International Journal of Pharmacy and Pharmaceutical Sciences

Print ISSN: 2656-0097 | Online ISSN: 0975-1491 Vol 15, Issue 4, 2023

Review Article

COMPREHENSIVE REVIEW ON NANOCRYSTAL TECHNOLOGY IN PHARMACEUTICAL FORMULATIONS

MANOJKUMAR K. MUNDE*, ANKITA M. SHINDE, NILESH S. KULKARNI, VRUSHALI S. TAMBE, HEMANT P. ALHAT

[a]**PES Modern College of Pharmacy (for Ladies), Affiliated to Savitribai Phule Pune University, Moshi, Pune 412105, Maharashtra, India**
Email: manojpcist@gmail.com

Received: 07 Dec 2022, Revised and Accepted: 03 Mar 2023

ABSTRACT

Many techniques have been developed to overcome the bioavailability problem of poorly soluble drugs. The nanonization is one of the techniques in that micronized particle is converted in nanoparticle. Several processes are applied for nanocrystal production, including precipitation, milling, high pressure homogenization and combination method. The nanocrystal formulation is administered via various routes like oral, intravenous, intramuscular, pulmonary, ocular and dermal but due to safety, patient compliance and ease of administration, oral drug delivery is preferred. There are two basic ways to prepare drug nanocrystals like "bottom-up" and "top-down" technologies. The present literature provides an overview of the achievement in improving the bioavailability of the poorly soluble drug by using different methods.

Keywords: Nanocrystal, Bottom-up, Top-down, Poor solubility, Bioavailability

DOI: https://dx.doi.org/10.22159/ijpps.2023v15i4.47317. Journal homepage: https://innovareacademics.in/journals/index.php/ijpps.

INTRODUCTION

About 60 % of new drugs are poorly water-soluble and it is believed that approximately 40% of drugs under development currently have solubility issues. The drug's low solubility is a major hurdle that must be overcome in order to create extremely potent pharmaceutical formulations. Low solubility medications have poor oral bioavailability and variable absorption, which is especially important for pharmaceuticals of biopharmaceutical class 2 (BCS) [1].

In oral administration, the drug must be present at the site of absorption in the dissolved state to achieve its pharmacological activity. The poor oral bioavailability of drugs caused by their poor aqueous solubility has always been a difficult issue in pharmaceutical research. To increase a drug's solubility in water, a variety of strategies have been explored including salt formation, co-solvents, complexes with cyclodextrins and solid-state changes. A promising method to increase the apparent saturation solubility, dissolving rate and oral bioavailability of hydrophobic medicines like BCS Class II sometimes also with BCS Class IV pharmaceuticals. Drug nanocrystals are carrier-free submicron colloidal drug delivery systems with a mean particle size in the nanometre range, typically between 10 and 1000 nm, made up of pure medicines and the bare minimum of surface-active agents needed for stability [2].

A logical progression is "nanonization," or the reduction of micronized particles to nanoparticles. Many different nanonization techniques have been developed to improve the bioavailability and solubility rates of numerous drugs that are poorly soluble in water. These techniques include boosting surface area, altering crystalline morphologies and creating brand-new nanomaterials that can serve as controlled release carriers.

Surface stabilised crystalline nanoparticles with sizes ranging from 200 to 500 nm are known as drug nanocrystals. They improve the oral bioavailability of drugs with dissolution rate-dependent bioavailability by increasing the saturation solubility, dissolution rate and possibly mucoadhesion [3].

Drug nanocrystals are a versatile formulation approach that can be used to improve the pharmacokinetic and pharmacodynamic properties of poorly soluble drugs. NCs (nanocrystals) stand out not only among pharmaceuticals but also among other nanoparticles due to their ease of formulation and production scaling flexibility, as well as their inherent small particle size and large surface area [4, 5].

The production of nanocrystals is just one method of modifying the intrinsic properties of the raw material: when particle size is reduced to nanosized area, intrinsic properties such as solubility are altered in comparison to bulk-sized drug powders. The overall advantages of small particle size can be divided into three categories: (I) fast dissolution (ii) increased solubility and (iii) improved membrane adhesion. The most important effect achieved with drug nanocrystals is a faster dissolution rate due to the large surface area per mass solid. However, the role of stabilisers and their careful selection should not be ignored. The primary function of stabiliser is to protect inherently unstable drug nanoparticles from aggregation and/or Ostwald ripening following the production and storage of nanocrystalline formulations. However, many of the stabilisers used can help to maintain the supersaturated state *in vivo* reached after fast dissolution of nanocrystals or they can act as permeation enhancers [6].

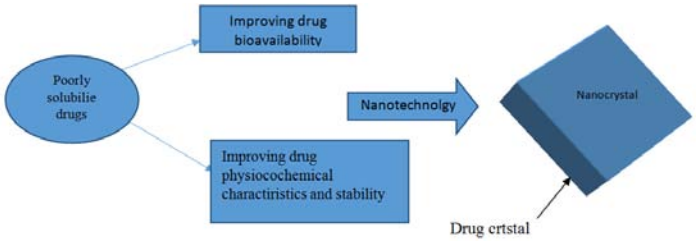

Fig. 1: Nanocrystal with surface modification

Characteristics of drug nanocrystals

Drug nanocrystals also known as solid micelles, are solid drug particles encased in a layer of stabilizer(s). Because the nanocrystals hundreds of nanometer-sized particles make them unstable, stabilizer(s) are needed to stop the aggregation of individual nanosized particles. Polymers like cellulose derivatives, PVP, poloxamers, vitamin E, TPGS, or amphiphilic surfactants like polysorbates, SDS, are examples of common stabilisers. These substances can also improve solubility through improved wetting and solubilizing effects [7].

Increase of dissolution velocity by surface area enlargement

According to the Noyes-Whitney equation, the rate of dissolution is proportional to the surface area available for

Equation:

dC\ dt = DA (C s − C)/h

Where:

dc/dt = dissolution velocity

D = diffusion coefficient

A = surface area

cs = saturation solubility

cx = bulk concentration

h = diffusional distance over which the concentration gradient occurs [8].

Higher saturation solubility

The saturation solubility Cs stays the same no matter what the compound is, what the dissolving medium is, or what the temperature is. But the saturation solubility also depends on the size of the particles below 1-2 m. It gets worse as particles get smaller than 1000 nm. Because of this, the saturation solubility of drug nanocrystals has gone up. The Ostwald-Freundlich equation shows how the saturation solubility of a drug and the size of its particles are related.

Cs stands for saturation solubility.

r = interfacial tension of substance

V = molar volume of the particle material

R = gas constant,

T = absolute temperature

r=radius of particle [9].

$$\text{Log}\frac{c_S}{ca} = \frac{2\sigma^v}{2.303\text{RT}p\gamma}$$

Supersaturated state

Drug nanocrystals produce a supersaturated state which is thermodynamically unstable similar to amorphous formulation due to their higher apparent solubility compared to thermodynamic solubility. When drug nanocrystals were compressed to a flat surface the concentration levels of the dissolved drug next to the sample surface with 580 nm nanocrystals were more than five-fold higher than the concentration levels achieved with bulk indomethacin. A traditional shake flask test was used in another study to determine the aqueous solubility values of nimodipine nanocrystals. When the aqueous solubility of crude drug after 72 h testing was 1.879 g/ml, the corresponding solubility values for nanocrystals with average particle sizes of 830 nm, 500 nm, and 160 nm were 22.526 g/ml, 30.093 g/ml, and 51.269 g/ml, respectively, indicating a very high level of supersaturation and a significantly long time period for the investigated the kinetic solubility of nanocrystalline coenzyme Q10 with particle size fractions ranging from 80 nm to 700 nm and discovered that the kinetic solubility increased as particle size decreased. Used real-time NMR spectroscopy to investigate the maintenance of supersaturated states with amorphous and nanocrystalline carbamazepine by monitoring the amount of dissolved carbamazepine. The concentration of carbamazepine nanocrystals was nearly constant for 50 h, whereas amorphous carbamazepine had a higher initial concentration but then dropped below the concentration of the nanocrystal sample. As a result, while there are examples of higher apparent solubility values associated with nanocrystals, this clear benefit achieved with nanocrystals is frequently overlooked in nanocrystal applications [10].

Advantages

Fig. 1: Thus, nanocrystal offer several advantages and drawbacks

Among the benefits there are

- The ability to administer a drug via various routes (oral, intravenous, intramuscular, pulmonary, ocular, dermal).
- The ability to formulate a drug in various pharmaceutical dosage forms (tablets, capsules, suspensions, ointments, etc.)
- Greater solubility (thermodynamic or kinetic, counting on the drug's solid physical state) than conventional particles.
- Faster dissolution rate than conventional particles.
- Possibility of passive and active drug targeting.
- Reduced tissue irritation in subcutaneous/intramuscular administration [11].

Fewer are the disadvantages, such as

- Stability issues involving physicochemical.
- When handling and transporting Bulking, extreme caution must be exercised.
- It is impossible to realize a uniform and accurate dose [12].

Table 1: Properties of nanocrystal

Properties of nanocrystal
1. Particles size less than 1 µm
2. There is 100% drug use. Nanocrystals do not utilise carriers.
3. Surface active agent stabilisation is typically required.
4. Amorphous or crystalline structure (Amorphous condition with benefits)
5. Saturation solubility increases.
6. A faster rate of disintegration [13].

History of nanocrystal

Before getting into the details of nanotechnology and nanoscale science, we should be clear about what we mean when we use nano terms like nanotechnology, nanoscience and nanoscale. The preform of the Greek word nanos, which means "very short man." The International Organization for Standardization (ISO) has defined nanomaterial (NM) as a material with any external dimension in the nanoscale or having internal structure or surface structure in the nanoscale and nanoparticle (NP) as a nano-object with all three external dimensions in the nanoscale (1–100 nm). The American National Standards made a Nanotechnology Standards Panel (ANSI-NSP), which put out a list of recommendations for what should be done first. Priorities for standardising nanotechnology fall into these four types (1) terminology for materials composition and properties (2) terminology for nanoscience and technology (3) metrology of analysis and standard test methods and (4) toxicity effects, environmental impacts and risk assessment.

The American National Standard Institute made a Nanotechnology panel and put the standard terminologies into four main groups: 1) Organising terminotics with respect to composition and features 2) Universal vocabularies for nanoscience and nanotechnology 3) Techniques for analysis; and 4) Harmful effects and risk assessment. There is no one definition of NMs that is accepted around the world. There are many scientific ways to explain what nanotechnology is. Here are some of them.

Nanoscale means that the size ranges from about 1 to 100 nm. It is assumed that approximately applies to both the lower and upper limits of the definition and that size can mean all three dimensions (OECD ;). The size of a feature is on the order of 100 nm or less. Having at least one dimension that is 100 nm or smaller Nanoscale technology is when we can use what we know about nanoscale science to make things that have new properties and abilities. To take advantage of all the possibilities it is important to understand how quantum interactions work at the nanoscale to be able to see nanoscale structures and to be able to make the change and even connect nanostructures.

Nanoscience is the study, discovery and understanding of matter at the nanoscale where properties and phenomena can arise that are different from those of individual atoms or molecules or large amounts of matter. The study and manipulation of phenomena and materials at the atomic, molecular and macromolecular levels where their properties are very different from those at larger levels [14].

Nanomaterials are substances that have any external dimension or internal or surface structure at the nanoscale. a manufactured substance that is insoluble or bio-persistent and has one or more external dimensions or an internal structure on a scale from 1 to 100 nm. One or more external dimensions of a natural, artificial, incidental or manufactured material, in an unbound state, as an aggregate, or as an agglomerate, where 50% or more of the particles in the number size distribution fall within the size range of 1-100 nm. Particles that are natural or artificial contain active or inactive substances, are unbound, aggregated, or agglomerated, and at least 50% of the particles in the number size distribution have one or more external dimensions that fall within the size range of 1-100 nm.

A nano-object is a piece of material with one, two, or three external dimensions. At the nanoscale, material is constrained in one, two, or three dimensions. a nanoscale object with all three external dimensions.

The term "nanoparticle" refers to a nanoscale object with all three external dimensions. The terms "nano rod" or "nano plate" should be used in place of the term "NP" if the lengths of the longest and shortest axes of the nano-object differ noticeably (typically by more than three times [15].

Preparation of drug nanocrystals

Several ways to make nanocrystals of drugs have been looked into. There are two basic ways to make drug nanocrystals, which are called "bottom-up" and "top-down" technologies. In the top-down processes, larger particles are broken up by milling or homogenization. In the bottom-up processes, precipitations at the nanometer scale are put together and controlled.

Bottom-up processes

From the molecules in solution, particles with crystalline or amorphous forms are created by aggregating the molecules. This process could be referred to as "a classical precipitation process" (in latin: via humida paratum). In this method, a solvent is used to completely dissolve the drug. The drug precipitates when the solvent solution is added to a non-solvent. Controlling influence factors and adding stabilisers like surfactants are important steps in controlling the particle structure and preventing the growth of the particles to the micrometre size range. Sonocrystallization, high gravity-controlled precipitation technology, confined impinging liquid jet precipitation, and multi-inlet vortex mixing are additional bottom-up technologies. Bottom-up processes facilitate the incorporation of multiple active ingredients into a single nanocarrier and the customization of nanoparticle surface functionality. However, a fundamental disadvantage of many precipitation processes is the need to remove organic solvent, which increases production costs. Large volumes of solvent are required for low water and organic solvent-soluble drugs in particular. Therefore the pharmaceutical industry has not utilised bottom-up processes for the production of marketed drugs [16].

Top-down techniques

The mechanical attrition or high-pressure collisions used in top-down methods for particle size diminishing can lead to contamination because of the equipment's wear and tear. The degree of contamination depends on process variables like bead size/material, stirrer speed, and energy input. By speeding up the process and using smaller bead sizes, the level of contamination can be reduced while still using the same bead material. High energy consumption is another drawback of top-down techniques especially if process times are lengthy. However, today especially in milling process times can be significantly reduced due to more energy-efficient milling equipment which reduces overall energy consumption. High pressure homogenizations and milling are carried out in suspension. Water is

typically used as the suspension medium, but oils or PEGs can also be used. These methods are environmentally friendly because it is possible to avoid using organic solvents. Because it increases molecular mobility and lowers the glass transition temperature, water also prevents the formation of amorphous material within the contents. The drug typically takes on a crystallised form after milling, though polymorphic changes are possible. Although high pressure homogenization may result in a decrease in crystallinity, the water in this situation also helps to stabilise the drug crystals. Technically, high pressure homogenization (HPH) can be divided into two different methods: (i) Piston-gap homogenization and (ii) Jet streaming (micro-fluidizer, IDD-PTM, insoluble drug delivery micro-particle technology). While in a piston-gap type homogenizer drug suspension is forced with high pressure through a small gap high energy suspension flows collide in a micro-fluidizer during jet streaming. Piston gap homogenization can be further subdivided into PEG (Nano-pure®) and non-aqueous media (Disso-cubes®) homogenization [17].

Combination techniques

Combination techniques can be used if the final product cannot meet the necessary CQAs in a single process. Combination techniques are two-step procedures that involve a high-energy top-down process and a pre-process step, such as pre-milling or precipitation (most often milling or high-pressure homogenization). Combination methods have the advantages of frequently achieving even smaller particle sizes, avoiding process-related issues like clogging high-pressure homogenizers, and speeding up the final top-down process time.

Despite the fact that combining techniques can be useful for considering the end product's properties or avoiding process-related difficulties, more complex processes raise overall costs and add to the complexity of the entire production process. As a result, combination techniques should never be used as a first option and should only be chosen when doing so will result in huge advantages. Anti-solvent precipitation pre-processing was the first combination technique, which was followed by high-pressure homogenization (Nanoedge TM; Möschwitzer, 2003). The Smart Crystal® group of technologies, which debuted more recently, combine high pressure homogenization with various pre-processes, including CT, H42 (spray-drying preprocess), H69 (precipitation preprocess), and H96 (lyophilization preprocess) (media milling pre-process). For example, in the case, anti-solvent precipitation and ultrasonication are less frequently studied combinations [18].

Nanocrystals (Nanosuspensions) and bioavailability

A drug's capacity to dissolve in biological fluids pass through membranes and effectively reach its pharmacological targ*et al.* l contribute to its bioavailability. Drugs in the BCS Class II group of the biopharmaceutical classification of drugs have a poor solubility but a good ability to cross membranes. Therefore increasing drug solubility and/or drug dissolution rate are required to improve the bioavailability of a BCS Class II drug.

Particularly for nanocrystals, the following scenarios can be considered:

1. According to the modified Noyes-Whitney law, a decrease in particle size leads to an increase in surface area available for interaction with the dissolution medium and subsequently an increase in the particle dissolution rate.

2. According to Kelvin's equation, an increase in particle curvature (especially for colloidal particles) causes an increase in dissolution pressure.

3. Increased solubility causes a greater concentration gradient at membranes resulting in greater penetration or permeation through membranes.

4. High adhesion to biological membranes of nanocrystals which is favoured by their size is also beneficial for high membrane penetration; however adhesion can also be improved by coating with mucoadhesive polymer.

5. According to a number of authors, another factor contributing to the improvement in bioavailability is the transcellular uptake of nanocrystals by epithelial cells. Nevertheless, it was determined that the results are conflicting and unclear and that no further explanation could be provided;

6. Nanoparticles can be injected intravenously (in the form of a nanosuspension) and are completely bioavailable once they reach the intended site of action in the body.

7. Coating nanocrystals with molecules able to interact with specific substrates can facilitate targeting.

Due to their promising potential, nanocrystals have been designed for use in a variety of drug delivery systems. Oral drug administration is the most typical scenario [19, 20].

Nanocrystal and oral drug delivery

Due to its safety, patient compliance, ease of production, and scalability, oral delivery is the preferred method for drug therapy; however, its main drawbacks are due to the drug's bioavailability. Through increased solubility, particle dissolution, increased gradient concentration at membranes and adhesion to the gastrointestinal wall, nanocrystals may enhance bioavailability. The rate-limiting step for BCS Class II drugs is typically drug dissolution and nanocrystals have been suggested to overcome this restriction.

One of the earliest examples of this concept was implemented to danazol, a poorly soluble drug with poor bioavailability, which was formulated as three distinct formulations: an aqueous nanosuspension (169 nm), a danazol-hydroxypropyl-cyclodextrin complex and an aqueous microsuspension (10 m). The area under the curve (AUC) following oral administration in beagle dogs revealed that the nanosuspension and the cyclodextrin complex had similar levels of bioavailability, while the microsuspension had a lower level of bioavailability. The superior performance of the aqueous nanosuspension over the aqueous microsuspension can be attributed to the former's ability to overcome the limited dissolution rate typically observed with conventional suspensions. The authors proposed nanoparticles as the ideal formulation for absorption restricted by dissolution rate. With this study as a reference, many other studies confirmed that nanocrystals improve the bioavailability of drugs when taken by mouth. This has led to a large number of drug products being tested in clinical trials or already on the market. Nanocrystals are becoming extremely important in the pharmaceutical industry; up until May 2017, the US Food and Drug Administration (FDA) received over 80 applications for drug products containing nanocrystals, with over 60% of those submissions being for the oral route of administration. The large number of pharmaceutical dosage forms, including tablets, capsules and oral suspensions are designed for oral administration. Additionally, it should be noted that media milling, a top-down technology that is probably better managed by the pharmaceutical industry, is the preferred technology used. Media milling requires accurate control of all the important production factors through in-process tests and quality control end tests [21].

The saturation solubility of nanocrystals in a lutein nanosuspension made by high pressure homogenization was 26.3 times greater than that of coarse powder. When delivered as pellets and hard gelatin capsules for use in nutraceuticals, nanocrystals released three to four times more *in vitro* than coarse particles did [22].

Rutin nanocrystals manufactured by lyophilization and incorporated into tablets exhibited a higher rate of particle dissolution than microcrystal-loaded tablets and commercially available tablets. According to particle size measurements obtained by photon correlation spectroscopy (PCS) and laser diffractometry, the primary factor in the increased dissolution was the particle size reduction.

Four batches of coenzyme Q10 nanocrystals (size range: 80–700 nm) were prepared without the use of any surfactant or polymer by the solvent/non solvent method. The dissolution rate of coenzyme Q10 increased as particle size decreased, and the increased bioavailability of coenzyme Q10 nanocrystals after oral administration was confirmed in beagle dogs, where AUC0–48 was 4,400 times greater than that of coarse suspensions [23].

A bioactive flavonoid called apigenin was made into nanocrystals using the supercritical antisolvent method. The dissolution rate of nanocrystals (400–800 nm) was faster than that of coarse powder.

In comparison to coarse particles, nanocrystals had a significantly lower tmax, 3.6-fold higher peak plasma concentration (Cmax) and 3.4-fold higher area under the curve (AUC) after the administration of a single oral dose to rats [24].

Fenofibrate, a lipophilic drug used to treat hypercholesterolemia and hypertriglyceridemia that is practically insoluble in water, was processed in a probe sonicator and freeze-dried into a dry powder to create a nanosuspension. The saturation solubility was significantly increased by a particle size reduction. White rabbit pharmacokinetic studies revealed a 4.73-fold increase in relative bioavailability compared to the pure drug form [25].

Bexarotene, a potent anti-tumour drug with low solubility and bioavailability, was converted into nanocrystals using a technique that combined precipitation and micro fluidization. With improved *in vivo* outcomes in rats, the decreased particle size thus obtained allowed for a significant increase in the dissolution rate. The oral bexarotene nanocrystals significantly improved the bioavailability of this critical medication and reduced its side effects, as shown by the higher AUC and lower Cmax. Because there was no first-pass effect and enterohepatic circulation, nanocrystals given intravenously had a higher bioavailability [26].

Microprecipitation and high-pressure homogenization were utilised to produce nimodipine nanocrystals of various size (159.0 nm, 503.0 nm, and 833.3 nm). The *in vitro* and *in vivo* behaviour was compared to that of Nimotop®, a commercially available nimodipine formulation. Even though Nimotop® exhibited a higher dissolution rate than the three different nanocrystal batches, the plasma concentration-time curves determined in beagle dogs revealed that the bioavailability of optimum nanocrystals (159.0 nm and 833.3 nm) was significantly greater than that of Nimotop®.

Table 2: Preparation of nanocrystal by various technology as nanoprecipitation, sonication, high-pressure sonication, high-pressure homogenisation, milling during the last 15 y

Drug	Techniques	Mechanism	References
Albendazole	Nanoprecipitation, Sonication, High pressure sonication High pressure homogenisation, Milling	Electrostatic repulsion (Prevent aggregation)	[29, 30]
Curcumin	High-speed homogenisation, High-pressure homogenisation, Nanoprecipitation technique		
Spironolactone	High-speed homogenisation, High-pressure homogenisation, Nanoprecipitation method Wet edge High-pressure homogenisation		
Nitrendipine	Precipitation+high pressure homogenisation		
Rutin	High pressure homogenisation		
Albendazol	Nanoprecipitation, Sonication, High–pressure homogenisation, High-speed homogenisation Edge , Antisolvent precipitation technique	Steric barrier against aggregation (prevent aggregation)	[31]
Nitrendipine	Precipitation+high pressure homogenisation		
Ibuprofen	Wet comminution		
Napoxen			
Prednisolone acetate			
Hydrocortisone acetate			
Anthracene			
Itraconazole	Wet comminution/Wet edge		
Indomethacin	Wet edge		
Quercetin	High-pressure homogenisation, Bead edge, Cavi-precipitation		
Apigenin	Bead milling+high-pressure homogenisation		
Hesperetin	High-pressure homogenization		
Resveratrol	High-pressure homogenization Precipitation	Biological active providing further functions to nanocrystals (promotion of a stable formulation)	[32]
Caffeine	Pearl edge		
Curcumin	High-speed homogenization, Wet milling, High-pressure homogenization		
Dexamethasone	Wet edge		
Diclofenac	Wet edge		
Pyrimethamin	Nanoprecipitation+high-pressure, homogenization		
Nifedipine	High-pressure homogenization		
Spironolactone	Wet edge		
Apigenin	Bead edge+high-pressure homogenization		
Cinnarizine and naproxen	Ball edge		
Indomethacin	Dry edge, Wet edge		
Fenofibrate	Milling		
Nimodipine	High-pressure homogenization		
Naproxen	Wet comminution		
Amoitone B	High-pressure homogenization		
Prednisolone, carbamazepine, itraconazole, baicalin, cyclosporine	High-pressure homogenization		
Paclitaxel	Antisolvent precipitation+sonication		
Curcumin	High-pressure homogenization		
Caffeine	Pearl edge		
Hydrocortisone acetate	High-pressure homogenization	Mucoadhesion (promote absorption)	[33]
Buparvaquone	High-pressure homogenisation		
Paclitaxel	High-pressure homogenization	Improving long circulation and interaction with specific receptors	[34]
Pioglitazone	Precipitation		
Piroxicam	High-pressure blending		
Meloxicam	High-pressure blending		

The *in vitro*/*in vivo* relationship between nimodipine nanocrystals and Nimotop® was explained by the fact that some nanocrystals

went through macropinocytosis and caveolin-mediated endocytosis by enterocytes as whole nanocrystals and then skipped the liver's first-pass metabolism [27].

Similarly, no correlation between *in vitro* and *in vivo* was observed between itraconazole solid oral nanocrystals and the Spranox® formulation. The results demonstrated the nanocrystals' rapid dissolution, but this behaviour was not observed in a rat model *in vivo*. The longer transit time of itraconazole from nanocrystals facilitates the drug's rapid entrance into the small intestine, where it is less stable due to the lower solubility of the drug at that pH. In Spranox®, dissolution occurs from the surface of the sugar beads, which presumably have longer stomach transit times than nanocrystals. The highly concentrated solution formed by the Spranox® formulation in the stomach can stabilise the solution as it enters the small intestine. Thus, the stomach acts as a reservoir from which the highly concentrated solution can be delivered to and absorbed by the small intestine.

In the previous examples, nanocrystals were made using different methods, such as high-pressure homogenization, lyophilization, supercritical antisolvent process, sonication followed by freeze-drying, and microprecipitation combined with high-pressure homogenization. This means that there is still a big gap between the results of current research and the real chance of using lab-scale technology in the real world. Shegokar and Müller proposed a very important review that shows how lab-scale technologies can be used in industry. Several pieces of evidence showed that milling procedures had the most scale-up studies [28].

CONCLUSION

Evidently, poorly soluble drugs are a good fit for nanocrystal technology. Drug nanocrystals can be used to treat any poorly soluble drugs in order to address their solubility and bioavailability problems. Particle size reduction to the nanoscale range has the advantages of increasing particle surface, curvature, saturation solubility, dissolving velocity, and further acceptable bioavailability. Drug nanocrystal synthesis involves a number of combined and applied technologies. Due to their increased bioavailability, drug nanocrystals have many benefits when administered orally. Additionally, because they dissolve quickly, drug nanocrystals enable speedy absorption, meeting the need for a quick onset.

ACKNOWLEDGMENT

We are thankful to PES Modern college of pharmacy (for ladies) Moshi, pune for the necessary support.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

The author declares no conflict of interests

REFERENCES

1. Kipp JE. The role of solid nanoparticle technology in the parenteral delivery of poorly water-soluble drugs. Int J Pharm. 2004 Oct 13;284(1-2):109-22. doi: 10.1016/j.ijpharm.2004.07.019. PMID 15454302.
2. Irache JM, Esparza I, Gamazo C, Agueros M, Espuelas S. Nanomedicine: novel approaches in human and veterinary therapeutics. Vet Parasitol. 2011 Aug 4;180(1-2):47-71. doi: 10.1016/j.vetpar.2011.05.028. PMID 21680101.
3. Chen H, Khemtong C, Yang X, Chang X, Gao J. Nanonization strategies for poorly water-soluble drugs. Drug Discov Today. 2011 Apr;16(7-8):354-60. doi: 10.1016/j.drudis.2010.02.009. PMID 20206289.
4. Ahuja BK, Jena SK, Paidi SK, Bagri S, Suresh S. Formulation, optimization and *in vitro-in vivo* evaluation of febuxostat nanosuspension. Int J Pharm. 2015 Jan 30;478(2):540-52. doi: 10.1016/j.ijpharm.2014.12.003. PMID 25490182.
5. Saini JK, Kumar S. Development of nanocrystal formulation with improved dissolution. J Drug Delivery Ther. 2018 Sep 9;8(5):118-29. doi: 10.22270/jddt.v8i5.1946.
6. Gao L, Liu G, Ma J, Wang X, Wang F, Wang H. Paclitaxel nanosuspension coated with P-gp inhibitory surfactants: II. Ability to reverse the drug resistance of H460 human lung cancer cells. Colloids Surf B Biointerfaces. 2014 May 1;117:122-7. doi: 10.1016/j.colsurfb.2014.02.016. PMID 24632038.
7. Gao L, Liu G, Ma J, Wang X, Zhou L, Li X. Application of drug nanocrystal technologies on oral drug delivery of poorly soluble drugs. Pharm Res. 2013 Feb;30(2):307-24. doi: 10.1007/s11095-012-0889-z. PMID 23073665.
8. Junghanns JU, Muller RH. Nanocrystal technology, drug delivery and clinical applications. Int J Nanomedicine. 2008;3(3):295-309. doi: 10.2147/ijn.s595. PMID 18990939, PMCID PMC2626933.
9. Tuomela A, Hirvonen J, Peltonen L. Stabilizing agents for drug nanocrystals: effect on bioavailability. Pharmaceutics. 2016 May 20;8(2):16. doi: 10.3390/pharmaceutics8020016, PMID 27213435, PMCID PMC4932479.
10. Mah PT, Laaksonen T, Rades T, Peltonen L, Strachan CJ. Differential scanning calorimetry predicts the critical quality attributes of amorphous glibenclamide. Eur J Pharm Sci. 2015 Dec 1;80:74-81. doi: 10.1016/j.ejps.2015.08.006. PMID 26296864.
11. Zhao R, Hollis CP, Zhang H, Sun L, Gemeinhart RA, Li T. Hybrid nanocrystals: achieving concurrent therapeutic and bioimaging functionalities toward solid tumors. Mol Pharm. 2011 Oct 3;8(5):1985-91. doi: 10.1021/mp200154k. PMID 21812439.
12. Hancock BC, Parks M. What is the true solubility advantage for amorphous pharmaceuticals? Pharm Res. 2000 Apr;17(4):397-404. doi: 10.1023/a:1007516718048. PMID 10870982.
13. Junghanns JU, Muller RH. Nanocrystal technology, drug delivery and clinical applications. Int J Nanomedicine. 2008;3(3):295-309. doi: 10.2147/ijn.s595. PMID 18990939, PMCID PMC2626933.
14. Rogers Hayden T, Pidgeon N. Moving engagement "upstream"? Nanotechnologies and the royal society and royal academy of engineering's inquiry. Public Underst Sci. 2007 Jul;16(3):345-64. doi: 10.1177/0963662506076141.
15. Lovestam G, Rauscher H, Roebben G, Kluttgen BS, Gibson N, Putaud JP. Considerations on a definition of nanomaterial for regulatory purposes. Joint Research Centre (JRC) Reference Reports. 2010 Aug 25;80:1-41.
16. Muller RH, Gohla S, Keck CM. State of the art of nanocrystals--special features, production, nanotoxicology aspects and intracellular delivery. Eur J Pharm Biopharm. 2011 May;78(1):1-9. doi: 10.1016/j.ejpb.2011.01.007. PMID 21266197.
17. Liu P, Rong X, Laru J, van Veen B, Kiesvaara J, Hirvonen J. Nanosuspensions of poorly soluble drugs: preparation and development by wet milling. Int J Pharm. 2011 Jun 15;411(1-2):215-22. doi: 10.1016/j.ijpharm.2011.03.050. PMID 21458552.
18. Shegokar R, Muller RH. Nanocrystals: industrially feasible multifunctional formulation technology for poorly soluble actives. Int J Pharm. 2010 Oct 31;399(1-2):129-39. doi: 10.1016/j.ijpharm.2010.07.044. PMID 20674732.
19. Shegokar R, Singh KK. Surface modified nevirapine nanosuspensions for viral reservoir targeting: *in vitro* and *in vivo* evaluation. Int J Pharm. 2011 Dec 15;421(2):341-52. doi: 10.1016/j.ijpharm.2011.09.041, PMID 21986114.
20. Chen L, Wang Y, Zhang J, Hao L, Guo H, Lou H. Bexarotene nanocrystal-oral and parenteral formulation development, characterization and pharmacokinetic evaluation. Eur J Pharm Biopharm. 2014 May;87(1):160-9. doi: 10.1016/j.ejpb.2013.12.005. PMID 24333772.
21. Chen ML, John M, Lee SL, Tyner KM. Development considerations for nanocrystal drug products. AAPS J. 2017 May;19(3):642-51. doi: 10.1208/s12248-017-0064-x, PMID 28281194.
22. Mitri K, Shegokar R, Gohla S, Anselmi C, Muller RH. Lutein nanocrystals as an antioxidant formulation for oral and dermal delivery. Int J Pharm. 2011 Nov 25;420(1):141-6. doi: 10.1016/j.ijpharm.2011.08.026, PMID 21884768.
23. Sun J, Wang F, Sui Y, She Z, Zhai W, Wang C. Effect of particle size on solubility, dissolution rate, and oral bioavailability:

evaluation using coenzyme Q_{10} as naked nanocrystals. Int J Nanomedicine. 2012;7:5733-44. doi: 10.2147/IJN.S34365. PMID 23166438, PMCID PMC3500035.

24. Fu Q, Sun J, Ai X, Zhang P, Li M, Wang Y. Nimodipine nanocrystals for oral bioavailability improvement: role of mesenteric lymph transport in the oral absorption. Int J Pharm. 2013 May;448(1):290-7. doi: 10.1016/j.ijpharm.2013.01.065. PMID 23384726.
25. Ige PP, Baria RK, Gattani SG. Fabrication of fenofibrate nanocrystals by probe sonication method for enhancement of dissolution rate and oral bioavailability. Colloids Surf B Biointerfaces. 2013 Aug 1;108:366-73. doi: 10.1016/j.colsurfb.2013.02.043. PMID 23602990.
26. Chen L, Wang Y, Zhang J, Hao L, Guo H, Lou H. Bexarotene nanocrystal-oral and parenteral formulation development, characterization and pharmacokinetic evaluation. Eur J Pharm Biopharm. 2014 May;87(1):160-9. doi: 10.1016/j.ejpb.2013.12.005. PMID 24333772.
27. Fu Q, Sun J, Zhang D, Li M, Wang Y, Ling G. Nimodipine nanocrystals for oral bioavailability improvement: preparation, characterization and pharmacokinetic studies. Colloids Surf B Biointerfaces. 2013 Sep 1;109:161-6. doi: 10.1016/j.colsurfb.2013.01.066. PMID 23668980.
28. Shegokar R, Muller RH. Nanocrystals: industrially feasible multifunctional formulation technology for poorly soluble actives. Int J Pharm. 2010 Oct 31;399(1-2):129-39. doi: 10.1016/j.ijpharm.2010.07.044. PMID 20674732.
29. Rao YM, Kumar MP, Apte S. Formulation of nanosuspensions of albendazole for oral administration. Curr Nanosci. 2008 Feb 1;4(1):53-8. doi: 10.2174/157341308783591807.
30. Liu P, Rong X, Laru J, van Veen B, Kiesvaara J, Hirvonen J. Nanosuspensions of poorly soluble drugs: preparation and development by wet milling. Int J Pharm. 2011 Jun 15;411(1-2):215-22. doi: 10.1016/j.ijpharm.2011.03.050. PMID 21458552.
31. Gigliobianco MR, Casadidio C, Censi R, Di Martino P. Nanocrystals of poorly soluble drugs: drug bioavailability and physicochemical stability. Pharmaceutics. 2018 Aug 21;10(3):134. doi: 10.3390/pharmaceutics10030134, PMID 30134537.
32. Pi J, Wang S, Li W, Kebebe D, Zhang Y, Zhang B. A nano-cocrystal strategy to improve the dissolution rate and oral bioavailability of baicalein. Asian J Pharm Sci. 2019 Mar;14(2):154-64. doi: 10.1016/j.ajps.2018.04.009. PMID 32104447, PMCID PMC7032205.
33. Kumar S, Kamath K, Shabaraya AR. Nanocrystals: a novel approach in the delivery of hydrophobic drugs; 2014.
34. Xiong S, Liu W, Zhou Y, Mo Y, Liu Y, Chen X. Enhancement of oral bioavailability and anti-parkinsonian efficacy of resveratrol through a nanocrystal formulation. Asian J Pharm Sci. 2020 Jul;15(4):518-28. doi: 10.1016/j.ajps.2019.04.003. PMID 32952674, PMCID PMC7486547.