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Review Article

Nanocrystal System: A Comprehensive Review of Method of Preparation and their Characterization, Patents and Marketed Products

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Abstract

Nanocrystal drug delivery systems have emerged as a promising method to improve the bioavailability, solubility and therapeutic efficacy of poorly water-soluble drugs. Developed many methods for their creation with top down, bottom down and combination technique. These nanosized particles, usually ranging from 100 to 1000 nm, provide increased surface area, improving dissolution rates and enabling drugs to reach their target more efficiently. This abstract outline the methods for preparing nanocrystals and their characterization, recent marketed formulations and the current trends in patent related to nanocrystal drug delivery systems and their applications.

Keywords: Nanocrystal, Method Nanocrystal, Patent, Application

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Introduction

For most new drug candidates as well as medications in clinical use, inadequate water solubility is a significant barrier to obtaining sufficient bioavailability. According to reports, between 80% and 90% of medication candidates in research may fail due to solubility issues, and about 40% of commercialised pharmaceuticals have low solubility [4]. The majority of medications in the treatment pipeline have inherent physical and chemical characteristics that make them insoluble or very poorly soluble in water. This complicates the conditions under which they must be administered and somewhat restricts their effectiveness, which can have negative effects on drug bioavailability and therapeutic effects[5]. The biopharmaceutics classification system (BCS) class II (poorly soluble, permeable) and class IV (poorly soluble, impermeable) molecules have so garnered a great deal of attention in the formulation development techniques for comparatively poorly soluble medications [6, 7]. Brick dust compounds and grease ball compounds are the two subclassifications of these poorly soluble medicines[8]. The molecules known as grease balls are an example of highly hydrophobic compounds (log P > 4, melting points < 200 °C) that are incapable of forming bonds with molecules of water. The solvation mechanism thus limits their solubility. Lower log P (< 2) values and greater melting points (> 200 °C) are observed in the molecules of brick dust. Since the crystal structure contains strong intermolecular interactions, its water solubility is limited. Over the years, several effective formulation approaches have been used to increase the solubility and bioavailability of medications that are insoluble in water. These procedures include salt production[9, 10], amorphous solid dispersion[11, 12], in situ amorphization[13, 14], cyclodextrin complexation[15, 16], co-crystals[17-19], co-amorphous systems[20, 21], melt extrusion[22]. Nanocrystals are pure drug crystals with an average particle size in the nanometre range (10 – 1000 nm) and enough stabiliser to make the solution both thermodynamically and sterically stable. Generally, there are two ways to generate nanocrystals: either by developing particles in

the nm size range (bottom up approach) or by reducing the particle size (top down approach), or by combining the two methods[23]. Features of nanocrystals include the following. As particle size reduce, the surface area of nanocrystals rises. Based on the Noyes-Whitney formula[24]. When rise in surface area causes a nanocrystal's dissolving rate to rise. The Ostwald-Freundlich equation states that[25], Reducing the size to the nanoscale range greatly improves a drug's solubility[26]. The surface of the gastrointestinal tract is protected by a mucus layer that has a porous structure. Because of its tiny particle size, it can quickly enter the mucus layer's pore channels and firmly cling to them such that it can extend the duration and effective range of medications in the gastrointestinal system. Each of these characteristics helps to improve the medication's bioavailability and absorption[27-29]. The reason for the invention of nanocrystals was actually to increase the oral bioavailability of insoluble medications[30]. Additional benefits have been investigated with the advancement of medication nanocrystal research. i) enhancing the way that medicines are metabolised[31]. lowering adverse effects and toxicities, encouraging patient adherence[32]. The rapidly developing field of drug nanocrystal technology offers new and favourable opportunities for pharmaceutical research. One of its main contributions is the ability to manufacture medications that are poorly soluble[33]. Numerous pharmaceutical nanocrystals have been effectively brought to market[34].

In comparison to the micronized aprepitant, a aprepitant nanocrystal known as Emend was released to the market in 2003 and shown enhanced absorption, less drug–food interactions, and improved bioavailability[35]. First generation nanocrystal comes under wet media milling and high pressure homogenization i,e (top down method) where freeze drying, spray drying comes under bottom up method[36, 37]. Second generation nanocrystal i,e smartcrystal particle size less than 100nm. The word "smart crystal" refers to a nanocrystal nanosuspension made using a mix of top-down and bottom-up techniques. Such as H69(Precipitation + HPH), H42(Spray drying + HPH), H96(Lyophilization +HPH)[38, 39].

In this review, focus on method of preparation such as, top down method, bottom up method, combination method (smartcrystal) First, the technologies used currently to create drug nanocrystals are described. Then application, patent and current market status are briefly mentioned.

Classification of Nanocrystal

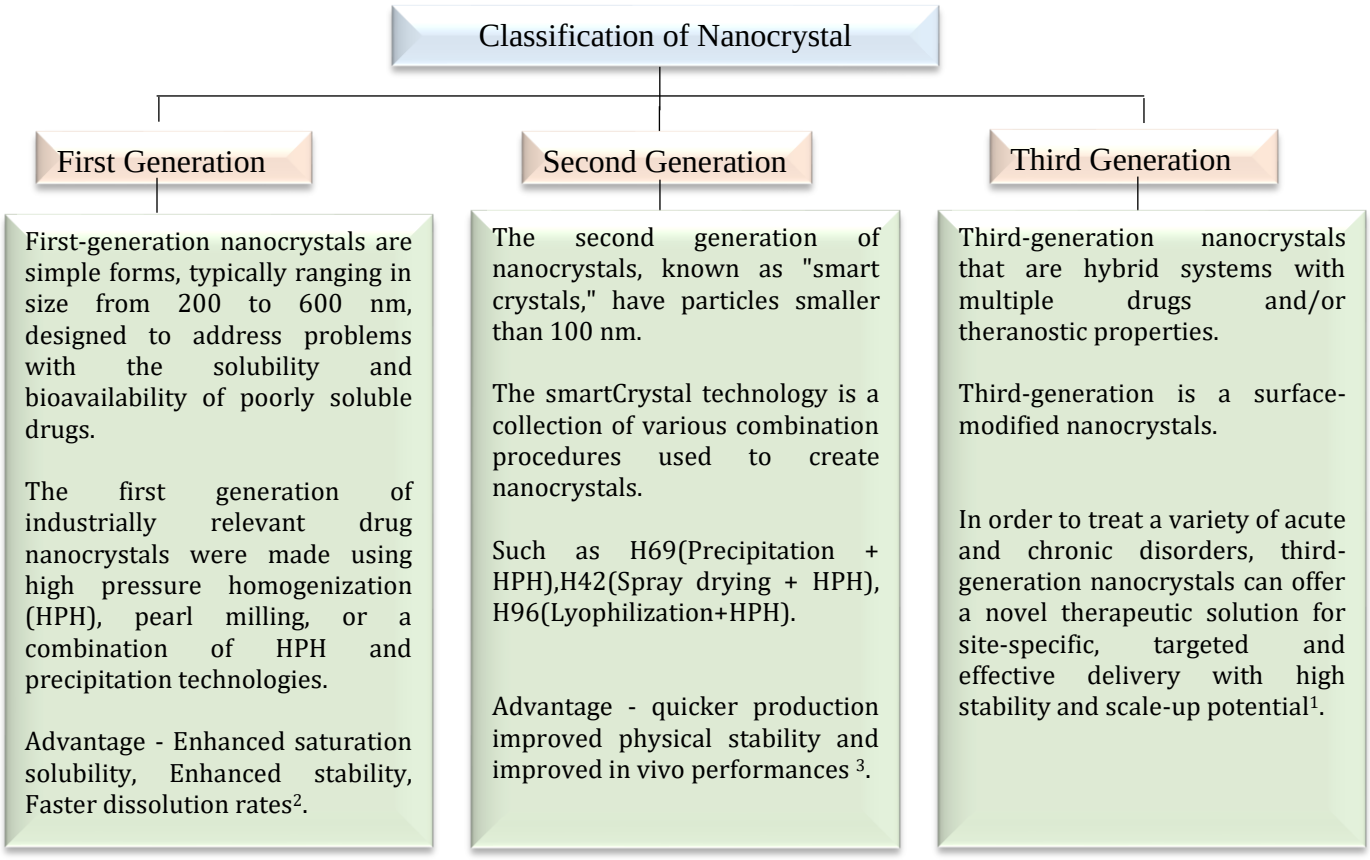

Figure 1: Classification of Nanocrystal

Preparation Technology

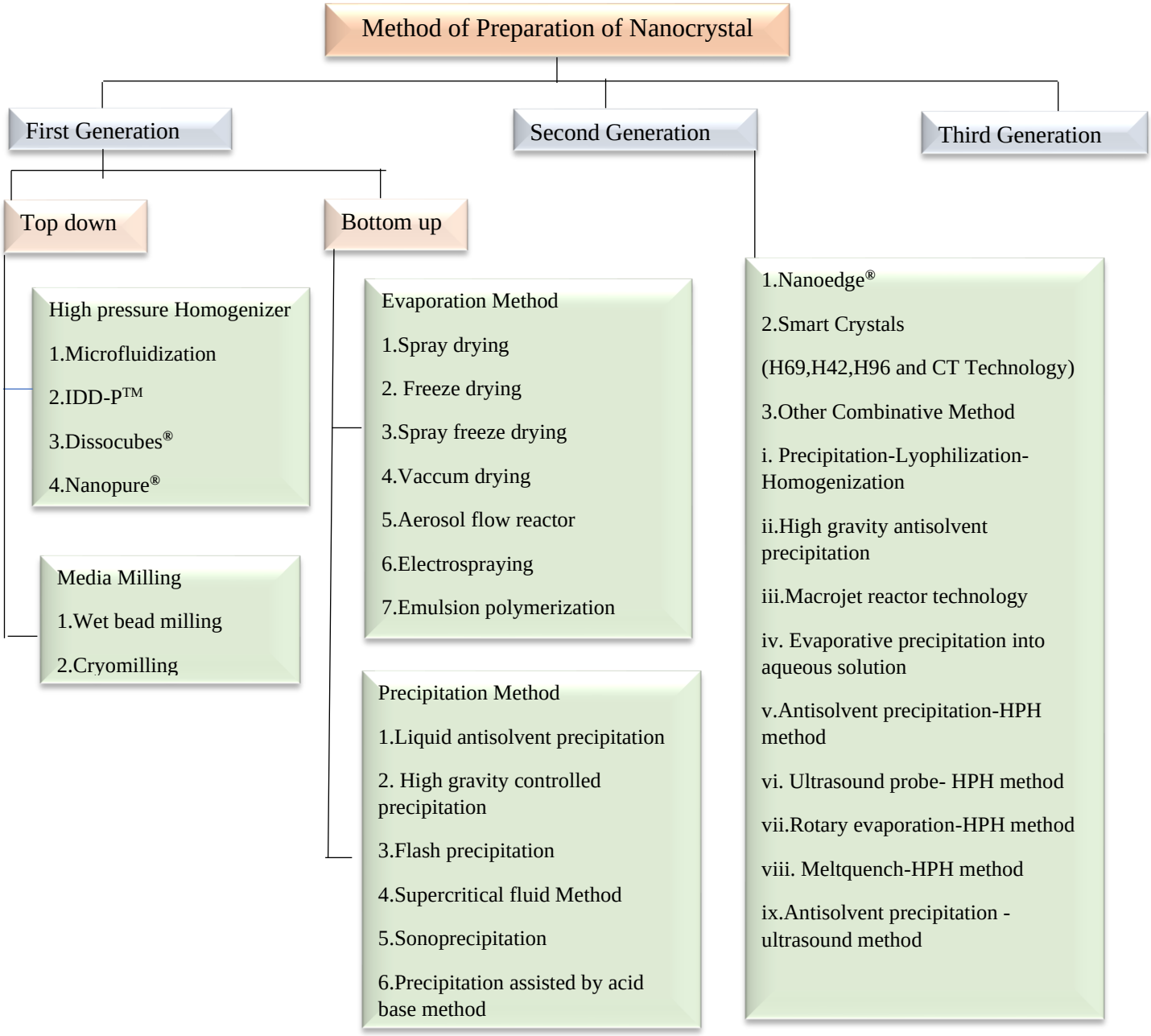

Figure 2: Method of Preparation Nanocrystal

1. Top Down Method

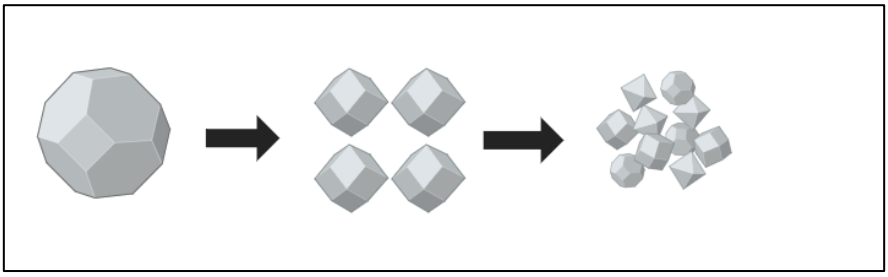

Figure 3: Top down method

In the top-down method, crystalline species fragmentation and secondary nucleus nucleation are followed by mechanically produced shear and collision forces that lower the size of drug particles[40]. Top-down

technology formation rate is not affected by supersaturation. Additionally, it works well with

A) Wet bead milling

Wet bead milling uses high-intensity mechanical force, stabilizers, and water to produce drug nanocrystals. Following the dispersion of drug particles in a stabilizing solution, the resulting macrosuspension is milled under energy[42]. Bead milling, or pearl milling, is the traditional milling method using NanoCrystalTM technology. Particle size reduction is achieved by the shear force of impact produced by the movement of the milling media when drug particles, stabilizers, and dispersion medium (usually water) are added to the chamber. Usually, strongly crosslinked polystyrene resin-coated beads, glass, stainless steel, or ceramics are used to create pearls or balls[34]. Because the temperature can be regulated during the preparation process, the pearl milling approach is particularly well-suited for creating thermolabile drug nanocrystals[28].

Drawbacks - The problems with contamination brought on by the grinding beads and the agglomeration-related poor physical stability of storage[43]. Since the beads can melt to prevent contamination, techniques utilizing dry ice beads have been suggested as a remedy to the troublesome concerns[44].

B) Cryomilling

Cryomilling is the process of mechanically milling materials at very low temperatures, ideally less than 123 K[45].

Advantage of cryomilling –

extremely low temperature, it can give powders a friable and brittle nature, minimizing agglomeration and speeding up fracture, which makes them refined and distributed quickly- two essential qualities in medical applications[46]. Furthermore, very low temperatures can shield pharmaceuticals from chemical deterioration by

medications that are insoluble in both organic and aqueous phases[41].

preventing nanocrystals from returning to their original crystalline state during subsequent milling[45].

C) High pressure Homogenizer

Drug particle collision, turbulent flow, cavitation and high shear powers produced in an HPH chamber are the methods used by HPH to break down drug particles[47]. **Example -** To improve quercetin's water solubility and bioavailability, Karadag et al. synthesized nanocrystals utilizing HPH technology[48]. Similar to this, Sun et al. used the HPH technique to generate an itraconazole nanosuspension[49]. The HPH approach is used to create the goods that are now on the market, such as fenofibrate tablets Triglide®, paliperidone palmitate intramuscular (IM) suspension Invega Sustenna, and luteolin nanocrystals [50].

D) Laser Ablation

After radiation is applied to the solid target, material is expelled and forms nanoparticles in the liquid around it. Then, laser-mediated fragmentation breaks up agitated suspensions of microparticles into nanoparticles[51]. Although no organic solvent is used in this method, a tiny amount of the drug may experience oxidative deterioration and crystal state alterations as a result of using too much power[52].

E) Ultrasound

Using the vibration of acoustic waves, ultrasound is an active way to breakdown drug particles into minor pieces. Through the creation of acoustic cavitation in solution and the quick dispersal of the drug in solution, ultrasound has been demonstrated to improve nucleation[53]. It is also frequently coupled with other procedures because to its great reproducibility and ease of usage in the laboratory[47].

2. Bottom-Up Method

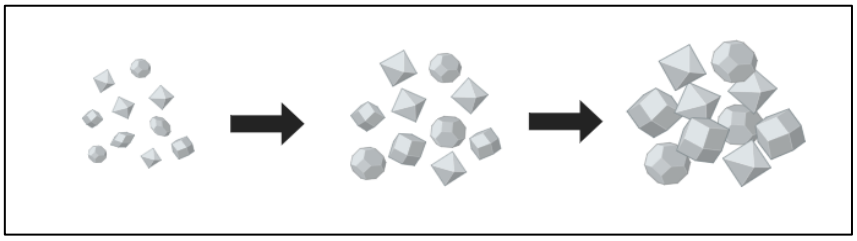

Figure 4: Bottom-up method

It mainly based on two basic principles, precipitation and evaporation[54].The main principle is to achieve drug nanocrystals from the supersaturated state of drugs and then manage the size distribution of the nanoparticles by suitable methods. There are two basic phases involved in the formation of nanocrystals in solution: nucleation and subsequent crystal development. Removing the solvent or combining with an anti-solvent can both cause nucleation. Certain techniques, like

sonication, which works through the cavitation effect, can be used to encourage nucleation. Numerous techniques, such as high gravity-controlled precipitation, are also available to regulate the formation of crystals.

Drawback – These precipitation methods' primary issue is their use of solvents, which necessitates their removal after use and raises manufacturing costs[47, 50].

A) Precipitation methods

a) Liquid anti-solvent precipitation (LAS)

An aqueous insoluble substance that is dissolved in the organic solution is combined with an aqueous anti-solvent to produce nanocrystals [28, 55].

The most frequently reported bottom-up technology is this solution anti-solvent approach for nanoprecipitation. This is a simple and economical procedure and its involves the nucleation and growth processes[55]. However, the use of organic solvent raises production costs and is not appropriate for drugs that are neither aqueous nor non-aqueous soluble[56].

b) High gravity controlled precipitation (HGCP)

High gravity controlled precipitation (HGCP) is an enhanced precipitation technique that uses gravity control to produce smaller and more homogeneous drug nanocrystals[57]. Drug-containing solvent and anti-solvent phases are combined in this technique and fed onto a revolving packed bed at a high gravity to create nanosuspensions, which are then collected and lyophilized to produce dried nanocrystals[41].

Drawback - The concurrent continual nucleation arising from local feed stream oversaturation during mixing at the turbulent edge limits its industrial use[41].

c) Flash nanoprecipitation method

Utilized in the formulation of numerous extremely hydrophobic drugs nanocrystals. According to the needs of the liquid jets, two kinds of flash precipitation: the multi-inlet vortex mixer and the confined liquid impinging jets (CLIJ) have been created.

i) Flash precipitation using CLIJ

When a jet of drugs solution and a jet of anti-solvent pass through two opposite nozzles placed in a tiny chamber, creating significant turbulence and intensive mixing, precipitation takes place in that area[58]. The antisolvent will cause the drug solute to precipitate as tiny submicron particles when two liquid jets are mixed[59].

ii) Multi-inlet vortex mixer

By adjusting the content and velocity of separate streams, it is possible to manage the solvent composition and supersaturation by mixing uneven volume stream flows through the use of 4-stream MIVM[60].

d) The supercritical fluid (SCF)

The supercritical fluid (SCF) method involves dissolving drugs in a supercritical fluid (such as CO2) and causing the fluid to vaporize quickly when it is atomized under low pressure through a nozzle with a narrow aperture, precipitating nanocrystals[61]. Uses the exclusive properties of SCF to precipitate nanocrystals, which have joint diffusivity like gas and solubilization like liquid[62]. The two primary techniques for SCF are supercritical anti-solvent (SAS) and rapid expansion in supercritical solution (RESS)[47].

i) RESS Technique

First, the drug particle is dissolved in a SCF (mainly CO2), and then an expansion chamber nozzle is used to abruptly depressurize the system. The approach can be further improved, depending on the placements of the nozzles. The rapid expansion of a supercritical solution into a liquid solvent method. In an aqueous solution nozzle is placed. Sometimes an organic solvent, like methanol, is utilized with RESOLV. In the precipitation vessel water is added which act as a receiving solvent because many of the desired active components are insoluble in water. In the latter instance, it is also known as rapid expansion of supercritical solvent into an anti-solvent(RESSAS)[63].

ii) SAS Method

Use supersaturated supercritical CO_2 ($scCO_2$) as an anti-solvent in a mixed solution to cause the precipitation of drugs nanocrystals. In order to operate the process, CO_2 is essentially supplied to the precipitator at a definite temperature and pressure. The drug solute and solvent-containing liquid solution is then poured through a nozzle into the precipitator and combined with the scCO2. As a result of scCO2 supersaturation, the solute precipitates as nanocrystals[64].

Drawback of SCF - The primary issue with this method is that most pharmaceuticals are poorly soluble in SCF-CO2, which can lead to low productivity and higher costs because SCF is used in significant quantities[51].

e) Precipitation Assisted by Acid-Base Method

In the carbon dioxide-assisted precipitation method utilizing acid-base reactions, the drug is typically dissolved as the acid phase in a weak acid solution and the base phase is a weak base solution with stabilizer. The drug nanocrystals are precipitated by vapor effervescence after the acid phase is gradually introduced to the base phase to create carbon dioxide[65]. Only relevant to insoluble drugs whose stability in acids and bases and solubility in relation to pH[31].

B) Evaporation methods

a) Spray drying

The method of evaporation that is most frequently employed involves atomizing drugs solutions into tiny droplets, which are then evaporated in a hot air current to produce dry particles[66]. Solution droplets are sprayed from top to bottom in a conical or cylindrical cyclone, dried by hot air in the similar direction, and then formed into spherical particles. An atomizer that rotates rapidly and scatters the fluid due to the centrifugal effect is used for spraying. A peristaltic pump transfers the solution at a specific flow rate to the inner tube, while nitrogen or air at a steady pressure is transferred to the outer tube. Spraying reduces the size of solution droplets, increasing the drying matter's surface area and accelerating drying[67, 68]. It is suitable for manufacturing heat-sensitive products owing to fast drying and short exposure time to heat.

b) Freeze drying

Lyophilization, often known as freeze-drying, is a drying technique in which moisture is extracted from the product via a sublimation and desorption process inside a container system[69]. It consists of three stages, freezing, primary drying and secondary drying[70].

first stage - The product temperature is lowered below the solvent's freezing point, typically water and the ice crystals from the freeze-concentrated phase are separated[71].

second stage - When a vacuum is used and the shelf temperature is increased, ice sublimates, initiating primary drying, which is responsible for the porous structure of the dried nanocrystals[72].

secondary drying stage - Further raising the shelf temperature allows the unfrozen solvent to desorb from the solid[69, 70].

c) Aerosol flow reactor route

Straightforward and effective one-step continuous procedure that can synthesize nanocrystals without the need for organic solvents or stabilizers that are toxic or environmentally hazardous and are employed in other nanocrystal preparation methods, such as different polymerization techniques. To create the required size of nanocrystals, the drug solution is atomized to create droplets, which are then forced through a heated tubular laminar flow reactor for solvent evaporation while suspended in the carrier gas.

d) Electrospraying facilitates

The typical electrospraying setup comprises four main parts: a metal nozzle connected to a high voltage power source, a grounded substrate acting as a collector, and a pumping device (often a syringe pump). Electrospraying, also known as EHDA, is a process in which an electrical field causes a conductive liquid jet to fragment into minuscule droplets[73]. Electrospraying involves slowly injecting a conductive liquid through a nozzle that has been charged with electrical potential. In the typical Taylor cone-jet mode, a conical meniscus will form at the nozzle tip when the voltage is high enough due to the electrical stress created by the repulsion of the free charges at the liquid surface[74].The jet can have two different results depending on the competition between the electrostatic repulsion, the surface tension stress on the liquid-gas interface, and the liquid's kinetic energy from the Taylor cone. In the first case - The jet, also known as the electrospinning process, will transform into ultra-fine polymeric fibers that range in size from nanometers to micrometers. The other type- is referred to as electrospraying, in which a process known as Rayleigh disintegration or Coulomb fission causes the charged liquid jet to fragment into nanoscale drops.

e) Emulsion polymerization method

Include liquefying API in volatile organic solvents or solvents that are partially combined with aqueous solution as the dispersion phase. The organic solvent is emulsified dropwise into the aqueous phase, where stabilizers are typically added, to create an oil-in-water (O/W) emulsion[75]. The drug nanocrystals are then obtained by evaporating, stirring, and extracting the emulsions.

3. Combinative technology

Because of the characteristics of the instruments and the properties of different drugs, it is usually hard to achieve the necessary nanocrystals using a single preparation technology. Combinative technology, which is the combination of top-down and bottom-up technologies, may overcome the drawbacks of a single preparation method and increase the effectiveness by decreasing the particle size.

A. Nanoedge® technology

It combines the precipitation method with the HPH method. After the initial generation of crystal particles precipitates, a high energy process typically the HPH process occurs[34]. A appropriate solvent, typically an organic solvent that is soluble in water, is used to dissolve the drug initially. After then, another aqueous liquid in which the drugs is less soluble is added to the drug solution. For stability, the aqueous liquid may include surfactants, which are carefully introduced to the drug solution with the use of an infuser device, for instance[76]. The particles are then further crushed using the homogenization process from the HPH method, which stops secondary growth and solves the issues of Oswald ripening and uneven particle size distribution in the precipitation method. It rises the physical stability of the nanocrystal particles. Additionally, for the high-energy procedure, alternate methods like microfluidization or ultrasound can be employed[54].

Drawback- One of the main issues with this combinative technique is the organic solvent residues in the nanosuspension, which get more problematic when production is done on a big scale. Compared to conventional methods, this technology produces noticeably larger particle sizes[77].

B. SmartCrystal® technology

SmartCrystal®, which have a particle size of less than 100 nm, are second-generation nanocrystals that improve the solubility and stability of drugs and therapeutic products[3]. Pre-treatment and high-pressure homogenization are the major components of SmartCrystal® technology. Wet bead milling, spray drying, freeze drying, or precipitation are a few examples of pre-treatment methods that can be used before HPH[78]. The second generation of SmartCrystal® technology includes combination technology (CT) procedures as well as H69, H42, and H96 methods.

1. <u>H69</u>

The NANOEDGE method is comparable to this combinative procedure. To reduce particle size, it combines a high-pressure homogenization stage with a microprecipitation step using organic solvents. The difference is that with the H 69 technology, the cavitation occurs either simultaneously with the particle production (also known as "cavi-precipitation") or at

most two seconds thereafter[79]. To facilitate the drug's precipitation, which occurs at the high-energy zone of a homogenizer, the drug is dissolved in an appropriate solvent and then carefully combined with an aqueous nonsolvent. This allows the fresh nanocrystals to undergo homogenization at the same time, preventing the crystal from growing too much under high pressure. Higher pressure is applied to further homogenize the coarse nanocrystals in order to produce the fine nanocrystals[80].

Drawback - Similar to the NANOEDGE technology, a disadvantage of this method is that the resultant nanosuspensions contain some residues of organic solvent that must be eliminated prior to additional processing.

2. H42

With this combinative technology, HPH is used to decrease particle size after spray drying is used as a precipitation and pretreatment phase. This method differs from the NANOEDGE and H 69 technologies in that the organic solvent is removed during the bottom-up phase.

Advantage - benefits include solvent-free dry intermediates, tiny drug nanocrystals following fewer HPH cycles, and comparatively fast processing periods during SD.

Drawback- The employment of high temperatures during SD, which could make this technology inappropriate to treat thermolabile chemicals[76].

3. H96

This procedure uses HPH to reduce particle size after freeze-drying as a bottom-up pretreatment step. Similar to the H 42 technology, the organic solvent component is eliminated in the bottom-up stage[77, 81].

For freeze the solution liquid nitrogen is used in order to prepare it for the subsequent freeze-drying procedure, drugs are initially freely dissolved in organic solvents with high freezing points. The freeze-dried product is subsequently dispersed in purified water with stabilizers and immediately passed through a homogenizer under high pressure in the HPH step. The H 96 technology's less temperatures and more FD yields make it particularly well-suited for processing costly or thermolabile medications.

Drawback- The extension of the lyophilization.

4. Combination technology (CT) techniques

The only combinative method that doesn't use organic solvents is CT technology.

A low-energy pearl milling step and high pressure homogenization are combined in the CT method to reduce particle size[82]. Rotor-stator and mills are the most widely used types of wet bead milling techniques. For example, the ARTcrystal® approach uses an efficient rotor-stator high-speed stirring process followed by the HPH method[83]. This method has been used to produce a large number of poorly water-soluble medications for oral and topical administration.

Advantage - This technology's benefits include better physical stability of the nanosuspensions and a decrease in the homogenization pressure and process duration.

Drawback- Particle sizes produced by the CT process are comparatively larger than those produced by other combinative methods.

C) Other combinative method

1. Precipitation - Lyophilization – Homogenization

Precipitation was the first stage, which was used to lower the drug's initial particle size. The drug was dissolved in an organic solvent and then added to an aqueous phase in this stage, which caused a precipitation of small, ideally friable crystals. In order to prevent the organic solvent's cosolvent activity, which could lead to particle growth, it was carefully eliminated from the nanosuspensions.

The second lyophilization process was then employed, which resulted in the starting material being changed and the organic solvent used in the precipitation step being eliminated. The crumbly particles were finally broken into the nanoscale range in the final step by applying high pressure homogenization[84].

2. High gravity antisolvent precipitation (HGAP)

HGAP is created by combining HGCP technology with the antisolvent precipitation technique. The advantages of the HGCP are maintained, while the negative effects of the product's contaminants are removed[55].

3. Macrojet reactor Technology

MRT is similar to HPH. In order to create a high-speed fluid that is sprayed into the reaction chamber, the drug solution is mixed in the high-pressure chamber via the nozzle's microhole. Convective shear in the reaction chamber creates turbulence. The product particle size is simultaneously decreased by cavitation, impact, and shear action. Continuous large-scale production is possible using this technique. Nonetheless, it is impossible to overlook the energy usage and obstruction of the way[52].

4. Evaporative precipitation into aqueous solution

The medication is heated above its boiling point after being dissolved in a solvent with a low boiling point. After that, the heated solution is sprayed into a stabilizer-heated aqueous medium[55].

5. Antisolvent Precipitation – HPH Method

Huang et al. used (PVP K30) and SDS as crystal stabilizers to create celecoxib nanocrystal suspensions by combining the HPH and antisolvent precipitation methods. Compared to the physical mixture and raw celecoxib, the solubility of celecoxib nanocrystals was clearly greater. Over ten days of storage, the product held up well at high temperatures and high moisture levels[47].

6. Ultrasound Probe – HPH Method

By choosing mixed surfactant poloxamer 188 as a steric stabilizer and SDS as an electrostatic stabilizer, Jin et al. created baicalin nanocrystals with an average particle size of 248 ± 6 nm and PDI 0.181 ± 0.065 using an ultrasound probe in conjunction with HPH and a fluidized drying process[85].

7. Rotary Evaporation Method – HPH Method

Zuo used the rotary evaporation-HPH method to create curcumin-artemisinin cocrystal nanomedicine. After optimization, the nanomedicine's particle size was 234.6 nm. Comparing the solubility and stability of curcumin-artemisinin cocrystal nanomedicine to raw curcumin, curcumin-artemisinin cocrystals, and curcumin nanocrystals, clear advantages were seen.

8. Melt Quench – HPH Method

Yu also synthesized nanoamorphous indomethacin using the combined melt quench-high pressure homogenization process. The prepared suspension has a particle size of 245 nm. The nanosuspensions' solubility was much enriched. Nevertheless, the nanoamorphous material lacked stability. Due to the presence of water and the occurrence of recrystallization, the particle size began to rise dramatically within 7 days and even reached 890 nm after 30 days[47].

9. Antisolvent Precipitation – Ultrasound Method

Zhang et al. used the ultrasound probe precipitation method to create fenofibrate nanocrystals. Ultrasonic probes can leave metal particles behind, which is a drawback that makes them unsuitable for industrial production[86]. In order to create carvedilol nanosuspensions, Liu et al. employed alpha tocopherol succinate as an additional stabilizer in the organic phase. For one week, the nanoparticles were stable at 25 °C with an average particle size of 212 nm. There was a notable rise in the nanosuspension's dissolution rate. When compared to commercial tablets, the nanosuspensions demonstrated an estimated two-fold rise in each index, according to in vivo studies. Moreover, the technique is quick, affordable, and simple to manage [87]. Using this technique, paclitaxel, zaleplon, and nintedanib nanocrystals are also developed.

Characterization of Nanocrystal

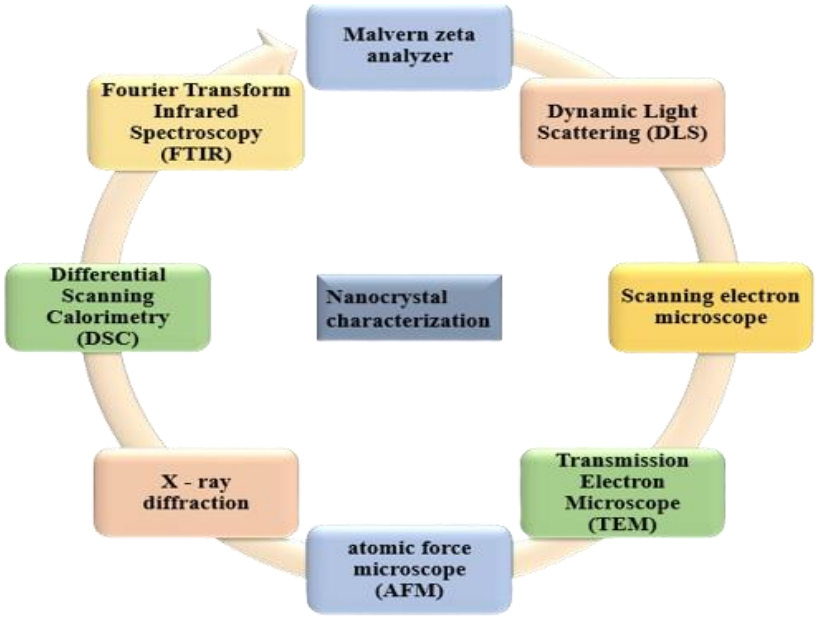

Figure 5: Characterization of Nanocrystal

Table 1: Marketed Formulation of Nanocrystal

Trade name	Product(drug)	Indication	Preparation Technology (Process)	Route of Delivery	Approval FDA
Gris-Peg®	Griseofulvin (GRF)	Anti-mycotic	Precipitation (PPT)	Oral	1982
Azopt	Brinzolamide	Glaucoma	Wet ball milling (WBM)	Ocular	1998
Verelan PM	Verapamil	Anti-arrhythmic agent	Milling, WBM	Oral	1998
Rapamune	Sirolimus (SRL)	Immunosuppressant (IS)	Wet ball milling (WBM)	Oral	2000
FocalinXR®	Dexmethyl-phenidate HCl	Control mental health	Wet ball milling (WBM)	Oral	2001

	(DP-HCL)				
Avinza®	Morphine sulfate (MS)	Anti- chronic pain	Milling	Oral	2002
Ritalin LA	Methyl-phenidate HCl	Stabilized mental condition	Wet ball milling (WBM)	Oral	2002
Herbesser®	Diltiazem (DTZ)	Anti-angina	Wet ball milling (WBM)	Oral	2002
Zanaflex™	Tizanidine HCl (TZD-HCL)	Muscle relaxant	Wet ball milling (WBM)	Oral	2002
Ritalin LA®	Methylphenidate HCl (MEPD-HCL)	Attention-Deficit Hyperactivity Disorder (ADHD)	Wet ball milling (WBM')	Oral	2002
Emend®	Aprepitant (APRT)	Anti-nauseants	Wet ball milling (WBM)	Oral	2003
Tricor®	Fenofibrate (FBT)	Hyper-cholesterolemia (HC)	Wet ball milling (WBM)	Oral	2004
Megace® ES	Megestrol acetate (MA)	Appetite enhancer	Wet ball milling (WBM)	oral	2005
Cesamet®	Nabilone (NBL)	Emesis suppressants	Precipitation (PPT)	Oral	2005
Triglide®	Fenofibrate	Hyper-cholesterolemia	HPH(microfluidizer)	Oral	2005
Naprelan®	Naproxen sodium (NS)	Anti-inflammation	Wet ball milling (WBM)	Oral	2006
Theodur®	Theophylline (TPL)	Bronchodilation	Wet ball milling (WBM)	Oral	2008
Invega * Sustenna	Paliperidone palmitate (PP)	Antidepressant	High pressure homogenization (HPH)	Parenteral	2009
Zyprexa Relprevv®	Olanzapine pamoate (OP)	Schizophrenia (SCZP)	-	Parenteral	2010
Aristada Initio®	Aripriprazole Lauroxil	Schizophrenia	-	Intramuscular	2015

Table 2: Recent Patent on Nanocrystal and their Description

Patent/ Application Number	Publication/ Application Date & Year	Patent Description	Ref
CN104814926	Aug. 5, 2015	According to this invention, a high-pressure homogenisation technique combined with nano-precipitation was used to create the lurasidone nanosuspension.	88
CN104814926	Aug. 5, 2015	The patented innovation display how the microfludization technology can be used to produce an suspension of a poorly water soluble drug.	89
US20150238446A1	Aug. 27, 2015	The creation of a stable hexaflumuron nanosuspension that fish can be injected with to reduce sea lice was reported by the researchers.	90
WO2016135753Al	Sept. 1, 2016	In this patented work, a milling technique is used to establish a system for topically applied nanosuspension.	91
WO2016081593Al	May 26, 2016	The therapeutically active moiety-fabricated nanosuspension is Explained in the patented invention. An active nutraceutical with low solubility profile is this Component.	92
US20160317534A1	Nov. 3, 2016	Information regarding a nanosuspension made using the lyophilised medication is provided by this patent. These nanosuspensions were stable enough to allow for extended storage.	93
US20160206577	Jul. 21, 2016	The process of creating an antibacterial moiety's nanosuspension, which rises the drug's stability and lowers its toxicity, is reflected in	94

		this patented work.	
CN105708844A	June 29, 2016	This patented work describes the development process of an ophthalmic nanosuspension containing tobramycin and dexamethasone. The process was found to be convenient, consistent, effective, and repeatable.	94
CN105315249A	Feb. 2, 2016	This patent covers the process of creating simvastatin nanosuspension to improve the effectiveness of drug distribution systems.	94
CN105534947A	Feb. 16, 2016	The patented invention consists of a method for producing a celecoxib nanosuspension capsule that can be lyophilized to turn to a dry form.	94

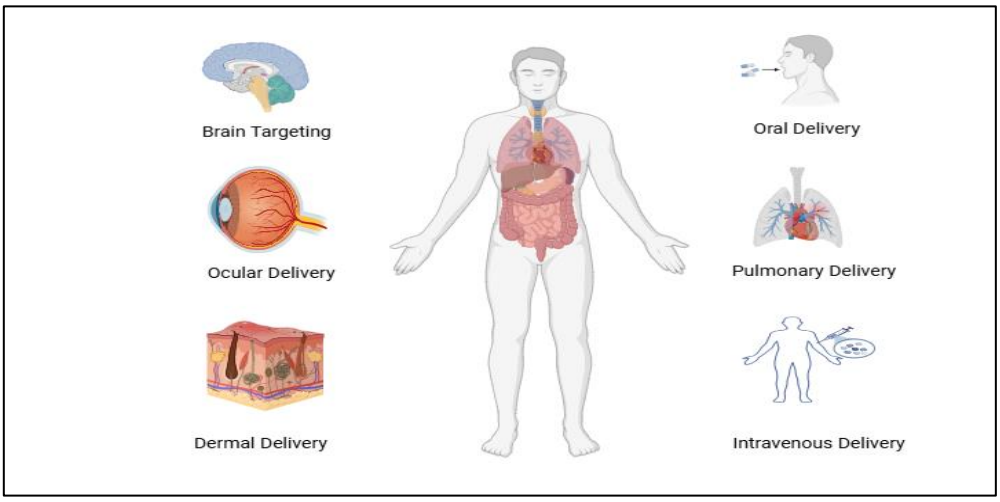

Figure 6: Application of Nanocrystal

Table 3: Advantages and Disadvantages of Nanocrystal Drug Delivery System

Route	Advantage	Disadvantage
Oral Delivery	1.The oral route is widely regarded as the most suitable, nontoxic, and ideal route for administering drug nanocrystal formulations. 2.Drugs with an upper intestinal tract absorption window advantage from rapid start of dissolution after oral administration, as a large proportion dissolves at the major absorption site[95]. 3.Example: aprepitant (Emed®) or fenofibrate (Tricor®).	1.Drug nanocrystals are facing one problem in the gut is the presence of electrolytes. 2.The nanocrystal zeta potential reduce due to presence of electrolytes leading to nanocrystal aggregation. 3.The benefits of nanocrystals are lost in the formulation when there is significant aggregation since the aggregates dissolve considerably more slowly[96].
Parenteral Delivery	1.For the non-oral administration of nanocrystal drugs, the parenteral route is the most crucial[97]. 2.Drug uptake and cellular interactions are important factors in parenterally given nanocrystals[98]. 3.It can decrease toxicity, increase bioavailability, release at targeted areas, provide rapid act in an emergency, and lower the dose of the drug. 4.When a medication is either poorly absorbed through the GIT or undergoes significant first-pass metabolism, the parenteral route is often used as an alternative[2].	1.When preparing nanocrystal suspensions for injection, one of the challenges is ensuring the drug's physical stability, which involves preventing aggregation through the use of stabilizers and preventing Ostwald ripening, which results in bigger particle sizes. 2.Larger aggregates of nanocrystals have the potential to mechanically clog microvessels, particularly in the lung, resulting in embolisms[97]. 3.Another challenge is fulfilling the sterility requirements for parenteral formulation, as terminal γ-irradiation or heat sterilization can cause changes in particle size due to the physical instability of the nanocrystal[99]. 4.The strict necessity of the aseptic production method, the restricted number of suitable excipients, the limitations on the amount of

		excipients accepted for parenteral use, safety concerns, patient noncompliance, and biological issues like thrombophlebitis and allergic reactions are some of the issues that are frequently linked to the critical nature of parenteral drug administration[2].
Pulmonary Delivery	1.Nebulized nanosuspension demonstrated stronger mucus adherence and a much higher inhalable fraction for pulmonary administration[47]. 2.Additionally, the nanosuspension stays affixed to the mucosal layers, preventing drugs loss through the pulmonary tract's ciliary activity[100]. 3.The nanosuspension not only increase the extent of medication absorption but also prevented the common microparticle deposition in the respiratory system[101].	1.Deposition in the mouth and pharynx, as well as drug clearance through the cilia of the pulmonary tract, which is the primary cause of drug loss, are some of the drawbacks of many weakly water-soluble drug microparticles given in aerosolized form for pulmonary doses.
Ocular Delivery	1.Nanodropable dosage forms that are delivered ocularly also exhibit substantial drug loads and long-lasting effects[51]. 2.Improved ophthalmic safety and retention of formulation in cul-de-sac, Improved corneal permeation, Rise ocular bioavailability, better tolerability[102].	1.The ability to stack medications is limited. At the beginning rapid discharge.
Dermal Delivery	1.A viable substitute for carrier systems is nanocrystals. Their great loading capacity is their primary asset. 2.Enhancing drug penetration is the goal of incorporating medication into a vehicle, such as nano-sized carrier systems[103].	1. The characteristics and surface charge of nanocrystals can affect how they interact with skin layers, which could result in dermatitis or other negative consequences
Targeted Delivery	1.NCs have demonstrated significant advantages in brain delivery research, particularly in their capacity to provide a strong therapeutic concentration of drugs that can be used to achieve therapeutic action in brain disorders[104].	1.Aggregation of the nanocrystals in the bloodstream, particularly in physiological settings, can reduce their stability, change their pharmacokinetic characteristics, and restrict their capacity to pass through the blood-brain barrier. Additionally, aggregation can result in an unequal distribution inside the brain, which would decrease the overall efficacy of treatment.

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