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A Novel Technique of Solubility Enhancement: Nanocrystals

Pharmaceutical Nanocrystals

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Abstract:- In the modern era, poor solubility is one of the major problems preventing drugs to reach to market. There are several methods for improving the solubility of medications that are poorly soluble. Nanocrystals have been identified as a helpful and effective method of drug delivery. Nanocrystals are a family of solid medications that combine the principle of nanoscience with the crystal structure to produce benefits in the area of dissolution rate and physicochemical properties. Various techniques are now available to prepare nanocrystals. In this review, a detailed insight on conventional and recent techniques of nanocrystals preparation along with route of administration, merits, and demerits of nanocrystals, has been provided. In addition, various nanocrystals formulations prepared by various researchers, characterization and marketed formulation with formulations available in clinical phase are summarized in this review. Quantum dots also termed semiconductor nanocrystals and Wulff construction are also discussed.

Keywords:- *Nanocrystals, Solubility, Quantum Dots, Cocrystals, Nanotechnology.*

I. INTRODUCTION

According to reports, up to 70% of drugs currently being developed by the pharmaceutical industry have low aqueous solubility, which can impair drug development due to the dangers of poor oral bioavailability and viability problems in pharmacologic and toxicological studies. Nearly 40% of currently marketed drugs also have this problem [1]. This challenge serves as a major impetus for scientists to explore methods for enhancing the biopharmaceutical properties of pharmaceutical products. Co-crystals have a lot of potential uses for improving solubility. According to research, the solubility of medicinal molecules made from co-crystals has increased by 4–20 times. Due to the extremely low oral absorption, it is still a significant difficulty for the pharmaceutical industry to generate suitable co-crystals for medicinal medicines. Compared to co-crystals, nano-cocrystals (NCs) can further increase a drug's solubility by having crystals in the nanometer size range. Furthermore, several scientists claimed that nano formulations are frequently dispersed to increase their stability. Co-crystals structure contributes to sufficiently enhance the bioavailability and dissolving rate of less soluble natural compounds, and nano-scale particles with larger surface areas also have an impact on these properties [2]. Another noteworthy benefit of nano-crystals is their nearly complete drug content, which increases the likelihood of achieving high therapeutic levels and the desired pharmacological effects, and sets them apart from conventional colloidal drug delivery technologies. Because they may be administered in several ways, such as injectable, ocular, oral, and pulmonary, they are incredibly versatile [3]. Co-solvents or solubilizing molecules are another approach that has been employed to improve the solubility of drugs that have low water solubility. Because of the solubilizing molecules or residues of organic solvents, this raises the risk of adverse effects or toxic reactions in the body. Thus, it is imperative to find safe and effective ways to increase methods to improve the solubility and bioavailability of medications that are poorly have low water solubility [4].

- *Nanocrystals*

It is thought that nanocrystals were the catalyst for the development of modern nanoscience, which started in the early 1980s and is still going strong today [5]. Nanocrystals are solid, pure medicine particles have a size within nanometer range. These compounds are 100% medicines,

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free of carriers or other molecules, and they are frequently stabilised using surfactants or polymeric steric stabilisers. Nanocrystals have special characteristics that help them to overcome challenges such as increased saturation solubility, higher dissolving rate, and greater cohesiveness to surface and cell membranes [6]. Due to the greater surface area to volume ratio and faster dissolution rates brought on by nanosizing, the solubility of hydrophobic medicines is improved by nanocrystalline drug technology. The Biopharmaceutical Classification System (BCS) Class 2 and Class 4 medications may be successfully reformulated using the drug crystals [7]. As their name would suggest, they are crystallised, yet based on the manner of manufacturing, they may also be partially or entirely amorphous [8]. "Nanosuspensions" are produced when drug nanocrystals are dispersed in liquid media. Typically, stabilisers like surfactants or polymeric stabilisers are needed to keep the dispersed particles from settling out of suspension. Water, aqueous solutions, or nonaqueous chemicals can all be used as dispersion medium. When converting drug microcrystals to drug nanoparticles, based on the manufacturing process, the final result may be either crystalline or amorphous, particularly when precipitation is used. It would be incorrect to refer to these amorphous drug nanoparticles as nanocrystals in technical terms. Still, the phrase "nanocrystals in the amorphous state" is a term that is frequently used [9]. Controlled release nanocrystal technology is incredibly adaptable and offers a number of benefits, including very high drug loading, simplicity in production, prevention of dose dumping, and consistent drug release. Drugs are typically nanosized to increase their intrinsic solubility, bioavailability, and dissolving rate [10].

➢ *Quantum Dots (QDs)*

Semiconductor nanocrystals called quantum dots have sizes between 2-10 nanometer, and they exhibit size-dependent optical features including absorbance and photoluminescence [11]. They are zinc sulfide-coated organic NCs with an inorganic semiconductor core (cadmium selenide) that glow when exposed to light. The zinc sulphide coating improves their optical properties. QDs are more easily soluble in aqueous buffers with the insertion of a cap [12]. Due to their extremely high surface-to-volume ratios, quantum dots illuminate with various colours. In contrast to the outer aqueous shell, which may be utilised to combine biomolecules like peptides, proteins, and DNA, the inner structure of quantum dots determines the colour that is produced. Due to their narrow emission, bright fluorescence, and great photostability, quantum dots can be employed to identify therapeutic substances within cells and tissues. They are excellent choices compared to other fluorescent compounds because of their versatile bio-conjugation, adjustable photo-physical properties for multiplexed detection, and improved stability for prolonged examination times [13].

➢ *Different Techniques of Preparation*

Different techniques have been used to make drug nanocrystals [14]. Top-down and bottom-up technologies are the two primary approaches used to create nanocrystals. During milling technique, the little milling bead or ball is rotated by a milling machine's agitator blade or by agitating the entire sample container. But in homogenization method, piston-gap and jet-stream are the two major types of high pressure homogenizers [15]. The ball milling process uses shear forces to produce nano-sized particles and high-pressure homogenizations are typical top-down technique [2]. The milling based nanocrystal technology is the one that is used the most in the pharmaceutical sector [16]. Many related review papers have provided extensive explanations of mechanisms of both techniques [2,7,9,15,17]. Precipitation is a bottom-up approach that uses crystal growth and nucleation processes [2]. The bottom-up approaches generally depend on the solvent-antisolvent precipitation principle. Initially, the API is dispersed in the solvent.When a solvent containing API is combined with a non-solvent, the precipitation that results creates drug nanocrystals. [18]. Typically, the bottom-up strategy needed less energy input than the top-down method. But before the complete process of formulation, organic solvent, which is typically used as the solvent, needs to be eliminated. The way that solvent and antisolvent are mixed in a bottom-up technique may have an impact on the size of the nanoparticles. In most trials, a drug-solvent mixture in a syringe was injected into an antisolvent [15]. Electrohydrodynamic atomization (EHDA), also known as electrospraying, and spray drying have also been frequently used to create nanocrystals for application in medicine because of its ease of use and potential for scalability. However, to maintain the physicochemical stability of nanoparticles over an extended period of time, it is not required to include any suspension stabilisers or surfactants [19]. This approach can simply work in a continuous manner and also has high reproducibility by regulating the process variables. EHDA is a single-step process that produces nanoparticles with a limited size distribution in contrast to other traditional techniques like nano-precipitation technologies [20,21]. The solid formulations produced by spray drying technique are also more structurally and chemically stable than liquid formulations since they exhibit less coagulation, deterioration, and other solvent-related problems [22].

- *Different Techniques used to Prepare Nanocrystals are Enlisted in Figure 1 and Figure 2:*

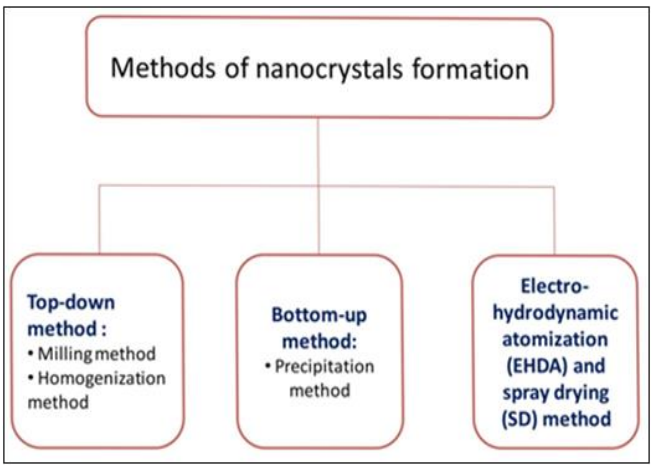

Fig 1 Different Methods of Nanocrystals Formation

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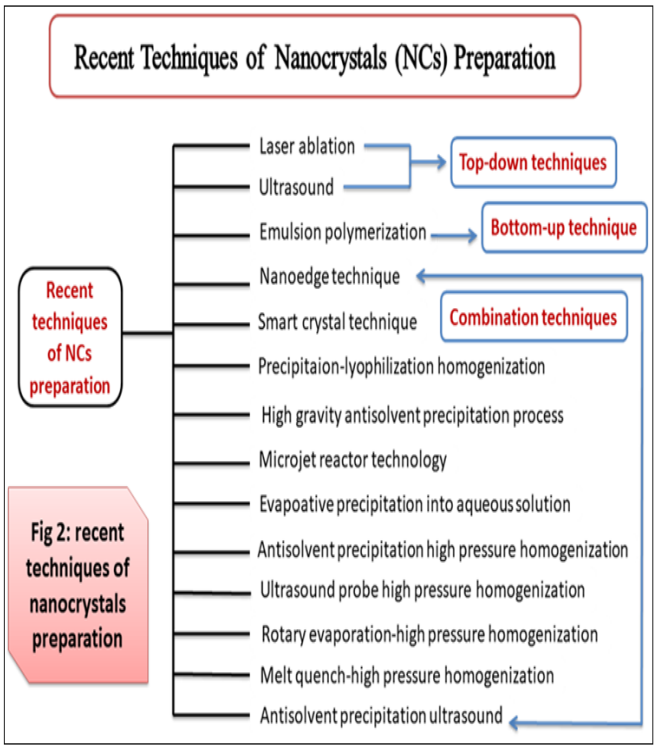

Fig 2 Recent Techniques of Nanocrystals Preparation

➢ *Top-Down Techniques*

- *Laser Ablation:*

The solid target is exposed to laser light during laser ablation, and the material that is expelled condenses into nanoparticles in the liquid around it. After that, the laser light converted stirred suspensions of microparticles into nanoparticles [23]. The intensity of laser, the speed of scanning, the characteristics of the suspension and other factors all have an impact on particle size. Although there are no organic solvents used in this procedure, a tiny amount of the medicine might experience oxidative degradation and crystal state alterations as a result of using too much power. The production of nanosuspensions containing paclitaxel, megestrol acetate, and curcumin has been accomplished using this technique [24].

- *Ultrasound:*

Through acoustic wave vibration, ultrasound is an effective way to fragment medication particles into smaller ones. The fast dispersion of drug solution and the creation of acoustic cavitation in solution caused by ultrasound have been proven to promote nucleation. It is frequently used in combination with other methods due to its simplicity of use and good reproducibility in the laboratory. The length of the horn, the immersion depth of the horn, the cavitation depth, and the strength of the ultrasonic treatment all affect the nanocrystal's size [25].

➢ *Bottom-Up Technique*

- *Emulsion Polymerization:*

An O/W emulsion is created by dissolving API in volatile organic liquids or liquids that are partly combined with water as the dispersion phase. Next, the organic liquid is added drop wise within the water phase by frequently adding stabilisers. It is simple to regulate the size of emulsion droplets. The emulsion is then evaporated, agitated, and extracted to get the drug nanocrystals. Temperature gradient, pH level, stirring rate, evaporation rate, and emulsifier all have a significant impact on the final product's quality. This emulsion polymerization process does not work well for large-scale pilot manufacturing since it needs the aid of homogenization and ultrasound [26].

➢ *Combination Techniques*

- *Nanoedge Process:*

It was the first integrated process for lowering the particle size designed for the manufacturing of nanodrugs. The precipitation method is used in conjunction with the high pressure homogenization (HPH) technique. Precipitation is employed to create the initial crystal particles, which decreases HPH slit obstruction and increases the effectiveness of particle size reduction during the homogenization technique [27]. In order to better grind the particles and avoid secondary growth as well as the issues with unequal particle size distribution and ostwald ripening in the precipitation approach, the homogenization procedure from the HPH method is utilised. As a result, the nanocrytal particles are more physically stable [28].

- *Smart Crystal Process:*

The basic components of smartcrystal technology are a pre-treatment stage and a HPH phase. Precipitation, spray drying, freeze drying, or wet bead milling are a few examples of pre-treatment steps that HPH can accompany [29]. Smartcrystal process is acknowledged as a 2nd generation technique for producing nanocrystals [30]. It uses combination technology (CT), H69, H42 and H69 approaches.

- *H69:*

H69, which combines nanoprecipitation and HPH techniques, is related to nanoedge technology. The high pressure homogeneous cavitation zone is where nanocrystals are formed, which results in extremely tiny and homogeneous particle sizes [31]

- *H42 and H96:*

This approach is paired with a different technique, such as freeze drying, spray drying, or HPH. To create drug nanocrystals, the mixture of an insoluble drug and a stabiliser is first spray/freeze dried, evenly scattered throughout the stabiliser skeleton, and then redispersed in the water using HPH. Combining the two techniques decreases particle agglomeration and boots processing effectiveness. It is appropriate for industrial-scale manufacturing [32].

- *CT:*

Top-down technology is combined in CT. Rotar-stator and mills are now the two commonly utilized wet bead milling techniques [33]. Using the former as an illustration, the ARTcrystal technique combines HPH with high-speed shear technologies. To create stable and homogenous

suspensions, the drug solution is first processed using a rotor-stator high-speed shear. Next, under intense pressure, the nanocrystals are homogenised [34].

- *Precipitation-Lyophilization-Homogenization Technique:*

This technique was used by Morakul et al. 2014, to produce clarithromycin nanaocrystals, with pluronic F-127 and sodium dodecyl sulphate (SDS) acting as costabilizers. The produced clarithromcin nanocrystals proved to be 400 nm cubic particles that were either completely crystalline or slightly amorphous. It was very soluble and permeable [35].

- *High Gravity Antisolvent Precipitation Technique (HGAP):*

The antisolvent precipitation technique and high gravity controlled precipitation technique (HGCP) are combined to produce HGAP. The advantages of the HGCP are maintained but the drawbacks of the product's contamination were removed [36]. Zhao and colleagues 2009; used the HGAP method to produce danazol nanocrystals with a consistent size distribution. 190 nm was the average size of particle. Danazol nanocrystals kept their crystalline structure and molecular state [37].

- *Microjet Reactor Technique (MRT):*

MRT is equal to HPH. A high-speed fluid spraying into the reaction chamber is produced by mixing the drug solution within the high pressure chamber with the nozzle's tiny aperture, and convective shear produces turbulence into the reaction chamber. Cavitation, impact, and shear affect all work together to lower the final particle size. This approach enables continuous, massive production. However, it is impossible to avoid the energy usage and obstruction of the passage [38].

- *Evaporative Precipitation into Aqueous Solution (EPAS):*

The less boiling point solvents are used in the EPAS technique to dissolve the API, which is then heated above boiling. The heated solution is then sprinkled over hot aqueous solutions that contain stabilisers after that [36]. By using EPAS, Chen et al. 2002, prepared cyclosporine A non-crystalline nanoparticles suspension. It has demonstrated a rapid rate of dissolution because of its low crystallinity, tiny nanoparticles size, and hydrophilic stabilisers [39].

- *Antisolvent Precipitation High Pressure Homogenization Technique:*

Utilizing PVP K 30 with SDS as crystal stabilisers, Huang et al. in 2015, coupled the antisolvent precipitation technique and HPH technique to produce celecoxib nanocrystalline formulation within size range of particles 283.67± 20.84 nm. Celecoxib nanocrystalline formulation had a clearly greater solubility than pure celecoxib and from the physical combination. For 10 days of keeping in intense heat and heavy moisture, the product remained remarkably stable [40].

- *Ultrasound Probe High Pressure Homogenization Technique:*

Baicalin nanocrystals were produced by Jin et al. 2013, using an ultrasonic probe, HPH, and a fluidized drying technique. They did this by using combination of surfactants pluronic F68 as steric stabiliser and SDS as an electrostatic stabiliser. Pharmacokinetic tests on rats revealed a considerable improvement in the drug's in-vivo bioavailability [41].

- *Rotary Evaporation High Pressure Homogenization Technique:*

The rotary evaporation-HPH approach was used by Zuo 2019, to produce curcumin-artemisinin cocrystal nanomedicine. In comparison to curcumin nanocrystals, curcumin-arteminsinin co-crystals, pure curcumin, curcumin-artemisinin co-crystal nanomedicine demonstrated significant solubility benefits and high stability [42].

- *Melt Quench High Pressure Homogenization Technique:*

Yu 2021, produced nanoamorphous indomethacin using a combination of the melt quench and HPH techniques. The produced suspension included particles that were 245 nm in size. The nanosuspensions' solubility was much improved. However, the nanoamorphous has low stability. The presence of moisture and the presence of recrystallization caused the particle size to start growing considerably during 7 days, reached 890 nm within 30 days [43].

- *Antisolvent Precipitation-Ultrasound Technique:*

Fenofibrate nanocrystals were produced by Zhang et al. 2014, utilising the ultrasonic probe precipitation technique. Ultrasonic probes, however, have a few drawbacks, including the possibility of leaving behind metal particles, which makes them unsuitable for use in industrial manufacturing [44]. For the purpose of producing carvedilol nanosuspensions, Liu et al. 2012, added α – tocopherol succinate used as additional stabiliser into the organic portion. The nanosuspension's dissolving rate substantially enhanced. In vivo testing revealed that when compared to conventional tablets, the nanosuspensions exhibited an approximately two-fold rise in each parameter [45].

- *Determination of Shape of Nanocrystals*

The properties of nanocrystals and, consequently, their applications in a variety of areas, like catalysis, plasmonics, therapeutics, and biological imaging, are greatly influenced by their shape and composition [46]. Using the surface energies of the substance, Wulff construction in 1901 provides an easy way to determine the equilibrium shape of nanoparticles [47].

- *Wulff Construction*

As identified by Gibbs in 1873, the surface energy minimization principle governs the thermodynamic equilibrium shape of a nanocrystal, the easiest to describe. The "Wulff construction," also known as the "classic" or "thermodynamic" wulff construction, was described by Wulff in 1901. This method uses a gamma plot, or a graph of the surface free energy that depends on orientation, to

calculate the equilibrium shape of single crystals. Over the past few decades, modifications to this primarily thermodynamic, single crystal Wulff structure have been created to include twinning, alloys, substrate(s), and kinetic effects, making it possible to mimic the majority of shapes and circumstances. All of these mathematical equations are basic, and specialised crystallographic implementations, for instance, the typical face centered cubic (FCC) metals, frequently depend on software created for the display and quantification of shape. The creation of computer-based platforms for shape models is much more recent than the models themselves, and it has been helped forward by the open source movement and the widespread accessibility of computing resources [48].

II. METHODS OF ADMINISTRATION OF NANOCRYSTALS

- *Various Methods for the Administering of Nanocrystals are shown in Table 1.*

Table 1 Different Methods of Nanocrystals Administration

Method	Properties	Reference
Oral administration	The procedure of administering medications orally involves dissolving them in luminal solutions before transferring them to the gastrointestinal epithelium. Numerous studies have shown the advantages of taking medications orally that are poorly soluble because they adhere to the gut wall and dissolve more quickly. Furthermore, when medications with low solubility are frequently taken with meals, the adsorption efficiency may be increased.	[49,50,51]
Parenteral administration	Cyclodextrins, surfactants, and liposomes have always been used for parenteral or intravenous delivery to enhance the dissolution rate of less soluble medications. These techniques, however, can have a number of drawbacks, including high injection volume and harmful effects. Therefore, nanocrystal medications are a prime candidate that can overcome these drawbacks.	[52,53]
Pulmonary administration	It has been discovered that nebulizing nanocrystal pharmaceuticals using mechanical and ultrasonic nebulizer technologies can directly deliver drugs with low solubility into the lungs. Nanocrystal technology can enhance the droplet dispersion of the less soluble medicines. Drug in the form of nanocrystals can persist in the body longer than drugs of larger sizes.	[54]
Dermal administration	The use of nanocrystal medicines for dermal application has many advantages, such as more penetration of cosmetic and medicinal ingredients into the skin despite their low water solubility. Because of the greater saturation solubility of nanocrystal technologies, concentration gradient might be increased. When compared to the rutin glycoside, which is only moderately soluble, the bioactivity of rutin nanocrystal products was shown to be more than 500 times greater.	[55]
Targeted drug delivery	Nanocrystal medicines are ideal for targeted medication delivery since they have extensive human body penetration. The ineffectiveness of drug distribution into specified body regions without causing side effects is generally known to be one of the main issues for pharmaceutical applications. To improve the targeting of drug delivery, nanocarrier drug delivery technology has been thoroughly researched. The most widely used nanocarriers for specific drug delivery include micelles, liposomes, and nanoparticles made of polymers. But, the loading rate is a significant issue.	[49,52,56]
Ocular drug delivery	The majority of drugs used for ocular therapy are administered topically as a solution or suspension. Traditional preparations have little ocular availability because they are quickly removed from the application site by lacrimation and fast blinking. After that, nanocrystal technology helped the delivery of ophthalmic drugs by addressing problems with poorly soluble drugs' dispersibility.	[57,58,59,60]

	Pharmacodynamic experiments showed that the nanocrystals and hydrogel effectively decreased intraocular pressure by upto 12 hrs when compared to standard solution.	
Intranasal route	Due to its potential for many activities, the intranasal route has recently become a popular method for treating a number of disorders. A medicine that has been applied to the nasal mucosa may have a local impact or it may perform a systemic activity after being absorbed into the circulation The nasal mucus layer has a wide, highly vascularised surface area and has a low level of enzymatic activity; which helps to improve absorption once the molecule has dissolved. In fact, systemic adverse effects like sleepiness connected with antihistamine oral administration are less likely when the medication is applied directly to the site of action.	[61]

➢ *Merits of Nanocrystals*

- Improved dissolution rate: The drug particle's size must be reduced in order to improve its surface area. Following the Noyes-Whitney equation, increased surface area speeds up the drug's dissolving rate, [62].
- Increased saturation solubility: The saturation solubility is a fixed quantity based on the composition of the component, the media used for dissolving, and the ambient temperature. This statement holds true for powder medications with a μm/nm size range. Particle size has an inverse relationship with the saturation solubility. The rate of dissolution of pharmaceuticals containing nanocrystals is strongly correlated with their saturation solubility (C) and surface area (A). For instance, increasing surface area (A) and saturation solubility (C) increases the dissolving velocity (dx/dt)

$$\frac{dx}{dt} = \frac{DA}{h} \times (Cs - Ct)$$

- dx/dt – dissolution velocity
- D – Coefficient of diffusion
- A – Surface area
- h – diffusional distance
- Cs – saturation solubility
- Ct – concentration of particles [14].

- Stability: Because the particles didn't aggregate and the Ostwald ripening mechanism wasn't present, the nanocrystals suspension was discovered to be stable [63]. Stability can be obtained by utilising a variety of stabilisers, surfactants, and amphiphilic copolymers, as well as by adding a suitable stabiliser [64,65].
- Permeability: Improved skin adhesion is a characteristic of nanocrystals that makes skin delivery easier. Delivery of drug through skin uses two different mechanisms: (1) concentration difference between skin and nanocrystals formulation, and (2) hair follicles. Nanocrystals within the size range of 200-300 nm helps to improved absorption through the skin [66].
- Adhesiveness: One of the distinguishing characteristics of nanocrystals is their improved adhesiveness; which is caused by their nano size range. The improved oral absorption is a result of the greater adhesiveness. A potential method for analysing adhesion properties is to use kinetics and adsorption isotherms. The particle size affects the adsorption kinetics process [67].

➢ *Demerits of Nanocrystals*

- Due to the medications' smaller size, the nanotoxicity problems attracted attention and are still not entirely resolved.
- The cost of the production equipment constantly drives up the price of the finished nanocrystals medicines.
- The price of these nanocrystal medicines for pharmaceutical applications might readily grow due to the equipment, solvents, and surfactants.
- They are also difficult to commercialise due to the lack of fabrication methods and processes that can be scaled up.
- They are only applicable to BSC class II medications [49].

➢ *Nanocrystals Formulation:*

Various nanocrystal formulations were prepared using different stabilizers and method of preparation, which are listed in table 2.

Table 2 List of Reported Nanocrystals

Drug	Co-former	Stabilizer	Method	Reference
Carbamazepine	Saccharin	HPMC, sodium dodecyl sulphate	Wet milling	[1]
Indomethacin	Saccharin	HPMC, sodium dodecyl sulphate	Wet milling	[1]
Furosemide	Caffeine, cytosine	HPMC, sodium dodecyl sulphate	Wet milling	[1]
Bexarotene	Poloxamer 188, PVP K 30	Soya lecithin	Precipitation-combined micro	[68]

			fluidization	
Docetaxel	Herceptin	Coumarin – 6, tween 80, dimethyl sulfoxide	Nano-precipitation and adsorption	[69]
Itraconazole	Maleic acid, adipic acid, glutaric acid, succinic acid	Tween 80	Wet milling	[70]
Paclitaxel	Succinic acid, N-hydroxy succimide	Pluronic grafted chitosan	High pressure homogenizer	[71]
Baicalein	Nicotinamide	Poloxamer 188	High pressure homogenization	[72]
Carfilzomib	Pluronic F 127	Human serum albumin	Precipitation	[73]
Fenofibrate	HPMC	Sodium dodecyl sulfate	Wet milling	[74]
Paclitaxel	Cremophore RH 40, kollidon VA 64, mannitol, trehalose, HPMC	Tween 80, sodium lauryl sulphate	Sonoprecipitation and high pressure homogenization	[75]
Rutin	HPMC	Pluronic F-17, tween 80, HP-β-CD, PEG 6000, PEG 200	Anti solvent nanoprecipitation-ultrasonication	[76]
Albendazole	Malic acid	Polyvinyl alcohol	Acid-base neutralization combined with high—speed mixing and dispersing	[77]
Naproxen	Mannitol	Poloxamer 188	Solvent-antisolvent precipitation method	[78]
Fisetin	-	Poloxamer P 407	Solvent-antisolvent precipitation	[79]
Rufinamide	Mannitol	HPMC, Poloxamer 407	Antisolvent precipitation	[80]
Repaglinide	PEG 4000	Poloxamer 188	High pressure homogenization	[81]
Apremilast	Hydroxyl propyl cellulose,	Poloxamer 407, tween 80	Wet media milling	[82]
Ropivacaine	-	Q 11 peptide	Precipitation	[83]
Rosuvastatin	-	SLA, ploxamer 188	Antisolvent precipitation	[84]
Carbotegravir	Folic acid, polyethylene glycol, polypropylene glycol	Poloxamer 407	High pressure homogenization	[85]
Aceclofenac	HPMC, PVP K 30	Sodium lauryl sulphate	Precipitation-ultrasonication	[86]

➢ *Characterization Techniques of Nanocrystals*

- *X – Ray Diffraction (XRD):*

To determine the crystallinity of a medication, the XRD method is commonly utilised. The modification of the polymorphic form served as evidence that the nanocrystals had really been formed. The crystalline compounds' XRD patterns are correlated with those of the pure substance. Every crystalline compound creates a distinct pattern, and the combination of the each compound reveals its pattern. A particle's unique fingerprint is shown by its XRD pattern [87].

- *Morphological Analysis:*

The size, structure and appearance of the NCs are evaluated utilizing the scanning electron microscopy (SEM) and transmission electron microscopy (TEM). For TEM examination, a wet sample with the right concentration is needed, but for SEM analysis, the generated nanosuspension must be transformed into a dried via lyophilisation / spray drying, which causes aggregation [88]. Certain ingredients are introduced as protectants when the particle size increases significantly. Mannitol is frequently used as a cryo-protectant during the lyophilisation process to eliminate water. It also reduces particle agglomeration and association. The final particle may aggregate up to certain extent within the acceptable range [89]. Additionally, the surface characteristics like as friction, magnetism and height, are assessed using atomic force microscopy [90]. A highly developed label-free technique called surface plasmon resonance (SPR) is used to look at how nanocrystal surfaces change, how well films disperse, and how well particles stick to one another [91].

- *Thermal Analysis:*

One of key techniques for examining the thermodynamic properties of drug nanocrystals is DSC. To assess the thermal behaviour, the drug's crystallinity and the production of nanocrystals using different polymers are examined. For those medications that come in a variety of polymorphic forms, this study is essential [92]. Thermogravimetric analysis (TGA) helps to assess the sample's quality while it is being heated and identify a solvent or hydrate's structure [93].

- *Raman Spectroscopy:*

This method relies on the inelastic scattering of laser-generated monochromatic light. The inelastic scattering is defined as the modification of the frequency of photon in monochromatic light due to contact with the material. The sample absorbs the laser photon light, which is subsequently reemitted. In compared to the frequency of the initial monochromatic light, the photons' remission frequency is moved down or up. This process is termed as Raman Effect. This shifting gives details about the compounds' low-frequency rotational, vibrational, and other transitions. It is

employed as a technique to describe the phases and transitions of different kind of nanoparticles as well as other nanostructured materials (such as nanocrystals) in order to characterise the different categories of nanoscale materials - crystalline and amorphous [94].

- *FT-IR Analysis:*

FT-IR is used to assess the chemical characteristics of drugs and how they interact with various excipients. For pulmonary administration of drugs, Liandong and his colleagues in 2015 developed and tested spray-dried powder of curcumin nanocrystals. To analyze the alteration in chemical properties and crystalline structure, FT-IR spectroscopy experiments were perfomed on curcumin nanocrystals and the produced spray dried powders of curcumin nanocrystals. The results showed that spray dried and milling products were not change the chemical properties of curcumin as they would in spray dried powder. This was due to the location of the formulation's peaks in relation to the pure drug [95].

- *Particle Size and Polydispersity Index:*

To demonstrate additional features like dissolving rate, saturated solubility, physical stability, and therapeutic effectiveness, particle size and their distribution were crucial criteria. The most often utilised methods for determining particle size were microscopy, static and dynamic light scattering methods [96]. The dynamic light scattering technique, commonly termed as photon correlation spectroscopy (PCS), is utilised to demonstrate the average nanosuspension particle size [97]. Particle sizes more than 6 µm cannot be analyzed using this method. Low-angled static light scattering methods, such as laser diffractometry (LD) and optical microscopy, may detect bigger particle sizes. For the examination of big particles and mixtures of tiny and big particles, LD, a reliable technology, has advantages over other approaches [98].

- *Solid-State NMR (ssNMR) Spectroscopy:*

The kinetic behaviour and chemical arrangement of molecules in crystals may be studied using ssNMR spectroscopy. Consequently, ssNMR spectroscopy is a crucial technique to evaluate and identify the crystal patterns. In Pinon's research 2015, the NMR method was used to examine how samples of the asthma medication theophylline were affected by three polymorphs and one hydrated state [99].

- *Nanocrystals Formulations Available in Market:*

The first items produced by industrial fabrication to hit the market for medicinal uses were nanocrystals medicines with an oral delivery mechanism [49]. List of nanocrystals formulation available in market are described in table 3.

Table 3 Examples of Nanocrystals Available in Market and Clinical Trials

Brand name	Drug	Method of preparation	Approval year	Dosage form	Company	References
Oral route						
Rapamune	Sirolimus	Pearl mill	2000	Tablet	Wyeth pharmaceuticals	[100]
Avinza	Morphine sulphate	Pearl mill	2002	Capsule	King pharma	[7]
Ritalin LA	Methylphenidate hydrochloride	Pearl mill	2002	Capsule	Noartis	[7]
Emend	Aprepitant	Pearl mill	2003	Capsule	Merck	[100]
Tricor	Fenofibrate	Pearl mill	2004	Tablet	Abbott lab	[4]
Megace ES	Megasterol	Pearl mill	2005	Suspension	Par pharmaceuticals	[101]
Triglide	Fenofibrate	High-pressure homogenization	2005	Tablet	Skye pharma and sciele pharma inc.	[7]
Naprelan	Naproxen sodium	Pearl mill	2006	Tablet	Wyeth pharmaceuticals	[102]
Theodur	Theophylline	Pearl mill	2008	Tablet	Mitsubishi tanabe pharma	[102]
Cesamet	Nabilone	Co-precipitation	2009	Capsule	Lilly pharmaceutics	[7]
Intravenous route						
Invega sustenna	Paliperidone palmitate	High-pressure homogenization	2009	Intravenous suspension	Johnson and Johnson/janseen	[4]
Aristada	Aripiprazole lauroxil	High-pressure homogenization	2015	Intravenous suspension	Alkermes	[103]
Anjeso	Meloxicam	Pearl mill	2020	Intravenous suspension	Baudax bio	[104]
Cabenuva	Cabotegravir & rilpivirine	Pearl mill	2021	Intravenous suspension	Viiv healthcare	[105]
Nanocrystal formulation in clinical trials						
Brand name	**Drug**	**Method of preparation**	**Clinical trials**	**Dosage form**	**Company**	**References**

Semapimod	Guanyl hydrazone	Self-produced	Phase II	Intravenous	Cytokine pharmasciences	[7,9]
Paxceed	Paclitaxel	Unknown	Phase III	Intravenous	Angiotech	[7,9,106]
Theralux	Thymectacin	Pearl mill	Phase II	Intravenous	Celmed	[7,9]
Nucryst	Silver	Self-produced	Phase II	Topical	Nucryst pharmaceuticals	[107,108]
Panzem NCD	2-methoxy estradiol	Pearl milling	Phase II	Oral	Entremed	[109]

III. CONCLUSION

One easy and efficient way to improve the dissolution of weakly soluble medications is to use nanocrystals. It improves the solubility by reducing the particles in nano range. Quantom dots are semiconductor nanocrystals helps to improve solubility by reducing the size of crystals in 2-10nm range. Nanocrystals are available in different shapes, but Wulff construction has been identified by Gibbs to describe the shapes of nanocrystals. Various recent techniques are available nowadays for nanocrystals preparation to overcome the poor solubility problem and for quick action of drug. This article discusses the several nanocrystals formulations prepared by various authors, marketed formulations and formulations which are under clinical trials.

- *Ethical Issues*
  No.

- *Conflict Interest*
  No.

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