation should be as simple as possible. Nanocrystals are considered as first choice in case simpler formulation approaches as e.g. oily solutions/microemulsions in soft gels do not work. The number of poorly soluble actives which cannot be formulated by traditional approaches is steadily increasing. In addition optimized nanocrystals formulations can reduce distinctly side effects; therefore they might also replace existing products. Each system can be improved which was achieved with the smartCrystals as second generation of drug nanocrystals.

**Acknowledgement**

Authors wish to express their sincere thanks to Mr. Vilas Tambe Patil, President Sharadchandra Pawar College of Pharmacy, Otur, Tal-Junner, and Dist- Pune, MS, India-413706 for their constant support and encouragement.

**References**

