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Nanocrystals and their applications in pharmaceutical technology: An up-to-date overview

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ABSTRACT: Due to their poor solubility and poor bioavailability, the majority of recently produced novel chemical entities pose significant challenges in the formulation and development of new dosage forms. The pharmaceuticals in Biopharmaceutical Classification System (BCS) classes II and IV have a solubility issue; nanotechnology is the most effective solution to this issue. The preparation of nanocrystals and the numerous methods utilized to create them are the major topics of this review article. Since there is no matrix material present in drug nanocrystals, they are a carrier-free form of drug delivery. For pharmaceuticals in BCS classes II and IV, nanocrystal technologies have been suggested as beneficial, all-purpose formulation methods. The dissolving rate and saturation solubility of active agent can be efficiently increased by nanocrystals because of their higher surface to volume ratio. Major used routes of administration, including oral, IV, SC, IM, and topical administration are acceptable for the nanocrystals drug delivery system. For use in sterile products, nanocrystals can also be added to tablets, capsules, quick melts, and lyophilized materials. Precipitation, milling, high pressure homogenization, and combination methods like Nano-Edge™, SmartCrystal® are just a few of the production techniques employed today.

KEYWORDS: bioavailability improvement; saturation solubility; dissolving velocity; pearl milling; high pressure homogenization; nanocrystal.

1. INTRODUCTION

Nowadays, interest in nano-sized materials is increasing due to their wide applications in the pharmaceutical industry. Nanotechnology has been developing rapidly in many different application areas in recent years. Nanoparticle drug delivery systems are one of the areas of pharmacy where nanotechnology is being used [1]. Nanocarriers are increasingly being investigated for their potential in the treatment of various diseases by reducing their side effects [2]. Nanoparticles have some important advantages because of their size and surface properties and these are; enhanced dissolution and solubility, improved absorption and bioavailability, safe dose enhancement, enhanced efficacy and safety profiles [3].

Due to achieving maximum bioavailability and effectiveness, drugs that are insoluble in water or hydrophobic pose a difficulty [4]. According to research from 2015, solubility issues exist for 90% of drugs in the discovery pipeline and 40% of drugs currently on the market [5]. Other reports indicate that, more than 40% of new chemicals are lipophilic compounds. At the same time, poorly soluble active pharmaceutical ingredients make up about 1/3 of the substances registered in the American Pharmacopoeia (USP) [6, 7]. To overcome these problems, new technologies like nanocrystals developed to improve solubility and bioavailability of lipophilic drugs [8]. Poorly soluble pharmaceuticals can be nanocrystallized to increase their physicochemical stability and bioavailability was shown in (Figure 1).

Pure solid components with a diameter of 1 µm or fewer and crystalline characteristics are called nanocrystals (NCs). Mainly constituted from 100% pure drug with stabilizers that surrounding the particles [9]. Nanosuspensions are dispersion of drug nanocrystals in liquid media [10], and also known as Nanocrystal Colloidal Dispersions (NCD) [11].

Nanocrystalline formulations are unstable due to their small particle size, hence stabilizers are required to stop aggregation and/or Ostwald ripening after manufacture and while the formulations are in storage. Different types of polymers can serve as stabilizers, including cellulose derivatives, poloxamers, Polyvinylpyrrolidone (PVP), vitamin E tocopheryl polyethylene glycol succinate (vitamin E TPGS), and

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amphiphilic surfactants including sodium dodecyl sulfate (SDS) and polysorbates. By improving wetting and solubilizing properties, solubility can also be increased [12].

Because of the higher surface area to volume ratio and faster dissolving rates provided by nanosizing drug molecules, nanocrystals increase the solubility of hydrophobic pharmaceuticals [13].

Many researchers have focused on the low water solubility issues with BCS Class-II and Class-IV pharmaceuticals in the past few years [14], and nanocrystals are uniquely well-suited for solving solubility issues of Biopharmaceutics Classification System (BCS) Class II and IV drugs [11]. A scheme that depicts solubility and permeability under specific circumstances is the BCS classification system. Pharmaceuticals and molecules are divided into four classes using this system. Class I pharmaceuticals therefore have high solubility and permeability, Class II pharmaceuticals have low solubility but high permeability, Class III molecules have high solubility and poor permeability, and Class IV drugs have low solubility and permeability [5].

Other superiority of nanocrystals over conventional formulations are:

- most affordable,
- it is easier to manufacture and scale up,
- fast dissolution and tissue targeting,
- reduce tissue irritation because of low surfactants and stabilizers usage,
- preferable bioavailability in ocular and inhalation drug delivery systems [15, 16].

The disadvantages of nanocrystals are:

- problems can be caused by physical instability, sedimentation and compaction,
- it is challenging to obtain a uniform and precise dose,
- handling and transportation must be done with care [17].

Nanocrystals can be administered by oral, intravenous, intramuscular, ocular, dermal and pulmonary routes of administration and this provides additional benefits to nanocrystals, expanding the range of therapeutic delivery options to the desired spot [11, 14].

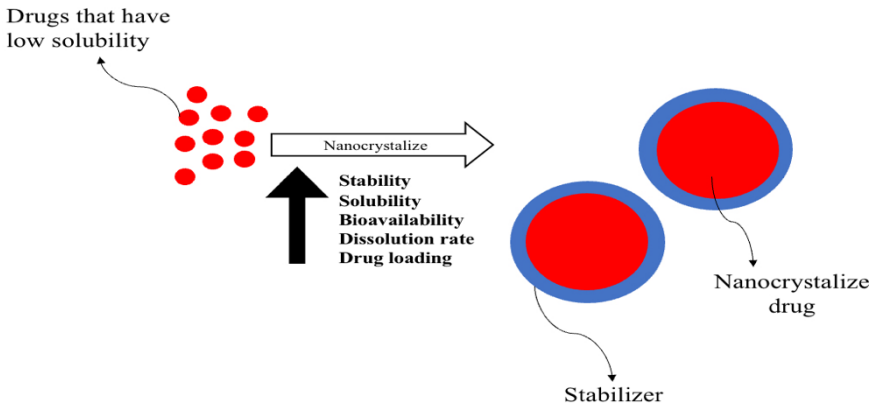

Figure 1. Poorly soluble pharmaceuticals can be nanocrystallized to increase their physicochemical stability and bioavailability.

2. CHARACTERISTICS OF NANOCRYSTALS

2.1. Accelerated Dissolution Rate

The Noyes-Whitney equation states that size reduction led to an increase in surface area and a faster rate of disintegration. Because of this, micronization is a successful method to boost the bioavailability of pharmaceuticals. The particle surface rises more as the process moves from micronization to nanonization, which likewise accelerates the rate of disintegration. A low dissolution rate is typically correlated with a low saturation solubility. Noyes-Whitney equation (**1**):

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

Where dc/dt refers the rate of dissolution, D denotes the diffusion coefficient, A represents the surface area, h defines the thickness of the diffusion layer, Cs is saturation solubility, and Ct is the concentration in liquid media [17].

2.2. Increased Saturation Solubility

Nanoparticles also have an impact on the Noyes-Whitney equation's thickness of the diffusion layer and saturation solubility. The solubility increases as the diffusion layer thins for particles with sizes less than roughly 50 µm. The Ostwald-Freundlich theory, which was initially proposed for liquid droplets in the gas phase, was found to be accurate for particle sizes below roughly 1µm for solid particles in the liquid media as well Ostwald-Freunlich equation (**2**):

$$Snp = S0(2Vm\gamma/RTr)$$

Where r is the radius of the nanoparticles, S_{np} is the solubility of nanoparticles, S_0 is the solubility of bulk material, Vm is the molar volume, γ is the interfacial tension, R is the gas constant, T is the temperature. At particle sizes below 1 µm, the impact of particle size on saturation solubility begins to be seen, however as the particle size is decreased, the impact becomes more evident; The rate of increase is exponential below 100 nm [18].

3. PREPARATION OF DRUG NANOCRYSTALS

Drug nanocrystals have undergone investigation using various preparation techniques. Bottom-up and top-down technologies are the two fundamental methodologies that can be used to produce drug nanocrystals. Top-down methods for creating drug nanoparticles require milling or homogenizing bigger particles, whereas bottom-up methods involve aggregating and managing precipitates at the nanometer scale [19]. Preparation of drug nanocrystals was shown in (Figure 2) and advantage and disadvantages of nanocrystals production methods was shown in (Table 1).

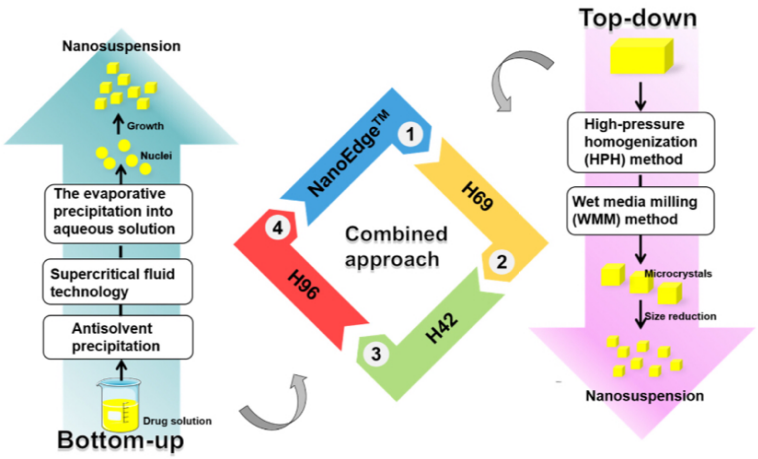

Figure 2. Preparation of drug nanocrystals [20].

3.1. Bottom-up Technology

The traditional precipitation technique known as "via humida paratum" is the foundation of bottom-up technology, which is the first method used in the manufacture of nanocrystals. The active substance dissolves in the solvent according to the fundamental principle. Then, a solvent that is miscible but insoluble with the medium is added to this solution, and the drug particles precipitate in the presence of stabilizer [21]. The industrial bottom-up method patents belong to Soliqs/Ludwighafen (Nanomorph™) and Sandoz (Hydrosols) [22].

The advantages of the bottom-up method are that it is simple and low-cost; However, for the method to be applicable, the active substance must be soluble in at least one solvent, there are no suitable systems for scale-up due to the use of organic solvents, and difficult processes are required to control the particle size (mixing speed, solvent selection) so other production techniques development are needed [23]. Scheme of precipitation technique was shown in (Figure 3).

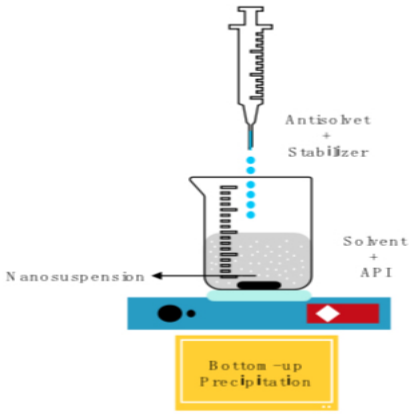

Figure 3. Scheme of precipitation technique [24].

3.2. Top-down Technology

Homogenization or milling can be used to implement "top-down" technologies [25].

3.2.1. Media Milling

Wet milling is used because dry milling (such as jet milling) is ineffective for achieving a size in the nm range. Wet milling refers to the process of dispersing the active substance particles in a surfactant/stabilizer solution before subjecting the resulting macrosuspension to grinding force.

The pearl mill (bead mill), created by Liversidge et al. for élan's company (Nanocrystal™ technology), is a low energy milling procedure. Almost all products on the market made with this technique. Typically, 0.2 mm or 0.4–0.6 mm in size, milling balls are placed in a grinding vessel together with the suspension. The crystals undergo grinding between the moving balls, and the resultant product is called a nanosuspension [21].

The quantity of milling pearls, the amount that is used of active ingredient and stabilizer/surfactant, the milling velocity, the sort of milling vessel, the milling period, and the temperature all affect the physicochemical properties of Nanocrystals [26].

The pearls are formed of porcelain, glass, zirconium oxide, stainless steel, chromium, agate, or certain polymer materials, while the milling chambers are constructed of stainless steel, porcelain, and hard materials [10].

The grinding technique has the benefit of being applicable to many active substances with water solubilities of less than 10 mg/mL, high drug loading (such as 30% w/w), and can be applied to many different types of dosage forms (tablets, capsules, sterile products, etc.) [27]. Scheme of wet ball milling was shown in (Figure 4).

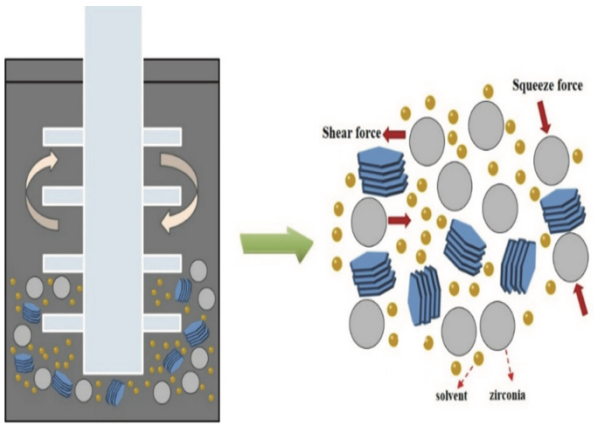

Figure 4. Wet ball milling [28].

3.2.2. High-Pressure Homogenization (HPH)

A size-reduction procedure involving high energy disintegration. In this manner, the drug suspension is forced through a small opening, leading to the production of cavitation, particle collisions, and size reduction under strong shear forces. The piston-gap homogenizer and the microfluidizer homogenizer are the two types of homogenizers that are typically used [29].

There are three significant homogenization technologies that can be used to create nanocrystals: the microfluidizer technology (IDD-P™ technology), the piston gap homogenization in water (Dissocubes® technology), and the nonaqueous or water-mixed media (Nanopure® technology) [10].

The basic principle of the Microfluidizer technology is jet steaming. High pressure causes a frontal collision of two fast-moving liquid streams. High shear force particle collision and cavitation cause the particle size to be reduced. The collision chamber might have a Y-type or Z-type shape. To stabilize the acquired particle size, surfactants or phospholipids are necessary. In order to produce submicron particles of poorly soluble pharmaceuticals, SkyePharma Canada Inc. (previously RTP Inc.) uses this idea in its Insoluble Drug Delivery - Particles (IDD-P™) technology [30, 31]. Microfluidizer scheme was shown in (Figure 5).

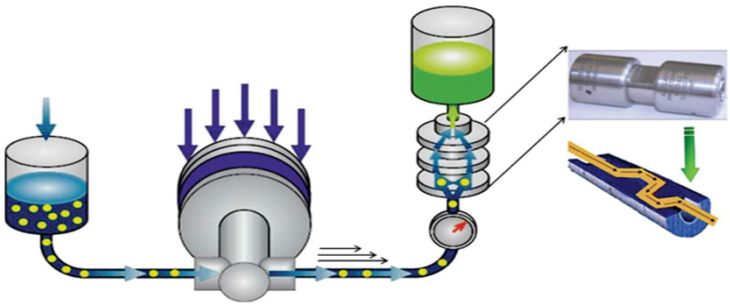

Figure 5. Microfluidizer [32].

Piston gap homogenizers are used in Dissocubes® technology. This technique was first created by Müller et al. (1995, 1999), which SkyePharma PLC later purchased. This method creates nanoparticle suspensions within water at ambient temperature. A piston forces a drug powder at pressures up to 4000 bar, typically 1500 to 2000 bar, through a tiny homogenizing hole after it has been dispersed in an aqueous solution containing surfactant. The breadth of the homogenization gap varies roughly between 5 and 20 microns, depending on the suspension's viscosity and the pressure being used.

The use of water can actually have drawbacks, such as the hydrolysis of pharmaceuticals that are sensitive to water and issues with the subsequent drying stages (such as removing too much water).

The drying procedure could call for pricey procedures like lyophilization when used with medications that have a low melting point. Therefore, the method is best suited for creating aqueous suspensions of Nanocrystals [33].

The Nanopure® technology, owned and created by Pharma-Sol GmbH in Berlin, is another method using the piston gap homogenizer with water mixes or nonaqueous media [34].

Low batch-to-batch variation, waterless manufacturing, and employed for the synthesis of diluted and concentrated nanosuspensions with low particle size dispersion are advantages, but high energy requirements, suspension formation, and the need for micronization of drug particles are adverse aspects [29]. Piston gap homogenizer scheme was shown in (Figure 6).

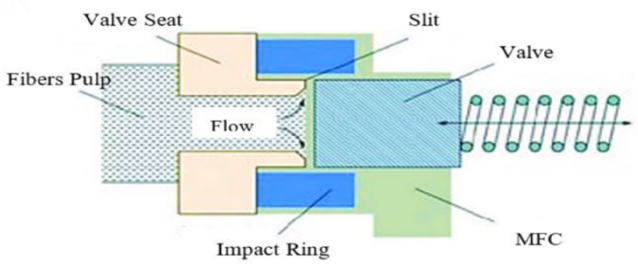

Figure 6. Piston gap homogenizer [35].

Combining bottom-up and/or top-down approaches offers an efficient way to reduce particle sizes while also doing away with the drawbacks of separate approaches, like equipment obstruction and extended processing periods. Combination procedures often start with a pre-treatment phase before applying a high-energy top-down process.

SmartCrystal® technology, which combines several pre-treatment techniques with the primary post-treatment HPH, has largely supplanted the initial combination approach, Nanoedge™ technology.

Pretreatment methods include; CT (media grinding), H42 (spray drying), H69 (precipitation), H96 (lyophilization), and Nanopure (no pretreatment).

Even though combination technologies enhance reduction in particle size and process effectiveness, every pre-treatment step actually makes the entire process challenging and is capable of significantly increasing costs. Therefore, it is evident that combination particle size reduction techniques will only be used in situations when more straightforward and well-established techniques like wet ball milling or conventional high-pressure homogenization cannot be used to produce a required final product [23, 36].

Table 1. Advantage and disadvantages of Nanocrystals production methods [37].

Technology	Advantages	Disadvantages
Precipitation	- Drug that is properly dispersed - Effective control of the required size.	- Requires stabilization - Organic solvent residue - Not applicable to all medications; only those with specific characteristics, such as being soluble in at least one solvent, may be used.
Milling	- Low energy method.	- Milling media residue - A lengthy procedure (a several days) - A requirement for stabilization - Difficulty in producing big batches due to milling chamber size.
Homogenization	- Universally applicable - No issues with huge quantities - Quick procedure (maybe takes a few minutes) - Potential for water-free production.	- High-energy approach - Extensive experience required.

4. APPLICATION

Many potential applications exist for nanocrystals, particularly when it comes to pharmaceuticals with poor solubility and bioavailability. The list of them is below.

4.1. Oral Drug Administration

Because of its ease and safety, oral administration is one of the most widely used methods for delivering pharmaceuticals, especially for those with low solubility. The solubility of oral active pharmaceutical ingredients in digestive fluids and how they circulate in the gastrointestinal tract determine how well they work. Particularly for medications with low solubility, the oral controlled release formulation in conjunction with nanocrystal technology has proven to be quite helpful. By removing the requirement for alternative drug forms (such as salt, prodrugs, etc.), high drug loading, and optimizing drug delivery, the integrated technology increases the versatility of the dosage form.

Elan Pharmaceutical Technologies has commercially introduced a variety of products using this combined technology [37-39].

The oral route is the recommended route for numerous pharmaceuticals due to its many benefits, particularly when antibiotics like atovaquone and buparvaquone are used orally. Their solubility and bioavailability will improve as they get nanosized. The absolute bioavailability of the nanosuspension in the case of danazol (a gonadotropin inhibitor) is 82.3%, while the usual distribution is just 5.2% [15, 40]. Recent studies for oral drug administration are given in (Table 2).

Table 2. Recent studies have shown that NCs can improve the absorption of pharmaceuticals taken orally.

Drug	Medical Condition	Preparation Method	Stabilizer	Particle size in nm	Effect	Reference
Albendazole	Helminthic infections	HPH	Poloxamer 188	522	Improved therapeutic response and oral absorption in dogs.	[41]
Lovastatin	Model drug	Round NC's: WBM; Flaked NC's: Cool Precipitation; Rod-Shaped NC's: Sonoprecipitation + HPH	Poloxamer 188	405-417	Different-shaped NCs are absorbed differently. Over spherical and flake-like NCs, rod-shaped NCs demonstrated a higher intracellular absorption and bioavailability.	[42]
Quercetin hybrid fluorescent NCs	Model drug	Crystallization	Poloxamer 188	250 and 550	Drugs' bioavailability was improved. Depending on the particle size and route of administration, in-vivo tracking of the NCs revealed various biodistributions.	[43]
Coumarin	Model drug	Sonoprecipitation	Pluronic F127	253	Instead of NC translocation, the drug's improved absorption was correlated with improved gastrointestinal tract (GIT) dissolution.	[44]
Valerolactam-Fenbendazole	Infections with parasites in cattle	WBM	Poloxamer 188	258	Consistency in the drug's distribution throughout the powdered NCs. An increased rate of dissolution.	[45]
Nintedanib	Non-small cell pulmonary cancer	Sonoprecipitation	Sodium carboxymethyl cellulose (CMC-Na)	370	Increased oral bioavailability through various routes of absorption.	[46]
Silibyn	Chronic and acute liver conditions	HPH	NCs stabilized in a pickering emulsion that is self-stabilizing	350	Increased bioavailability and dissolution rate in rats.	[47]
Hydroxy-camptothecin	Many different cancers	Precipitation carried on by a change in pH, then ultrasonication	Polyvinylpyrrolidone (PVP)	160	NCs loaded into crosslinked chitosan microparticles demonstrated higher bioavailability in rats.	[48]
Ricobendazole	Helminthic infections	WBM	Poloxamer 188	129	Increased oral absorption and dissolution rate in dogs.	[49]

4.2. Ocular Drug Administration

Applications for ocular drug delivery are also being investigated by a number of researchers, including specific applications of nanocrystals in ocular drug delivery. Ocular drug delivery, assess the possible advantages of nanocrystals in oral drug delivery. There isn't just one medication for eye illnesses based on nanocrystals available on the market. This might be because manufacturing methods for the creation of nanocrystals are covered by a patent. The benefits of using nanocrystals for ocular drug delivery have been demonstrated by research, and these holds promise for the treatment of a number of ocular

disorders. It has also sparked the creation of improved substitute medication formulations for pharmaceuticals that are poorly soluble. These benefits include improved corneal permeability, improved ocular bioavailability, improved tolerability, and improved ocular safety [38, 39, 50].

Some pharmaceuticals don't dissolve well in ocular fluid. Saturation solubility and bioavailability will rise with nanoparticle formulation. It extends the residence period of hydrophobic medicines, which is its principal purpose. Ibuprofen is the best illustration of nanosuspension. Ibuprofen's anti-inflammatory effect is substantially greater than the aqueous formulation [51]. Recent studies for ocular drug administration are given in (Table 3).

Table 3. Recent studies for ocular drug administration of nanocrystals.

Drug	Medical Condition	Preparation Method	Stabilizer	Particle size in nm	Effect	Reference
Acetazolamide	Ocular hypertension	Precipitation + sonication	Polyvinyl alcohol (PVA), Hyaluronic acid salt (HY) or Poly-δ-glutamic acid (PG), Soya bean lecithin	100-300	Improved saturation solubility and effective ocular hypotensive action were observed. Tolerability and safety were demonstrated on the eye by the modified Draize test.	[52]
Triamcinolone acetonide	Ocular hypertension	Nanoprecipitation	~~Polyvinyl alcohol (PVA), Poloxamer 407~~	150	High physical stability, enhanced loading capacity, and solubility were attained.	[53]

4.3. Dermal Drug Administration

Dermal use of nanocrystals was a route of administration that was not completely utilized until a few years ago, despite the benefits of nanocrystals like as adhesion, quick dissolution, and enhanced penetration, which may be helpful when used for dermal application. The development of nanocrystals for skin delivery began with cosmetics and eventually expanded to include pharmaceutical delivery. Rutin and hesperidin antioxidant nanocrystals are found, respectively, in Juvedical 1 (Juvena of Switzerland, Juvena Marlies Möller AG) and Platinum Rare collection (La Prairie 1) cosmetic goods [39, 50, 54]. Recent studies for dermal drug administration are given in (Table 4).

4.4. Parenteral Drug Administration

Low solubility pharmaceuticals administered parenterally perform better when nanocrystal technology is used. The dose is reduced by increasing drug loading, increasing dissolution (due to nano size), inhibiting macrophage absorption and switching solvents that are organic with aqueous-based solvents. Nanocrystals enable sterile filtering for safety; stiff excipients should also be avoided [29, 54, 58].

In order to avoid the need for cyclodextrins and surfactants to increase tarazepide's bioavailability, it has been produced as a nanosuspension [59]. Recent studies for parenteral drug administration are given in (Table 5).

Table 4. Recent studies for dermal drug administration of nanocrystals.

Drug	Medical Condition	Preparation Method	Stabilizer	Particle size in nm	Effect	Reference
Flurbiprofen (FB)	Analgesic and anti-inflammatory	WBM	Plantacare® 2000 UP (PL)	237.7	In comparison to gels containing coarse suspension and physical combination, NC gel demonstrated greater penetration and improved plasma-blood concentration of FB in rats during pharmacokinetic experiments.	[55]
Nitrofurazone (NTF)	Antioxidant and anti-inflammatory	WBM	Sodium dodecyl sulfate (SDS), Tween 80, Tocopheryl polyethylene glycol succinate (TPGS), Hydroxypropylmethylcellulose E3 (HPMC E3), Polyvinylpyrrolidone K30 (PVP K30), Hydroxypropylmethylcellulose E5 (HPMC E5) (alone or in combination with other surfactants), Poloxamer 188	300	When compared to the NTF marketed gel, the NTF nanogel dissolved more readily. In the ex vivo rat skin permeation trials, the amount of NTF that had penetrated the nanogel's skin after 24 hours was more than that of the commercial gel. Rats' skin retained 5.5 times more NTF after applying NTF nanogel than it did after using NTF-marketed gel.	[56]
Flurbiprofen (FB)	Analgesic and anti-inflammatory	HPH	Plantacare® 2000 UP (PL)	665-700	With nanosuspension, the saturation solubility of FB was enhanced 5.3 times. In rat skin, the permeability of FB NC was greater than that of the FB solution.	[57]

Table 5. Recent studies for parenteral drug administration of nanocrystals.

Drug	Medical Condition	Preparation Method	Stabilizer	Particle size in nm	Effect	Reference
p-terphenyl derivative (H2)	Anticancer	Microfluidization + Precipitation	Lecithin, Poloxamer 188	201.7	Faster rate of dissolution and greater saturation solubility. Five times more area under the curve (AUC0~∞). A higher average retention duration.	[60]
Bexarotene	Anticancer	Microfluidization + Precipitation	Soybean lecithin, Poloxamer 188, Polyvinylpyrrolidone K30 (PVP K30)	279	Increased solubility by about ten times. Greater maximum serum concentration (Cmax), AUC, and mean retention time.	[61]

4.5. Pulmonary Drug Administration

The greatest particle size required for central airways deposition is around 5 µm, as particles with the proper aerodynamic size, shape, and density are fundamental requirements for an optimal pulmonary drug delivery. When used for pulmonary drug delivery, jet-milled suspension aerosols or dry powders (often micron-sized) typically produce unfavorable results because of the poor ability to flow, limited bioavailability, and unfavorable buildup in the mouth and pharynx. Utilizing nanosuspension is a concluding and alluring method in this regard. Nanocrystal technology offers preferential delivery of pharmaceuticals to the lung for systemic or local effect. It can be used on a range of pharmacological molecules, whether they are in the form of liquid droplets or powder, for inhalation [29, 58]. Recent studies for pulmonary drug administration are given in (Table 6).

Table 6. Recent studies for pulmonary drug administration of nanocrystals.

Drug	Medical Condition	Preparation Method	Stabilizer	Particle size in nm	Effect	Reference
Telmisartan	COVID-19 lung disease, other respiratory ınfections	Sonication	Polysorbate 80	322	In rodents and/or non-human primates, the created nanosuspension showed good pharmacokinetics, good lung applicability, and tolerable tolerance. The formulation is currently being clinically evaluated for use as an inhaler in patients with COVID-19 or other respiratory diseases.	[62]
Beclomethasone Dipropionate (BDP) and Curcumin (CUR)	Bronchial asthma	WBM	Poloxamer 188	CUR NS: 202 BDP+CUR NS: 240	Enhanced CUR apparent solubility in comparison to the raw material by about 54 times. The results, which demonstrate multicomponent nanosuspension, ideal dimensional properties, and aerodynamic parameters, point to the need for the formulation to be precisely and effectively administered to deeper lung regions.	[63]
Fluticasone propionate (FP)	Corticosteroid	WBM + HPH	Citric acid, Tween 80, Ethylenediaminetetraacetic acid disodium salt (EDTA-2Na), Sodium chloride (NaCl), Sodium citrate	246	This study showed that inhalable nanosuspensions are a feasible method for FP to be delivered to the lungs over an extended period of time, and that the degree to which they have local anti-inflammatory effects depends primarily on how well they dissolve. The local anti-inflammatory effect of FP was significantly prolonged when administered intratracheally in the form of nanosuspensions, which also improved local retention, prolonged the pulmonary absorption time, and attenuated mucociliary clearance.	[64]
Mometasone	Asthma	HPH	Dipalmitoylp	MFM:	The findings	[65]

Furoate Monohydrate (MFM) + Formoterol Fumarate Dihydrate (FFD)		+ Spray drying	hosphatidylcholine (DPPC)	1.71(µm) FFD: 2.20(µm)	unequivocally demonstrated that a DPI formulation containing MFM and FFD with a particle size of less than 5 µm is appropriate to enter alveoli when combined with spray drying and homogenization techniques.	
Loratidine	Urticari, allergic rhinitis, atopic dermatitis	Precipitation + Sonication	Pluronic F6 or Tween 80 + Polyvinylpyrrolidone K-25 (PVP K-25)	353–441	It is possible to prepare dried loratadine nanoparticles that are appropriate for creating potent medication preparations.	[66]

4.6. Targeted Drug Administration

Nanosuspensions, which are also utilized to adjust the stabilizer and target surface qualities, are simple to manipulate in vivo. The mononuclear phagocytic system will take up the pharmaceutical to enable regionally targeted drug distribution. Using this, fungicides and antimycobacterial agents can be directed onto macrophages. To target the brain, atovaquone nanosuspension is employed [67].

5. MARKETED NANOCRYSTAL FORMULATIONS

For use in clinical settings, the FDA has approved 50 formulations of liposomes, nanocrystals, and polymer-based nanopharmaceuticals. Additionally, they are being researched in clinical studies for a wide range of therapeutic uses. One of the greatest approaches to increase the solubility and rate of dissolution of insoluble or weakly soluble active pharmaceutical ingredients through nanocrystallization [68, 69].

In roughly 25 years, the liposome's commercialization was approved; nevertheless, Emend®'s development took only about 10 years. 1990 saw the acquisition of Emend's first patent, and 2000 saw the product's approval. As a result, the majority of nanocrystal formulations have been developed and successfully authorized in less time than previous nanoformulations. Some nanocrystal formulations that approved by FDA was shown in (Table 7).

In 2000, Wyeth Pharmaceuticals introduced Rapamune®, a sirolimus immunosuppressant with limited solubility, as the first nanocrystalline product. One of the top-down methods, the pearl mill method, was used to create Rapamune. Sirolimus oral bioavailability was 21% greater than its dosage form than usual.

Emend® was subsequently given approval by Merck in 2003. Emend was created from an antiemetic medication that is sparingly soluble, has a very narrow absorption, and is capable of being absorbed only in the GI. The pearl mill approach used in the formulation of Emend's nanocrystallization boosts the oral bioavailability of drugs with low water solubility [36, 70].

Abbott Lab introduced Fenofibrate Tricor®, a lipophilic medication for hypercholesteremia, in 2003 applying the pearl mill technology technique. The oral bioavailability of the medication fenofibrate nanocrystalline is increased by 9% without being impacted by eating or fasting. Additionally, Skye pharma granted approval for the Triglide® nanocrystalline medication product in 2005.Triglide was manufactured by using the high-pressure homogenization (HPH) technique and offers therapeutic advantages like Tricor. Triglide nanocrystals improved their independent bioavailability in the fasting or fed state and boosted their adherence to the intestinal wall. Sciele Pharma Inc. now manufactures and distributes triglide nanocrystals [11].

Table 7. Some nanocrystal formulations that approved by FDA [6, 10, 11].

Trade Name	Company	Drug	Indication	Applied Technology	Delivery System	Dosage Form	Approved Date
Rapamune®	Wyeth	Sirolimus	Immunosuppressant	Pear mill	Oral	Suspension, Tablet	2000
Emend®	Merck	Aprepitant	Antiemetic	Pear mill	Oral	Capsule	2003
Tricor®	Abbott	Fenofibrat	Hypercholesterolemia	Pear mill	Oral	Tablet	2004
Triglide®	SkyePharma	Fenofibrat	Hypercholesterolemia	HPH	Oral	Tablet	2005
Cesamet®	Lilly	Nabilone	Antiemetic	Precipitation	Oral	Capsule	2005
Megace ES®	Par Pharmaceutical	Megestrol acetate	Appetizing	Pear mill	Oral	Suspension	2005
Naprelan®	Wyeth	Naproxen sodium	NSAID	Pear mill	Oral	Tablet	2006
Theodur®	Mitsubishi Tanabe Pharma	Theophylline	Asthma, COPD	Pear mill	Oral	Tablet, capsule	2008
Invega Sustenna®	Johnson &Johnson	Paliperidone palmitate	Antipsychotic	Pear mill	I.V.	Suspension	2009

6.CONCLUSION

For poorly soluble pharmaceuticals, nanosizing has become a well-established and successful formulation strategy during the past twenty years. Drug nanocrystal production has given rise to a wide variety of approaches thanks to extensive study. Because they have also evolved through time, the traditional top-down methodologies WBM and HPH have been able to maintain a dominant position in this field up until now. As a consequence of the persistent and committed work of numerous researchers in this field, many unanswered concerns and technological drawbacks from the beginning have been addressed and may be resolved.

Undoubtedly, a key factor in the success of the nanosizing strategy is its enormous adaptability. It can be used to practically every substance and administration method. Despite the fact that very few items have yet to hit the market, nanosizing is undoubtedly well established and used extensively in the pharmaceutical sector. From the earliest investigations through the last stages of commercial production, drug nanocrystals can be used in all phases of industrial pharmaceutical development.

The understanding of the biopharmaceutical issues has evolved along with technological advancement. It is now obvious that oral medication administration using drug nanocrystals can only improve bioavailability when the compounds exhibit dissolution rate limited bioavailability. However, this method can significantly increase dosage flexibility for various modes of administration, particularly when extremely concentrated formulations are required.

The initial concept of creating extremely small pharmaceutical particles in order to increase drug effectiveness will still be used by researchers in this field. This strategy's full potential has not yet been completely realized.

It is possible that more sophisticated medication administration methods on the basis of drug nanocrystals will be created in the future. To further improve the effectiveness of these systems, it will be feasible to direct the nanosized drug particles to their target site using unique ligands or other surface modifications. In the end, the route of administration can only be a tool to enhance a pharmacological substance's pharmacodynamic effect in order to treat patients as effectively as possible.

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