IJPSR (2025), Volume 16, Issue 4 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 20 October 2024; received in revised form, 18 December 2024; accepted, 23 December 2024; published 01 April 2025

NANOCRYSTALS FOR IMPROVED DRUG DELIVERY: A REVIEW

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Keywords:

Nanocrystals, Bioavailabilty, Metaxalone, Control Release, Solubility, Crystallization

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ABSTRACT: Nanocrystals are crystalline particles having particle size range of 100 to 1000 nm. However, these nano-sized systems are thermodynamically unstable, stabilizers are required to incorporate them. The poorly soluble drugs lead to problems like poor absorption and therapeutic failure. One such method to overcome these solubility problems is the development of nanocrystals. These systems reduce particle size that increases surface area and hence dissolution. Nanoscience technology results in improving solubility, bioavailability and dissolution rate of poorly water-soluble drugs. According to the Noyes-Whitney equation, there is a direct relationship between dissolution rate and surface area of drug particles. Various methods of preparation nanocrystals are Crystallization method, Anti-solvent crystallization, High gravity-controlled precipitation. Evaluation of nanocrystals with different parameters.

INTRODUCTION:

Nanocrystals: Nanocrystals are crystalline particles having particle size range of 100 to 1000 nm. However, these nanosized systems are thermodynamically unstable, stabilizers are required to incorporate them. These formulations are used for the drugs with poor solubility and bioavailability [1]. Solubility is the important parameter for the bioavailability of poorly soluble drugs. The poorly soluble drugs lead to problems like poor absorption and therapeutic failure. One such method to overcome these solubility problems is the development of nanocrystals. These systems reduce particle size that increases surface area and hence dissolution.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.16(4).900-07

This article can be accessed online on www.ijpsr.com

DOI link: https://doi.org/10.13040/IJPSR.0975-8232.16(4).900-07

In these systems the drug should be in crystalline form if amorphous state nanoparticles can remain stable for longer period of time during production and storage [2, 3]. Nanoscience technology results in improving solubility, bioavailability and dissolution rate of poorly water-soluble drugs. According to the Noyes-Whitney equation, there is a direct relationship between dissolution rate and surface area of drug particles. Thus, by developing the nanoparticles, the saturation solubility of drug can be highly enhanced [4].

These systems can be developed by various methods and few of them are spray drying method for nano crystalline suspension or solutions, antisolvent precipitation method, emulsion solvent diffusion method, crystallization method, bottom-up techniques, top-down techniques, ultrasonic homogenization fluid bed drying method, etc. These systems can be characterized for surface morphology, crystalline, drug entrapment efficacy, *in-vitro* drug release *etc* [5, 6, 7].

Advantages:

- Size reduced of drug and formulated nanocrystals results in increased surface area, improved dissolution profile and oral bioavailability.
- It improved pharmacokinetic performances of formulation.
- There is easy drug administration by all routes, low dose required and faster onset of therapeutic action.
- There is decreased pharmacokinetic variability such as fed fasted variability and Patient to patient variability [8, 9].

Disadvantages:

- The disadvantage of nanocrystal as time consuming Manufacturing processes because it is a sensitive method to formulate nanocrystals & difficult to achieve uniform size distribution and results low yield [10].

Properties of Nanocrystals:

- Nanocrystals formulation Size between 100 to 1000 nm.
- There is 100% drug, no carrier for developed formulation.
- Generally, it needed to be stabilized so stabilizers used for their formulation.
- These should be Crystalline or amorphous structures their property and amorphous particle state offers advantages.
- These increases of dissolution rate and saturation solubility [11].

Nanocrystal Preparation Methods: Several manufacturing methods have evolved, and the implemented manufacturing methods of nanocrystal formulations can be classified into "bottom-up", "top-down", "top down and bottom-up" and "spray drying" can. Bottom-up technology starts with the molecule active ingredient. The substance is dissolved by adding an organic solvent and then the solvent is removed by precipitation. "Top-down" technology applies a dispersion process using different types of grinding and homogenization techniques.

"Top-down" technology is more popular than "bottom-up" technology. It is called "nano-ization". In other words, it is the process of breaking down large crystal particles into smaller pieces. Both methods are used together in "top-down and bottom-up" technology. Spray drying is also a method of producing drug nanocrystals, which is faster and more convenient than other methods [12, 13].

1. Bottom-up

a. Nano precipitation

2. Top-down a) Milling b) Homogenization

3. Top-down and Bottom-up

4. Spray drying

5. Other Techniques used for the Production of Drug Nanocrystals

a. Rapid expansion from a liquefied-gas solution (RESS)

b. Nanopure technology

c. Spray Freezing into Liquid (SFL) technology.

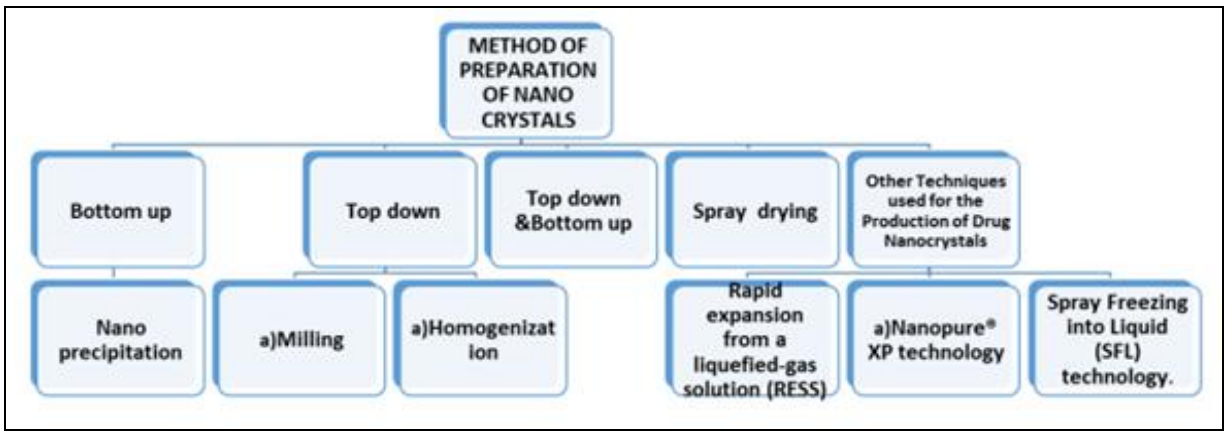

FIG. 1: NANOCRYSTAL PREPARATIONS

Bottom-up Technology: The principle of this method is based on the dissolution of the active drug substance in an organic solvent which is then added into a nonsolvent (miscible with the organic solvent). In the presence of stabilizers, thereafter, the nanocrystals are precipitated. The basic advantage of the precipitation technique is that it is simple and has a low cost. Also, scale-up is simple in this method. It should be kept in mind that several parameters, such as stirring rate, temperature, solvent/ nonsolvent rate, drug concentration, viscosity, type of solvent, and stabilizer should be controlled to obtain homogenous nanocrystals by this technique [14].

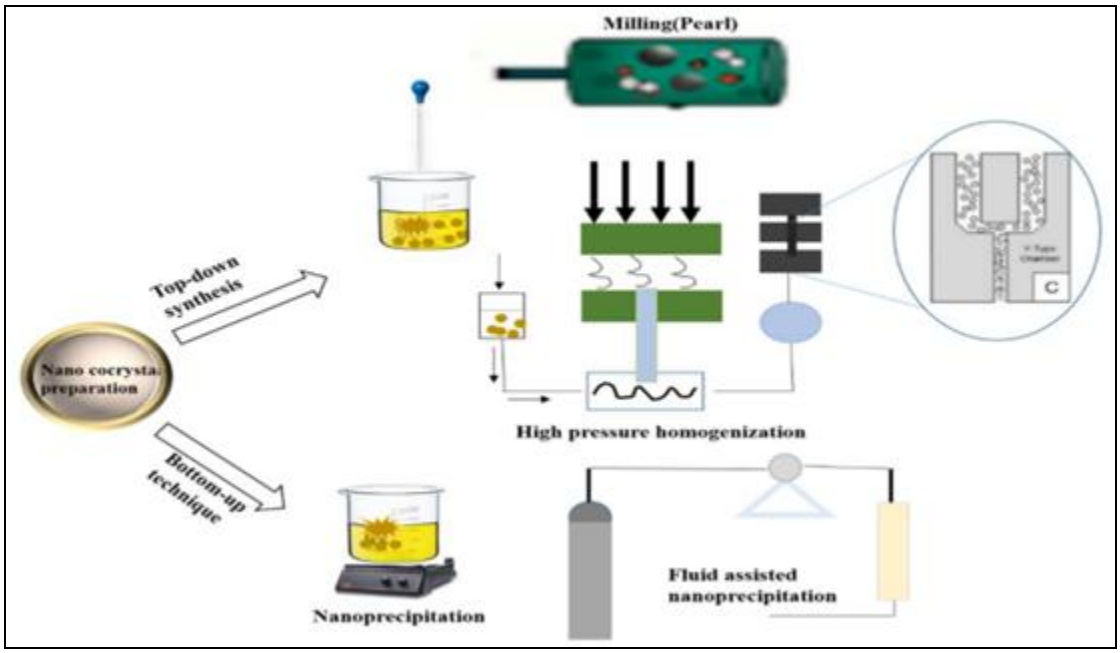

FIG. 2: TOP –DOWN AND BOTTOM –UP TECHNIQUES

Nano-Precipitation Process: Dissolving the drug in a solvent and then adding it to a non-solvent will precipitate finely dispersed drug nanocrystals. It should be noted that if these nanocrystals are not allowed to grow in the micron range, then these nanocrystals must be stabilized. In addition, the drug must be soluble in at least one solvent. This creates problems with newly developed drugs that are insoluble in both aqueous and organic media. For some of these reasons, this technology has not yet been applied to the product. The solution of surfactant and carotenoid indigestible oil is mixed with the appropriate solvent at a particular temperature. To obtain the solution a protective colloid is added. This leads to an O/W two-phase system. The carotenoid stabilized by the colloid localizes in the oily phase. After Lyophilization X-ray analysis shows that approximately 90 % of the carotenoid is in an amorphous state [15].

Top-down Technology: “Top-down” technology applies to disperse methods by using different types of milling and homogenization techniques. "Top-down" technology is more popular than "bottom-up" technology. It is known as "nano-ization". In other words, it is the process of breaking down large crystal particles into smaller pieces. Both methods are used together in "top-down and bottom-up" technology. Top-down techniques can be applied either by homogenization or grinding [16].

Milling Machine Process: Nanocrystal technology uses ball mills or bead mills to reduce particle size. Ball mills have been known for producing the finest suspensions since the first half of the 20th century. Grinding media, dispersion media (usually water), stabilizers, and drugs are charged into the grinding chamber. The impact shear force generated by the movement of the grinding medium leads to a reduction in particle size. In contrast to high-pressure homozygation, this is a low energy grinding technique. Smaller or larger crushed beads are used as the crushing medium. The beads or spheres are made of ceramic (cerium-yttria-stabilized zirconia), stainless steel, glass, or beads coated with highly crosslinked polystyrene resin. Erosion of crushed material during the grinding process is a common problem with this

technique. Grinding beads are coated to reduce the contamination caused by the erosion of the grinding medium. Another problem is that the product sticks to the inside of the mill. There are two basic grinding principles. The grist is agitated by the agitator, or the entire container is agitated with complex movements, resulting in the grist moving. Assuming that 76 % of the volume of the crushing chamber is filled with gravel, it is difficult to produce large batches when moving new vessels, so a large number of stirrer mills are used. Grind large batches. Grinding time depends on many factors such as detergent content, drug hardness, viscosity, temperature, energy input, grinding medium size, and much more. Grinding time is about 30 minutes to hours or days. This new technology is a significant particle size reduction demonstrated by the four FDA-approved drugs described below in this text [17].

Homogenization Methods: The Microfluidizer is a jet stream homogenizer in which two liquid streams collide head-on at high speeds (up to 1000 m/s) under pressures up to 4000 bar. Turbulence, high shear, and particle collisions reduce particles in the nanometer range. The high pressure applied, and the high flow rate of lipids can also cause further cavitation, which contributes to size reduction. Stabilization with phospholipids or other surfactants and stabilizers is required to prevent particle size. In many cases, sufficient particle size reduction requires 50-100 time-consuming passes [18].

Top-down and Bottom-up Technology: Both methods are used together in "top-down and bottom-up" technology. NanoEdge® is a product obtained by such a combination technology. Nanoedge technology explained how to prescribe poorly water-soluble drugs. It is a useful technology for active ingredients with a high melting point and a high octanol-water partition coefficient. It is based on direct homozygation, microprecipitation, and lipid emulsions. In microprecipitation, the drug is first dissolved in a water-miscible solvent to form a solution.

The solution is then mixed with a second solvent to form a presuspension and the presuspension is energized to form particles with an average effective particle size of 400 nm to 2 μm [19].

Spray Drying: One of the methods for producing nanocrystals is spray drying. This method is commonly used to dry solutions and suspensions. In a conical or cylindrical cyclone, droplets of solution are sprayed from top to bottom and dried in the same direction by hot air to form spherical particles. Spraying is done using a nebulizer that spins quickly due to the centrifugal effect and sprays the solution. The solution is pumped to the inner tube at a specific flow rate using a peristaltic pump, and nitrogen or constant pressure air is fed to the outer tube. The spray is done through the nozzle. When sprayed, the droplets of the solution become very small. Therefore, the surface area of the desiccant increases, resulting in rapid drying. You can adjust the concentration, viscosity, temperature, and spray rate of the solution to optimize particle size, fluidity, and drying rate [20, 21].

Nanopure Technology: This is a registered product name of Pharma Sol GmbH / Berlin. Equally effective particle size reduction can also be achieved with non-aqueous or water-reduced media. Preparation of nanocrystals in a non-homogenized medium is a very effective way to obtain a direct formulation. Nanocrystals of the active ingredient dispersed in liquid polyethylene glycol (PEG) or various oils can be filled directly into HPMC capsules or gelatin as an active ingredient suspension. Cavitation is the main force in reducing particle size. This technology was developed against this theory. Particle size reduction can also be achieved with nonaqueous media. It is necessary to form tablets, pellets, and capsules. The advantage of this process is that there is no need to remove the distributed medium. Evaporation occurs faster and under milder conditions (when using water and miscible liquids). This is useful for temperature-sensitive drugs. For IV Injection, isotonic nanosuspension is obtained by homozygation in a water-glycerol mixture. The reduction in water causes a reduction in the energy required for the various steps performed, such as fluidized bed drying, spray drying, or stratification of suspensions on sugar globules. Pharmasol's intellectual property includes water mixtures and anhydrous dispersion media (PEG, oil, etc.). NANOPURE technology has the main features of scaling and the ability to produce on a large scale using mild and normal conditions.

Pharmasol uses a pretreatment step followed by homozygation with Nanopure technology. This produces particles below the size range of 100 nm. The final nanosuspension looks translucent because the particle size is about 50 nm, which is smaller than the wavelength of visible light [22].

Spray Freezing in Liquid (SFL): The University of Texas (Austin) was the first university to develop and patent the SFL method in 2003. This technology was first commercialized by the Dow Chemical Company (Midland, Michigan). As used herein, spraying of an aqueous, organic, aqueous organic cosolvent solution, aqueous organic emulsion, or suspension containing a drug is of a compressed gas (e.g. CO 2, propane, ethane, or helium) or a cryogenic gas. It happens directly to either. Liquid (e.g. argon, nitrogen, or hydrofluoroether) [23, 24].

Nanocrystal Characterization:

Particle Size: Analysis The size and size distribution of dry morphological crystals is redispersed in water containing 0.1 % polyvinyl alcohol (PVA and 403) and then dynamically light scattered by a particle size analyzer Nanotrac 150 (Japan) equipped with a wet sampling system. Determined by and the diameter was calculated from the reported average particle size distribution [25].

Determining Drug Content: The drug content of the lyophilized sample was checked using a UV and spectrophotometer to confirm the purity of the prepared sample. To quantify the drug content in the product, the aqueous dispersion of the product (25 mg/10 ml distilled water) was passed through a 0.8 µm filter. A filtrate containing fine particles smaller than 0.8 µm was dissolved in a 4% sodium lauryl sulfate solution, and the drug concentration was measured by spectrophotometry at a wavelength of 291 nm. The amount of drug infiltration relative to the total amount of drug in the dispersion was calculated and expressed as nanocrystal yield [26].

Scanning Electron Microscopy: The surface morphology of the commercial drug powder and the freeze-dried formulation samples was examined by SEM. Before examinations, the samples were mounted on top of double-sided sticky carbon tape on metal discs and coated with 80 nm Gold/palladium in Blazers 120B sputtering device [27].

Powder Xray Diffraction (PXRD): The XRD patterns were recorded on an X-ray diffractometer (PW 1729, Philips, Netherlands). Samples were irradiated with monochromatized Cu-Ka radiation (1.542A˚) and analyzed from 50 to 500 2θ. The voltage and current used were 30 kV and 30 mA, respectively. The XRD procedure to estimate the degree of crystallinity was based upon the measurement of the total scattering and the scattering from the crystalline region of formulations and pure drugs [28].

Differential Scanning Calorimeter: DSC, equipped with a liquid nitrogen cooling system was used to measure the thermal behavior of the commercial griseofulvin powder and the freeze-dried samples. For DSC analysis, 2 and 5 mg samples were placed in aluminum pans and tested at a scan rate of 100 ° C / min at 25-300 ° C [29].

Solubility: Saturation solubility measurements were examined by UV absorbance measurements at 291 nm using a UV spectrophotometer. Excess amounts of drug powder and the formulation were added to 150 ml of 4% SLS solution and the mixture was stirred in a mechanical shaker at a temperature of 37 ± 0.05 for 24 hours [30].

Dissolution Test: Dissolution tests of and the pharmaceutical product on the market were performed by filling with Reinhard gelatin capsules (Zydus Cadila, Goa, India). The prepared sample and drug powder were packed in capsules (125 mg), subjected to a dissolution test using 900 ml of 4 % SLS solution as the dissolution medium, and preheated to maintain 37 ± 0.5 ° C. The basket rotated at a speed of 75 rpm. Samples of at least 10 ml were taken at specific time intervals, filtered through a 0.2, and measured for concentration with UV and spectrophotometers [31, 32].

Application of Nanocrystals to Pharmaceuticals in Drug Development [33, 34]:

1. Parent management
2. By oral administration
3. Administration of ophthalmic drugs

4. Delivery of the drug via the lungs
5. Targeted drug delivery
6. Skin administration of the drug

Parenteral Administration: Drug nanocrystals in the form of nanosuspensions can be administered via a variety of parenteral routes of administration ranging from intra-articular to intra-articular. Intravenous injection from the abdominal cavity. Nanosuspension has been shown to enhance the effectiveness of parenteral drugs. Clofazimine nanosuspension, a less water-soluble antileprosy drug, is more stable and effective than liposomal clofazimine.

By Oral Administration: Nano sizing the drug dramatically improves oral absorption and subsequent bioavailability. Aqueous nanosuspension can be used directly in a liquid dosage form such as tablets and hard gelatin capsules with pellets.

Pulmonary Drug Delivery: Aqueous nanocrystals can be nebulized using mechanical and ultrasonic nebulizers for lung delivery. The dispersion can be of high concentration due to the presence of many small particles instead of a few microparticles; all aerosols` droplets contain drug nanocrystals. Budesonide, a poorly water-soluble corticosteroid, has been successfully prepared as nanosuspension is formulated for the treatment of lungs infections by using nebulization.

Target Drug Delivery: Nanocrystals can be used for target delivery. Targeting of Cryptosporidium parvum, the causative organism of cryptosporidium disease, was achieved using a surface-modified mucosal adherent nanosuspension of buplavauon. Similarly, diseases such as pulmonary aspergillosis can be easily addressed by using appropriate drug candidates such as amphotericin B in the form of lung nanosuspensions instead of stealth liposomes.

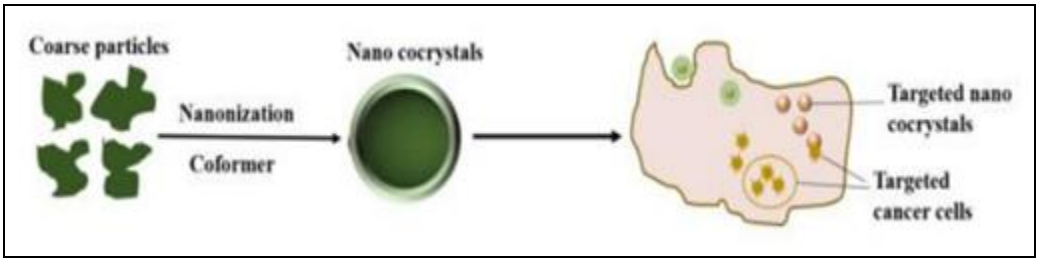

FIG. 3: TARGET DRUG DELIVERY

Skin drug delivery Skin nanosuspensions are of particular interest if the conventional formulation approach fails and the use of active ingredient nanocrystals leads to an increase in the concentration gradient between the formulation and the skin. Increased saturation solubility results in supersaturated formulations, thereby enhancing drug absorption through the skin. This effect can be further enhanced by using a positively charged polymer as a stabilizer for drug nanocrystals. Opposite charges lead to increased affinity of drug nanocrystals for negatively charged Stratum Conium.

CONCLUSION: Nanocrystals offer a promising solution for addressing the challenges associated with poorly water-soluble drugs. By reducing particle size and increasing surface area, they significantly enhance dissolution rates and bioavailability. The incorporation of stabilizers ensures the thermodynamic stability of these nano-sized systems, enabling their practical application in drug delivery. Overall, nanocrystals represent a cutting-edge advancement in pharmaceutical technology, paving the way for improved therapeutic efficacy and patient outcomes.

ACKNOWLEDGEMENT: The authors are thankful to Department of Pharmacy, IEC University, Solan, H.P, India and thankful to Dr. Dinesh Kaushik from Hindu college of Pharmacy, Sonipat, Haryana for good guidance.

CONFLICT OF INTEREST: Authors declare no conflict of interest.

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How to cite this article:
Anand V and Kaushik D: Nanocrystals for Improved Drug Delivery: A Review. Int J Pharm Sci & Res 2025; 16(4): 900-07. doi: 10.13040/IJPSR.0975-8232.16(4).900-07.