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Short review (expert opinion)

Twenty years of drug nanocrystals: Where are we, and where do we go?

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1. How it started

Drug nanocrystals were invented at the start of the 1990s, based on the dates of the first patent filings by Nanosystems (now Élan) [1], RTP Canada (now SkyePharma Canada) [2] and DDS Drug Delivery Services GmbH (IP now owned by SkyePharma) [3]. Pioneering work was performed by Liversidge et al. at Nanosystems [4–6]. Initially, companies were reluctant to use nanocrystal technology to formulate poorly soluble drugs. Pharmacists have attempted to conservatively solve this problem using available, proven technologies instead.

2. Where are we now in 2011?

Attitudes towards nanocrystals have changed, and the first oral product, Rapamune by Wyeth, was launched in 2000. In the meantime, other products have entered the market, including Tricor®, the re-formulation of fenofibrate. Approximately twenty products are currently under clinical trial, several of which are listed in the references [7–9].

3. Why did the reluctant attitude towards nanocrystals change?

We believe that companies realized that, with several compounds, the established technologies were no longer functional. The first major problem was that the new compounds were becoming progressively less soluble. The old solubilization technologies were unable to adequately solubilize these molecules. In addition, many compounds were simultaneously poorly soluble in aqueous media and organic solvents, which excluded solvent mixtures, microemulsions, etc. as formulation approaches. Nanocrystals became the last option to "save" a molecule for the market. A very important consideration for a technology is the ability to use it in products on a large scale, and a contract manufacturer must be available. This was the case when Nanosystems provided their facilities towards the end of the 1990s.

4. What is the current decision tree for formulation development?

The principle pharmaceutical paradigm is to render a formulation as simple and cost-effective as possible. To some extent, nanocrystals are more complex and/or costly than other formulations. Therefore, simpler formulations (e.g. oil- or microemulsion-filled capsules for oral delivery) remain the first choice. The next option that needs to be selected is certainly nanocrystal formulation. Given that approximately 70–90% of new molecules have solubility issues (classes II and IV in the biopharmaceutical classification system); many molecules will need to be evaluated as nanocrystal formulations.

5. How scientific is nanocrystal production?

The first public grant application for nanocrystal technology was soundly rejected as being non-scientific because it was classified as simple milling for size reduction. Size reduction is not science, and instead, nanocrystal formation is only a part of the product development that the pharmaceutical industry should perform. The science behind nanocrystals was not clearly recognized. In fact, nanocrystal development requires multidisciplinary knowledge, including knowledge of crystal formation, the physical background of crystal stability, formulation processing and affecting fates *in vivo*. Initially, even the industry might have considered this to be a very simple process, and some essential complementary research was not performed, leading to developmental failure [9].

6. What are the marketing options for nanocrystals?

In the beginning, nanocrystals were considered to be novel formulations for placing products on the market. Since, the potential of life-cycle management has been realized. Off-patent drugs can be reformulated in a smarter nanocrystal formulation, providing clear pharmaceutical advantages and securing sales. A classic example is Tricor®. Fenofibrate nanocrystals exhibit a reduced difference between their fed and unfed states and their dose could be reduced [8]. In addition, nanocrystals may provide new treatment options (e.g. targeted intravenous (i.v.) delivery). Completely new products could also be generated.

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7. What formulations were expected to result from nanocrystals? Why did some reach the market and others not?

In the beginning, nanocrystals were considered for use in oral, i.v. [4] and pulmonary [10] administration routes. After almost twenty years of nanocrystal development, several oral products, one injectable product and no i.v.-injectable or pulmonary products are on the market. There are two reasons why we mainly have oral nanocrystal products: the oral market is the largest market segment and oral products are easier to manufacture.

Intravenous products are more complex. One idea was to replace the toxicologically problematic i.v. products on the market with well-tolerated injectable nanosuspensions. Examples are Taxol (paclitaxel) containing Cremophor EL (for anaphylactic reactions) and Sporanox (itraconazole) solubilized in cyclodextrin (for nephrotoxicity). However, the injected nanocrystals dissolved too slowly, and the crystals were phagocytosed by liver and spleen macrophages. This resulted in different pharmacokinetics compared to the commercial products, which are solutions [11,12]. Generic products could not be produced. Therefore, research on the use of small crystals that dissolve quickly and mimic solution pharmacokinetics is necessary [13].

Pulmonary products are essentially feasible. Nanosuspensions can be aerosolized using commercial nebulizers [14], but no products have been created. The reason may be commercial and not technical. It makes little sense to replace a well-selling product with a nanosuspension simply because pulmonary deposition might be superior. The cost of market introduction is too high. Even with a new molecule, an established routine delivery technology is preferable.

8. How successful are nanocrystals compared to other nanotechnologies?

Many nanotechnology delivery systems have been developed since 1986, the year that liposomes were introduced into the market. (The first cosmetic product was Capture by Dior, and the first pharmaceutical products were introduced around 1990.) Most nanosystems remained in the laboratory and very few entered the market. By considering cyclodextrin complexes, micelles and drug-loaded i.v. nanoemulsions as nanosystems, until the introduction of the nanocrystals, liposomes may still have performed the most optimally. Strictly speaking, one should also consider their cosmetic use and commercial success. Liposome cosmetics continue to be sold.

Their performance criteria are the number of products and of course, the related sales. Some pharmaceutical liposome products perform very well, but the costs for treatment and their broad use are too high. An example is Ambisome®: it does not exhibit nephrotoxicity, but the treatment costs are in the range of about $1000 per day. However, the treatment costs are approximately $10 when using the amphotericin solution. In contrast, nanocrystal technology may be less expensive and have fewer physical stability problems compared to liposomes. With Tricor®, the first nanocrystal blockbuster on the market, annual US sales exceed $1 billion. When considering products in clinical trials, judging nanocrystals as the most successful pharmaceutical nanotechnology product of the last twenty years appears justified.

9. What will come in the future?

The pharmaceutical nanocrystal product landscape will change. Even more products are expected to arrive because the covering patents (e.g. the patents owned by Élan and SkyePharma) are invalidated or will expire. This gives companies free access to this technology. Fenofibrate nanocrystal products have already been fully developed by companies to be placed on the market after their patents expire. However, it should be noted that we are discussing first-generation technologies (i.e., "simple" nanocrystals). Only these are freely available. Of course, these will suffice for many applications.

However, for more challenging delivery problems, a second generation of smarter nanocrystals is required. These include nanocrystals that are $\ll$100 nm in size, immediately dissolve after i.v. injection and mimic solution pharmacokinetics. Of course, these are more difficult to produce, especially on a large industrial scale and with acceptable quality. These will be the new generic versions of paclitaxel, etc. Other smarter crystals are coated with polymers to enable them to travel to the target site without dissolving. Such nanocrystals can also be used to specifically target intracellular sites. Intracellular delivery of nanocrystals has generally been neglected until recently.

In addition, we will have more efficient production technologies. This can be realized by combining a pretreatment step with subsequent diminution (e.g., via high-pressure homogenization or bead-milling). Patent applications in this area have already been filed (e.g. H42, H69, etc.), but scientific and developmental work is still required to render these processes industrially feasible for products [8,9]. It is certain that such products will arrive on the market, but the time period ultimately required for this remains unsure. Both scientific progress and the relevant health insurance systems need to be determined. Science can create an extremely intelligent delivery system, but the health system may be unable to pay for it.

10. Future nanocrystal innovations in non-pharmaceutical contexts

A delivery system can be used to deliver many different active substances. Therefore, to fully exploit the ability of a system, it should be used in various areas. Generally, the cosmetics industry closely monitors developments in the pharmaceutical industry and transfers these ideas to their products. Examples include liposomes and cosmetic microemulsions. Surprisingly, with respect to nanocrystals, the cosmetics industry failed to "climb on the bandwagon". With respect to liposomes, Dior was four years ahead of the pharmaceutical industry. The first pharmaceutical nanocrystal product appeared in 2000. The first cosmetic nanocrystal product was Juvedial age-decoder face cream and face fluid in 2007 (Juvena Switzerland), which was followed by Platinum Rare (La Prairie). In the future, many more cosmetic products can be expected.

Another interesting area is the field of nutraceuticals. Many active nutraceuticals possess a low oral bioavailability (e.g., coenzyme Q10). Advertisements are already promising 100% bioavailability (solubilization) using nano-Q10. Nanocrystals could be broadly applied to such products. However, a prerequisite is that such products need to display the composition on the label and regulations require some proof of bioavailability. Only this would enable bioavailable and more expensive nanocrystal nutraceutical products to exhibit market differentiation with respect to non-bioavailable products that have already been commercialized.

Furthermore, other application areas can be imagined (e.g., agrochemical formulations and the delivery of poorly soluble, plant-adhesive pesticides). However, for such areas, achievable prices are the main limitation. Many nanocrystal products would be more expensive and farmers may prefer to use cheaper products instead of more environmentally friendly, but costly nanocrystal products. Hopefully, additional options will emerge in the next twenty years of nanocrystals.

References

[1] G.G. Liversidge, K.C. Cundy, J.F. Bishop, D.A. Czekai, Surface modified drug nanoparticles, United States Patent 5145,684, 1992.

[2] S. Khan, G.W. Pace, Composition and method of preparing microparticles of water-insoluble substances, US Patent 6337092, 2002.

[3] R.H. Müller, R. Becker, B. Kruss, K. Peters, Pharmaceutical nanosuspensions for medicament administration as systems with increased saturation solubility and rate of solution, United States Patent 5858,410, 1999.

[4] E. Merisko-Liversidge, P. Sarpotdar, J. Bruno, S. Hajj, L. Wei, N. Peltier, J. Rake, J.M. Shaw, S. Pugh, L. Polin, J. Jones, T. Corbett, E. Cooper, G.G. Liversidge, Formulation and antitumor activity evaluation of nanocrystalline suspensions of poorly soluble anticancer drugs, Pharm. Res. 13 (1996) 272–278.

[5] G.G. Liversidge, P. Conzentino, Drug particle size reduction for decreasing gastric irritancy and enhancing absorption of naproxen in rats, Int. J. Pharm. 125 (1995) 309–313.

[6] G.G. Liversidge, K.C. Cundy, Particle size reduction for improvement of oral bioavailability of hydrophobic drugs: I. Absolute oral bioavailability of nanocrystalline danazol in beagle dogs, Int. J. Pharm. 125 (1995) 91–97.

[7] B.E. Rabinow, Nanosuspensions in drug delivery, Nat. Rev. Drug Discov. 3 (2004) 785–796.

[8] R. Shegokar, R.H. Müller, Nanocrystals: industrially feasible multifunctional formulation technology for poorly soluble actives, Int. J. Pharm. 399 (2010) 129–139.

[9] R.H. Müller, S.H. Gohla, C.M. Keck, State of the art of nanocrystals – special features, production, nanotoxicology aspects & intracellular delivery, Eur. J. Pharm. Biopharm. 78 (2011) 1–9.

[10] C. Jacobs, R.H. Müller, Production and characterization of a budesonide nanosuspension for pulmonary administration, Pharm. Res. 19 (2002) 189–194.

[11] B.H.L. Böhm, Herstellung und Charakterisierung von Nanosuspensionen als neue Arzneiform für Arzneistoffe mit geringer Bioverfügbarkeit, PhD-thesis, Freie Universität Berlin, 1999.

[12] B. Rabinow, J. Kipp, P. Papadopoulos, J. Wong, J. Glosson, J. Gass, C.S. Sun, T. Wielgos, R. White, C. Cook, K. Barker, K. Wood, Itraconazole IV nanosuspension enhances efficacy through altered pharmacokinetics in the rat, Int. J. Pharm. 339 (2007) 251–260.

[13] L. Gao, D. Zhang, M. Chen, T. Zheng, S. Wang, Preparation and characterization of an oridonin nanosuspension for solubility and dissolution velocity enhancement, Drug Dev. Ind. Pharm. 33 (2007) 1332–1339.

[14] N. Hernandez-Trejo, O. Kayser, H. Steckel, R.H. Müller, Characterization of nebulized buparvaquone nanosuspensions – effect of nebulization technology, J. Drug Target. 13 (2005) 499–507.