



ADVANCES IN PHARMACEUTICAL NANOCRYSTALS: STRATEGIES FOR PREPARATION AND DRUG DELIVERY APPLICATIONS

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Abstract

Nanocrystal technology serves as a successful method which improves the solubility, dissolution speed, and body absorption of drugs that poorly dissolve in water. Pharmaceutical nanocrystals consist of pure drug particles which measure between 10 and 1000 nanometers and stay stable through appropriate surfactant or polymer protection. The distinct particle size of nanocrystals together with their extensive surface area results in special physicochemical characteristics and biological behavior which boost drug effectiveness. The modern pharmaceutical industry faces its biggest obstacle because many new chemical entities experience difficulty dissolving in water where approximately 70 to 90 percent of drug candidates fall into Biopharmaceutical Classification System categories II and IV. The technology of nanocrystals solves this problem through its ability to accelerate dissolution rates while enhancing the body's ability to absorb drugs through the mouth. Various methods exist for producing nanocrystals which include top-down methods that use high-pressure homogenization and wet media milling and bottom-up techniques which include antisolvent precipitation and solvent evaporation and combined methods which feature NanoEdge and SmartCrystal technology. The strategies used for particle preparation enable precise management of particle dimensions and particle structure and particle stability. Researchers have investigated pharmaceutical nanocrystals through multiple drug delivery methods which include oral administration and parenteral administration and ocular administration and pulmonary administration. Researchers continue to investigate multiple fields which create obstacles for products which require physical stability and large production capacity and need to meet regulatory guidelines and need to prove their safety over extended time periods. The comprehensive review explains basic principles and techniques for making nanocrystals and their physical characteristics and their uses in drug delivery systems which operate in modern medical environments.

Keywords

Nanocrystals; Top-down methods; Bottom-up techniques; Solubility enhancement; Drug delivery systems; Pharmaceutical nanotechnology

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1. INTRODUCTION

Nanocrystals share an atomic structure with big crystals, but they have distinct physical, chemical, optical, and biological characteristics due to their small size. Nanocrystals can solubilized more quickly, react more simply, and show Particle size-dependent behaviors like enhanced solubility or adjustable optical properties due to their high surface area to volume ratio. By reasons of these characteristics, nanocrystals are valuable in biotechnology, electronics, medicaments, cosmetics, and semiconductors.¹ Drug discovery and development, poor solubility of therapeutic compound is a difficult issue; roughly 70–90% of novel compounds fall into class II or class IV of the (BCS) classification.² The synthetic process can be easily determined by the nucleation process (from precursors to nuclei) and the growth process (from nuclei to nanocrystals). One major problem of Nano-catalysis is the understanding of the intrinsic variation between homogeneous and heterogeneous catalysis, corresponding to the processes from one atom to bunch and nanocrystals. So clarifying the relationship between the nucleation and growth processes is an important necessity to make the perfect structure dependent activity of nanocrystal catalysts. The development stage of nanocrystal synthesis and then turn our energy to the recently developed experimental techniques to research the nucleation process.³

2. IMPORTANT OF NANOCRYSTALS IN PHARMACEUTICAL SCIENCE

- I. It help to enhances the solubility of class ii and class iv of Biopharmaceuticals classification systems drugs.⁴
- II. Their light driven catalysis antimicrobial activity makes them an amazing material for food packaging.⁵
- III. Nanoparticles have metallic & semiconductor potential which help for the diagnosis & therapy of cancer by the light scattering and absorption properties due to LSPR effect.⁶
- IV. Nanocrystals are successfully used in different pharmaceuticals health care such as cellular imaging, or in biosensors for nucleotides, carbohydrates, protein and heavy metal ion, and also help to determine blood glucose level, and for the diagnosis of bacteria & virus.⁷
- V. It helps for different types of novel drug delivery system like pulmonary, transdermal patches, ocular drug, dermal drug, and ophthalmic drug delivery system.⁸

3. CLASSIFICATION OF NANOCRYSTALS

There are different types of nanocrystals which are useful for various pharmaceuticals medicament like drug delivery systems, for the formulation of different dosage form.⁹

3.1 Based on their dimensionalities,

Zero-dimensional (0D) size of nanocrystals are found in the 3-dimensional (x, y, z) size are less than 100nm nanoscale.¹⁰

One-Dimensional (1D) nanoparticles are very fine, coil-like structures with diameters less than 100 nanometers. Examples include nanowires, nanotubes, and Nano rods. Because of their different size and shape, these materials are considered very useful for making small electronic and optoelectronic devices.¹¹

Two Dimensional (2D) are extremely fine sheets made of one or a few atomic layers. Examples include graphene, MXenes, and transition metal dichalcogenides (TMDs). Because the atoms are strongly linked within the fine sheet but weakly held between layers, these particles have special electronic, optical, and mechanical properties. They have a large surface area, good electrical conductivity, and adjustable energy gaps, which make them useful in flexible electronics, sensors, energy storage, catalysis, and medicament, such as novel drug delivery.¹²

Three-dimensional (3D) they have small structures where the length and width and height are all in nanoscale 1 to 100 nm. Combine all tiny nanoparticles together to form a 3D nanoparticle. It occupied large surface area and some unique properties. They are also used in various types of novel drug delivery system.¹³

3.2 Based on their composition,

Organic Nanoparticles – these are made from carbon-based materials like proteins, lipid, nucleic acid and polymeric materials and the properties of these particles are biodegradable, biocompatible targeted drug delivery and controlled release. Mainly this is used for the gene therapy, chemotherapy, vaccine development and diagnostic purpose, etc. Example such as liposome, Nano emulsion, polymeric micelles etc.¹⁴

Inorganic Nanoparticles – this is made from non-carbon materials like metal, metal oxide, ceramics, etc. their properties like high surface area, improved strength, tailorable optical enhanced reactivity. This is used in basically biomedical imaging diagnostic,

catalysis etc. Example such as Silver nanoparticles, iron oxide nanoparticles, gold nanoparticles, etc.¹⁵

4. METHOD OF PREPARATION OF NANOPARTICLES

There are different types of method which are used for the preparation of Nanoparticles. Here are mentioned some methods of preparation (Fig 1).¹⁶

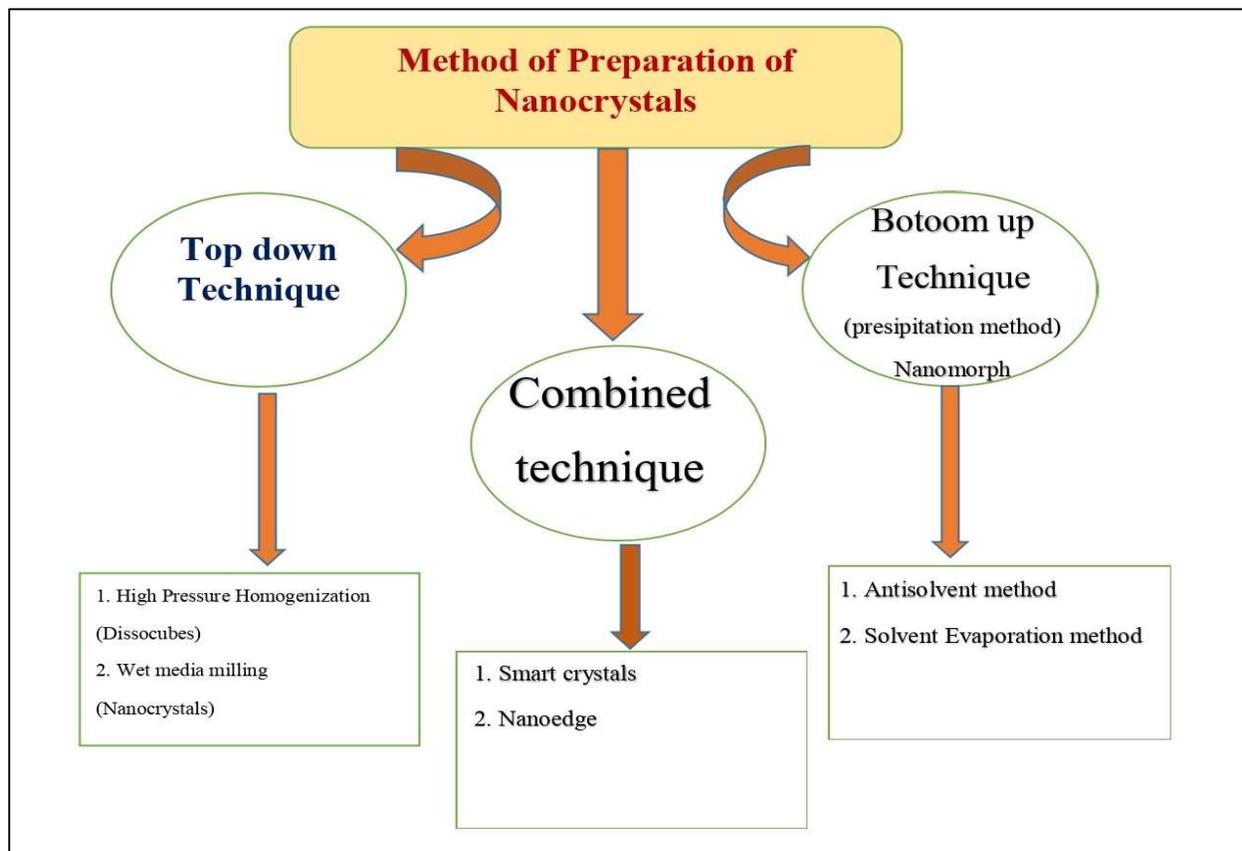


Figure 1: Preparation method of Nanocrystals

4.1 Top-down Technique

It is also known as mechanical grinding. It is an easy and popular method. Here the materials are milled into very fine powders. It is one of the most important processes used in industries to synthesize nanoparticles.^{17,18} this method has many advantages such as compact design, energy efficiency, minimum maintenance, inexpensive and scalable. It works on the principle of impact. The size reduction is achieved through the impact caused when the balls drop from the top of the chamber in which the source material is placed.¹⁹

4.1.1 High Pressure Homogenization

It is a method which is basically used in preparation of nanoparticles by reducing the coarse size of drug particles. High pressure homogenization is based on the principle that is break down of large particle into nanocrystals. By providing the force of air pressure between 100 to 2000 bar. Sudden decrease the pressure its results in, shear forces, cavitation and particle–particle crash.²⁰ in this method dispersed the class 2 drug (that is poorly water-soluble drug) in an aqueous stabilizer solution (polymer or surfactant) and

the gross suspension is milled to avoid clogging. After the suspension go through the high-pressure homogenizer respectively 10 to 30 times. Crystal's size is reduced to nanometers (100 to 500 nm). Nanocrystals are obtained.²¹

4.1.2 Wet media milling

It is also known as Nano milling technique. This technique are basically used in pharmaceutical industry to prepare drug nanoparticles by decreasing the gross drug particles by the help of mechanical attrition in a aqueous medium.²² wet media milling based on the principle of drug reduced to the nanometer range by the help of shear, impact, and attrition forces generated when the drug suspension is agitated with milling media in the presence of stabilizers. Basically class 2 drug which are poorly water-soluble drug is disperse in an aqueous medium containing stabilizer (polymer or surfactant).²³ Milling bead like zirconium oxide, polymer and glass bead are added to the suspension. And the mixture is placed in a media mill and agitated at high speed. Continuous collision between bead & drug crystals reduces its crystal size milling is continued until nanocrystals (100 to 500 nm) are obtained.²⁴

4.2 Bottom-up technique

This technique is used for the preparation of nanoparticles and is commonly referred to precipitation method. Self-assemble of ions, molecules, and individual's atom into nanoparticles with the help of physical and chemicals process.²⁵

4.2.1 Antisolvent method

There are various Technique used for the preparation of nanocrystals by the precipitation method. The precipitation of nanoparticles by adding liquid solvent-antisolvent addition are reported. It is the easiest method for making a nanocrystal by precipitation method. There are different molecules are there that is synthetics as well as natural sources like silymarin.²⁶ The drug has high solubility in which the drug molecules are dissolved in a solvent by using water miscible solvent after that solution was mixed properly with antisolvent (water) which are miscible with solvent phase. The ratio of solvent and antisolvent are selected by the given appropriate parameter. Precipitation occurred by the simple mixing.²⁷

4.2.2 Solvent evaporation method

This method is basically used in bottom-up technique in which the drug and solvent are mixed properly with the help of mechanical stirrer.²⁸ After that the solution is passed through various type of dryer such as nano spray dryer. In which the solutions are introduced, and the solution are convert into droplets then by the help of atomizer droplets are converted in to mist form then evaporated and the nanocrystal are obtained. Mainly the instrument which are used to formulate the nanocrystals in this method are nano spray dryer.²⁹

4.3 Combined method

This technique is mainly based on the combination of both top-down method and bottom-up technique. This technique is based on Nano edge and smart crystals. The size of nano crystals are not more than 100nm. Sometime this method are used for the novel drug delivery system and also helps in the formulation of different dosage forms. The properties of these nano particles are biodegradable, biocompatible, nontoxic.³⁰

4.3.1 Nano edge method

The Nano Edge method is a technique used to make very tiny crystals (nanocrystals). It combines two approaches: bottom-up and top-down. First, the drug is made to form small crystals using precipitation (bottom-up method). These crystals are already smaller than normal particles.³¹ Mechanical force, such as High-Pressure Homogenization (HPH), is applied to break these crystals down into nano size particles (top-down method). Because the crystals are already small before homogenization, this method prevents clogging of the homogenizer and works more efficiently. The Nano Edge method is especially useful for poorly soluble drugs, as the very small particle size improves drug dissolution and increases bioavailability in the body.³²

4.3.2 Smart Crystals

The Smart Crystals method is a modern way to prepare very small drug particles called nanocrystals, mainly used in pharmaceutical applications. This method combines two techniques instead of using only one. First, a bottom-up method like precipitation is used to form small drug crystals. Then, a top-down method such as high-pressure homogenization (HPH) or

milling is applied to further reduce the particle size to the nanoscale (less than 100 nm).³³ By combining both methods, Smart Crystals avoids problems seen with single techniques, such as poor size control or equipment blockage. The resulting nanocrystals are very fine, stable, and help poorly soluble drugs dissolve better, which improves their bioavailability in the body. Common Smart Crystals combinations include Precipitation + HPH (H69), Spray Drying + HPH (H42), Lyophilization + HPH (H96).³⁴

5. APPLICATION OF NANO CRYSTALS IN PHARMACEUTICAL SCIENCE

- i. There is broad spectrum of uses of nanocrystal in pharmaceutical science. There are different uses not only pharmaceuticals science such as electronic devices etc. some applications are given below.³⁵
- ii. Nanocrystals greatly improve drugs that do not dissolve well in water. By making the drug particles extremely small, they dissolve faster in the body and are absorbed better. This increases the drug's solubility and bioavailability.³⁶
- iii. Because of this, nanocrystals can be used in many types of medicines, such as oral tablets, injections (IV), creams, and inhalers. Their surface can also be modified to help the drug reach specific sites in the body, which is very useful for cancer and long-term diseases.³⁷
- iv. Overall, nanocrystals help medicines work better at lower doses, reduce side effects, improve patient comfort and compliance, and solve major formulation problems for drugs that normally have poor absorption.³⁸
- v. Improved Solubility & Bioavailability- Nanocrystals help drugs that do not dissolve well in water dissolve much faster. This allows the body to absorb more of the drug, so it works better and gives improved results.³⁹
- vi. Versatile Delivery Routes- Nanocrystals can be used in many types of medicines, including oral tablets or liquids, injections, inhalers for the lungs, skin patches, and eye drops. This makes them very flexible for different treatments.⁴⁰
- vii. Targeted Drug Delivery- The surface of nanocrystals can be modified so the drug reaches specific areas of the body, such as tumors. This supports more accurate and effective treatments, especially in cancer therapy.⁴¹

- viii. Reduced Dosing & Variability- Nanocrystals provide more consistent drug levels in the body. This allows lower doses, reduces the effect of food on the drug, and makes treatment more convenient and comfortable for patients etc.⁴²

6. CHALLENGES AND FUTURE ASPECTS OF NANOCRYSTALS

Natural ingredient nanocrystals have great potential in drug delivery, but they still face many challenges. Natural ingredients are complex, which makes them difficult to purify and sometimes affects their effectiveness. Nanocrystals can also be unstable during storage and while traveling inside the body.⁴³ In addition, large scale production and studies on how these Nanocrystals behave in the body are still slow, which delays their use in clinics. Another major challenge is regulation. Nano pharmaceuticals must meet strict rules related to stability, manufacturing quality, and safety. These strict regulatory requirements make it difficult to develop and approve nanocrystal based pharmaceutical or API drugs.⁴⁴ High surface energy- Nanocrystals tend to stick together or release the drug too quickly. To prevent this, special stabilizers are needed, but these stabilizers can also cause problems, such as skin irritation.⁴⁵ Scalability and cost- Making nanocrystals in the laboratory is easier than producing them on a large industrial scale. Large-scale production needs costly equipment and new manufacturing methods.⁴⁶ Surface control- It is difficult to accurately attach targeting molecules or form strong protective layers (like ZnS or SiO₂). This makes targeted drug delivery and long-term stability harder to achieve.⁴⁷ Health and environmental safety- The long-term effects of nanocrystals in the body and environment are not fully known. There is concern about toxicity, buildup in organs, and environmental harm, so strict safety testing is required.⁴⁸ Reproducibility and purity- Producing nanocrystals with the same size, shape, and composition every time is challenging, especially when making multiple batches.⁴⁹ Sterilization- Sterilizing nanocrystal drugs for injections is difficult because common sterilization methods can damage their structure or reduce their effectiveness.⁵⁰

There are some future aspects of nanocrystals which are mentioned below in sequence wise. Advanced Surface Engineering- Scientists coat tiny particles (nanocrystals) with protective layers like ZnS or organic shells. These coatings make them safer, stop harmful leakage, and help them last longer.⁵¹ Hybrid Synthesis- Researchers combine two methods

breaking big materials into small ones and building small ones step-by-step. This helps make nanocrystals that are more uniform in size and shape.⁵² Smart & Responsive Systems- Some nanocrystals are designed to react to things like light or changes in acidity (pH). This allows them to release medicine only when needed or assemble themselves automatically.⁵³ Bio-inspired Designs- Scientists copy ideas from nature, such as how plants do photosynthesis, to make better systems for producing and storing energy.⁵⁴ Sustainable & Biocompatible Materials- Efforts focus on using non-toxic and plant-based nanocrystals that are safer for the body and the environment.⁵⁵ Enhanced Imaging & Displays- Quantum dots help create brighter, sharper screens and improve medical imaging so doctors can see things more clearly.⁵⁶ Targeted Therapies- Specially designed nanocrystals carry drugs directly to tumors or infected areas, reducing side effects and improving treatment efficiency.⁵⁷

7. CONCLUSIONS

Nanocrystals are an important and useful technology in modern pharmaceutical science. They help solve major problems such as poor solubility, low absorption, and reduced effectiveness of many drugs. Because nanocrystals are extremely small and have a large surface area, they dissolve faster in the body and are absorbed more easily. This improves the drug's

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bioavailability and allows their use in different dosage forms, such as tablets, injections, inhalers, skin patches, and eye drops. Nanocrystals are also useful in areas like medical imaging, diagnostics, biosensors, and antimicrobial applications. Different preparation methods, including top-down, bottom-up, and combined techniques like Nano Edge and Smart Crystals, have made it easier to produce stable and effective nanocrystals. These methods are especially helpful for formulating poorly water-soluble drugs from BCS class II and IV into useful medicines. However, some challenges still exist, such as stability problems, difficulty in large-scale production, strict regulatory requirements, safety concerns, and maintaining consistent quality. In the future, improvements in surface modification, smart drug delivery systems, and the use of safe and eco-friendly materials will make nanocrystals even more effective. With continued research and development, nanocrystals have great potential to improve drug therapy by increasing effectiveness, reducing dose and side effects, and enhancing patient comfort and treatment success.

Conflict of interests

Authors declare that there is no conflict of interest.

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