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New Prospects for Therapeutic Organic Nanocrystals

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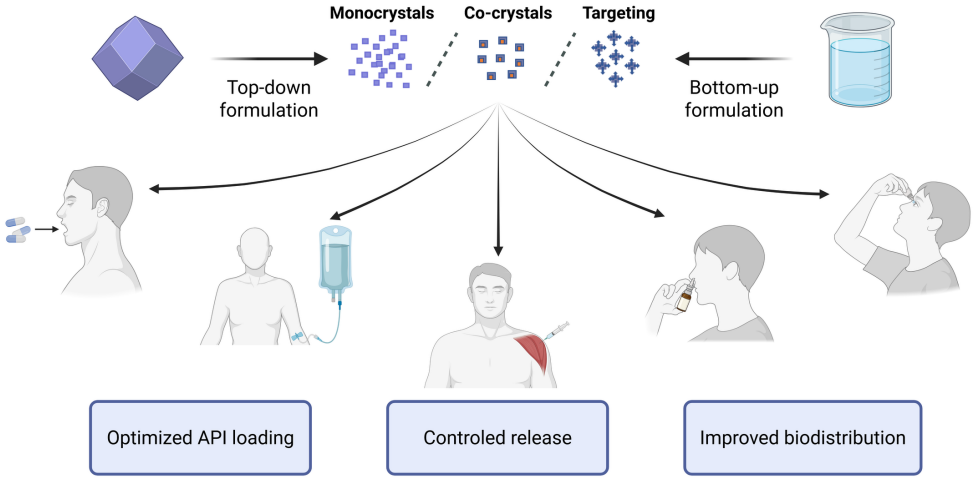
Graphical Abstract



Abstract

Nanocrystals have emerged as an interesting class of delivery systems for solubilizing pharmaceuticals in classes II and IV of the Biopharmaceutics Classification System (BCS)[†]. This can be attributed to their small size and high drug content. More than 20 nanocrystal formulations have already been approved by the Food and Drug Administration (FDA) for oral and parenteral administration, with additional clinical trials in progress. This review provides an update on FDA-approved nanocrystals and on current literature on their production via bottom-up techniques. Controlling drug supersaturation is a key step in this context. The favorable surface-to-volume ratio enhances the dissolution rate of drugs relative to their solid forms. Most monocrystal studies focus on diseases related to cancer and inflammation. We have concentrated on these areas, as well as new strategies aimed at combining drugs, including co-crystallization of drugs in nano-forms. Finally, we reviewed targeting approaches proposed for nanocrystals, which are primarily based on two main strategies: either grafting a ligand onto their surface or incorporating them into natural or modified membranes to facilitate homing to specific cells or tissues.

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[†]List of abbreviations: API: Active pharmaceutical ingredients; ASP: Anti-Solvent precipitation; BCS: Biopharmaceutics Classification System; CMC-Na: Sodium Carboxymethyl Cellulose; HPMC: Hydroxypropyl methyl cellulose; FDA: Food and Drug Administration; FCS: Fetal Calf Serum; GIT: Gastro-Intestinal Tract; HPH: High Pressure Homogenization; F127: Pluronic P407; MDR: Multiple Drug Resistance; PVP: Poly(vinylpyrrolidone); SDS: sodium lauryl sulfate; US: ultrasonication; 3LL: Lewis lung carcinoma

Keywords: Nanocrystals, nanomedicines, crystalline nanosuspensions, co-formulations, bottom-up synthesis, administration routes, in vivo delivery.

Introduction

Pharmaceuticals are primarily formulated in a solid state because this form generally allows easier storage and greater stability than other physical states. However, drugs in solid form must first dissolve within the body, and those with poor water solubility often display limited absorption and bioavailability. According to the Biopharmaceutics Classification System (BCS), drugs in a solid state are divided into four categories: highly soluble and permeable (class I), poorly soluble and highly permeable (class II), highly soluble and poorly permeable (class III), and poorly soluble and poorly permeable (class IV). The solid state offers extensive structural variability for active pharmaceutical ingredients (APIs), including polymorphs, solvates, salt crystals, co-crystals, amorphous solids, or combinations thereof. Selecting the most appropriate solid form to optimize physicochemical properties such as crystallinity, particle size, and surface area is essential to enhance the solubility of Class II and IV drugs, thereby improving their therapeutic efficacy [1].

Nanoparticle technologies have gained significant attention in the medical field due to their potential to improve API efficiency by prolonging circulation time within the blood and minimizing cytotoxicity [2]. Among these, nanocrystals (NCs) have shown great promise and are of particular interest for various clinical applications [1]. Indeed, nanocrystallization enables API solubilization while leveraging the advantages of the nanoscale, including a higher surface-to-volume ratio, enhanced accumulation in tumor environments or inflammatory areas, and reduced cytotoxicity. Despite the challenges in mastering the production process, the first nanocrystal drug was approved by the FDA as early as 1982 [3]. Since then, 22 additional nanocrystallized drugs have been approved for various medical applications, primarily for the treatment of inflammatory and infectious diseases. More recently, in 2021, Cabenuva® was approved by the FDA for the sustained release of two antiretroviral agents, namely cabotegravir and rilpivirine, as part of HIV therapy [4]. Today, 23 nanocrystal formulations are commercially available: 18 administered orally, four via parenteral routes, and one via ocular route (Table S1).

The development of NC formulations incorporating various APIs with antitumor and anti-inflammatory properties has been extensively pursued [5]. Enhancing the solubility of highly hydrophobic drugs through nanocrystal formulation is a key area of investigation. Reducing particle size increases the dissolution rate, as described by the Noyes–Whitney and Prandtl equations. Moreover, NCs offer several advantages over traditional APIs: (i) improved solubility of poorly soluble APIs; (ii) no need for a carrier; (iii) improved dissolution rates; (iv) multiple administration routes; (v) potential passive and active targeted delivery; (vi) compatibility with hybrid nanocrystal formulations [6].

This review aims to summarize the progress made over the past decades in the formulation, characterization and performance of therapeutic organic NCs, and provides an update on FDA-approved nanocrystals. It also summarizes the knowledge gained at the UTCBS laboratory, from screening several antitumor and anti-inflammatory drugs for their nanocrystallization potential, data that were presented at the international conference on recent advances in nanomedicine held at KIIT University in Bhubaneswar in 2025.

Discussion

Organic therapeutic nanocrystals

Definition

This presentation focuses on organic NCs used for therapeutic purposes. An organic therapeutic NC is a nanoscale crystalline structure composed of an organic drug, designed to enhance the delivery of therapeutics. The formulation of such organic NCs involves surface-active agents or polymeric steric stabilizers that prevent aggregation in aqueous solutions. This allows for an extremely high drug-loading capacity compared to other pharmaceutical forms based on encapsulation, thereby expanding the administration route options available for BCS class II and IV APIs [7], [8].

Procedures to formulate nanocrystals

To obtain NCs, there are two approaches: top-down and bottom-up. In the top-down approach, larger bulk materials are reduced into nanosized particles using techniques like ball milling, high-pressure homogenization (HPH),

grinding, and extrusion. These processes are better suited to large-scale production. They have already been well-explained and reviewed in the literature [9], [10].

The other approach to forming NCs is bottom-up, which includes methods such as solvent-antisolvent precipitation (ASP), chemical vapor deposition, spray drying, microemulsions, and supercritical fluids [1]. This approach enables the engineering of NCs at the molecular scale, with fewer API degradants and more controlled conditions. These approaches have been neglected due to concerns about reproducibility and scalability. In the solvent antisolvent approach, which is the most described method, when the solubilized drug is mixed with the antisolvent, two critical steps occur: nucleation due to reduced solubility and a subsequent crystal growth that needs to be controlled (Figure 1C) [11]. Polymorphism is a key concern in NC production, and changes in crystalline structure must be determined and controlled during manufacture to understand the bioavailability of the drug better [12]. Despite these concerns, improvements have been made in understanding the key variables that allow for the formulation of reproducible NC suspensions using the ASP technique [13].

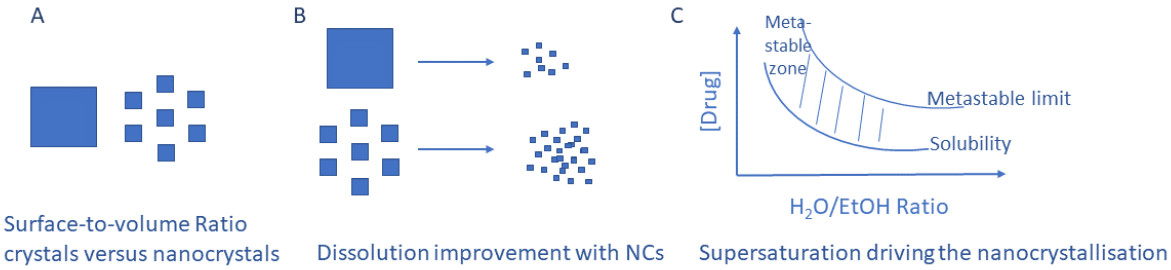

Figure 1. The interest of nanocrystallization is related to A. the increase in surface-to-volume ratio of the crystals and B. their improved dissolution. C. Supersaturation drives the formation of nanocrystals and should be determined to control the crystal growth.

Our group has recently patented an innovative nanocrystallization process for different poorly water-soluble pharmaceuticals to enhance their bioavailability and efficacy in vitro [14]. This process is based on the bottom-up solvent/antisolvent precipitation method to prepare nanosuspensions comprising NCs of the API with a small amount, or none, of stabilizing agents. Initially applied to etoposide drug nanocrystals [15], this process was successfully applied to other drugs, such as prednisolone, fisetin [16], curcumin [17], or a mixture of prednisolone and etoposide [6]. Manufacturing NCs using this process is of high interest for producing nanostructured powders, particularly those well-suited for medical use, because the powders are stable and easier to store before use. A recent study using curcumin as a drug model describes a systematic step-by-step approach to , synthesizing organic NCs by a semi-automated nanoprecipitation method [17].

Nanocrystal characterization

In general, nanomedicine characterization can be approached using a range of analytical techniques to investigate the physicochemical properties of NC formulations. Techniques such as Dynamic Light Scattering (DLS) [18], Nanoparticle Tracking Analysis (NTA) [19], or a Nano-kin particle size analyzer are commonly employed to determine the size distribution of a suspension of NCs. However, it is worth noting that nanocrystals are not always spherical, and particle size measurements may not be entirely accurate. Therefore, additional techniques such as Transmission Electron Microscopy (TEM) or Scanning Electron Microscopy (SEM) should also be performed. Moreover, while knowing the particle size distribution of NCs in a dispersion medium is important for understanding pharmacokinetics and reproducibility, crystallinity is equally crucial. A given particle size distribution of a suspension can exhibit significantly different pharmacokinetic behavior depending on its crystalline structure [20].

Since liquids are continuous and amorphous, it is difficult to accurately determine the crystalline structure and potential polymorphism of NCs in a liquid medium using traditional analytical techniques such as TEM, SEM [21], Atomic Force Microscopy (AFM) [22], or X-Ray Diffraction (XRD) [23]. One way to overcome these limitations is by using Cryo-TEM [21]. By flash-freezing the suspension, native and hydrated structures are preserved, so Cryo-TEM should be preferred for characterizing NC suspensions (Figure 2).

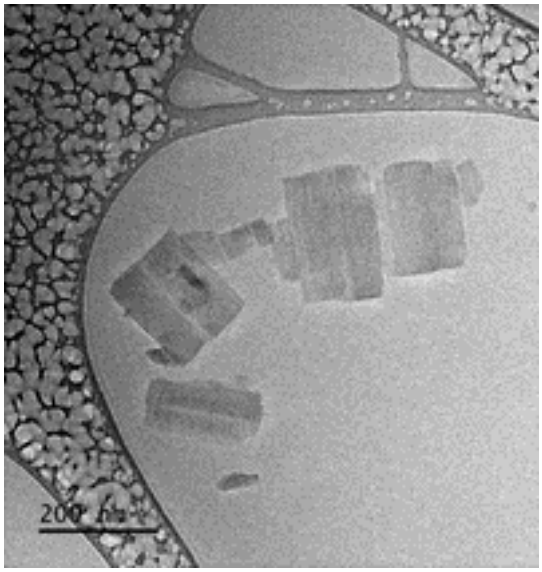

Figure 2. Cryo-TEM image of fisetin-based nanocrystals. Original image from unpublished data.

Currently, traditional TEM and SEM techniques are still widely used for analyzing ultrafiltrate-dried NC suspensions, even though they were initially designed for administration in their hydrated suspension form [24]. While these methods remain the simplest for determining NC morphology, precise crystallinity assessment — requiring compositional and atomic-structure analysis — necessitates XRD. However, XRD is almost exclusively used on dried nanosuspensions.

Finally, other analytical techniques are used to gather information on physico-chemical properties of NCs: Differential Scanning Calorimetry (DSC) [25] to determine the melting point and phase transitions, Raman[26] and Fourier-Transformed Infrared Spectroscopy (FTIR)[27] to determine the chemical composition if necessary or to identify surface modifications, Zeta potential [28] to determine the surface charge.

Nanocrystal formulation evolution and variability of the administration routes

Oral delivery

The oral route is the preferred administration route for both patients and the pharmaceutical industry. However, for poorly water-soluble drugs and especially class II drugs in the BCS, the oral administration route presents several hurdles to bioavailability. First, drug absorption through the gastrointestinal tract (GIT) is a challenge for these types of drugs. Second, the likelihood of the drug reaching its target tissue is low due to the reduced absorption caused by low solubility in the blood. This is why NCs were first developed to overcome these challenges by increasing bioavailability through particle size reduction (Figure 1A, B). Indeed, the extent of dissolution of these drugs in the GIT is directly related to the particle downsizing and thus the performance of the formulated product [29]. This explains why a large majority of marketed NCs are orally administered. Currently, 18 NC formulations have been approved by the FDA as oral dosage forms and used to treat a wide variety of diseases (Table S1). Among them, most are formulated using a top-down approach since particle size is not a primary concern for orally administered drugs because even larger particles can be administered. However, to achieve optimal bioavailability, downsizing is crucial and bottom-up approaches should be more investigated.

Parenteral delivery

Intravenous administration

NCs have shown unique advantages over conventional drug delivery systems for treating cancer and inflammation. Thanks to their nanometric size and large surface area (Figure 1), it is expected that NCs can benefit, upon intravenous administration, from the ELVIS (Extravasation through Leaky Vasculature and subsequent Inflammatory cell-mediated Sequestration) [30]and the EPR (Enhanced Permeability and Retention) effects [31], as shown for most nanoparticles. These advantages enable them to target inflamed tissues more specifically while minimizing side effects on healthy tissues. However, NC suspensions must contain particles with sizes below 200 nm to prevent rapid accumulation of NCs in the liver. Indeed, while circulating in the bloodstream, the mononuclear phagocytic system takes up larger size NCs, thus reducing API activity. Covering the nanoparticle with a low protein-binding agent such as polyethylene glycol delays the accumulation in the liver [32], while small size helps to overcome biological barriers and deeply penetrate tumor or inflamed tissues through active and/or passive pathways (Figure 3) [33]. This accumulation effect is particularly advantageous for NCs, as the encapsulation of APIs is very high compared to other nanosystems, where only 0.7% of the drug was detected in the tumors [34]. Therefore, from these highly concentrated nanodrugs, one can expect a higher efficacy in cancer and inflammatory diseases [35].

However, this efficacy also depends on the structure formed. From bottom-up approaches, crystals as well as amorphous forms have been described [36]. Their stability is highly different and will not lead to similar efficacy. The formation of mixtures might also hamper the overall efficacy of tested nanodrugs.

This is why it is crucial to develop reliable physical methods and protocols for their characterization as described in part 2.3. Difficulties in formulation (monodispersity, reproducibility), stabilization and characterization also explain why there are so few NC suspensions on the market [37]. Invega Sustenna®, an antipsychotic drug using paliperidone palitate as API is currently the only FDA-approved NC formulation to be administered by intravenous injection.

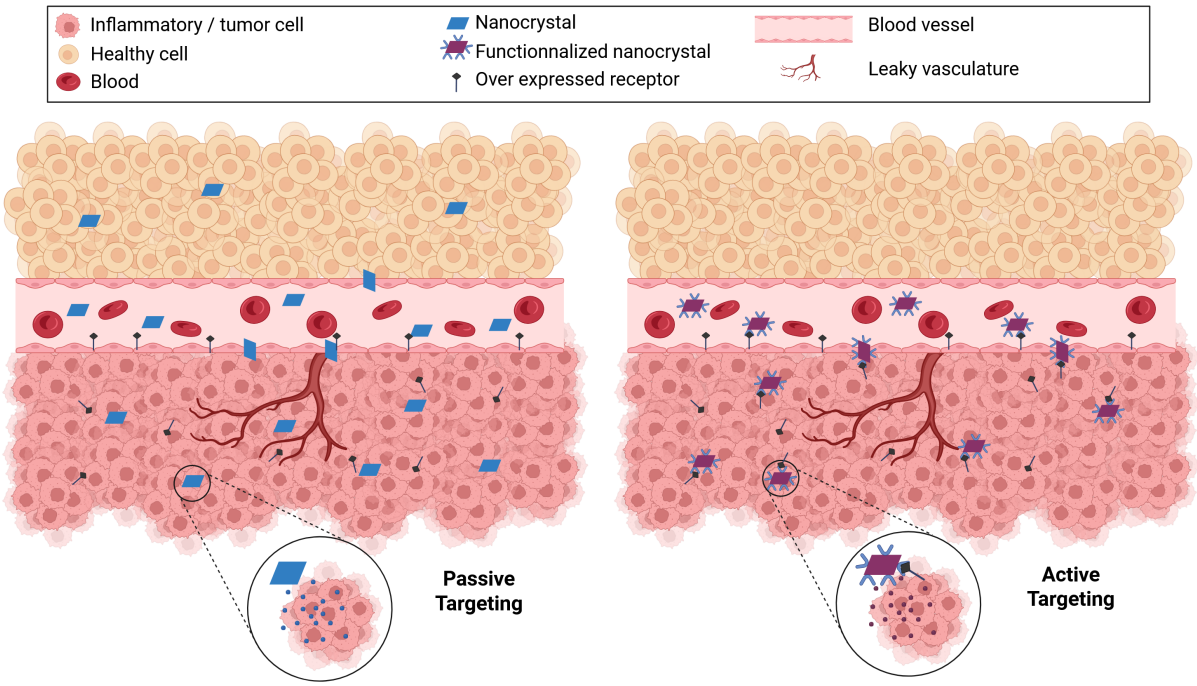

***Figure 3**. Schematic representation of passive (left) and active (right) targeting of nanocrystals within damaged tissue, such as cancer burden.*

NC suspensions can also be administered by direct injections in the bloodstream, enabling rapid onset of action, independent from the GIT, and avoiding the first hepatic pass [29]. To date, four NC suspensions that use parenteral administration have been FDA-approved (Table S1). The advantages of intravenous or intramuscular injections are numerous, including: (i) improved pharmacokinetic behavior; (ii) Minimization of secondary effects related to high local drug concentration of non-soluble drugs, since NCs dissolve uniformly in the plasma; (iii) Long-lasting drug delivery and action time. This last advantage indicates that the frequency of administration could be reduced if the NCs are administered via parenteral route [29]. Moreover, using NC suspension increases resistance to hydrolysis and oxidation of the API as the drug is present in solid form [37].

Intramuscular administration

To overcome issues linked with the mononuclear phagocytic system leading to an accumulation of NCs in the liver and the spleen, suspensions containing larger NCs (above 200 nm) can be administered intramuscularly, enabling the formation of a drug reservoir at the injection site which extends the duration of the action [29]. Recently, cabotegravir and rilpivirine, two retroviral agents, were associated to form a new HIV treatment, Cabenuva®. This nanosuspension is injected via intramuscular route for two schizophrenia treatments, namely Aristada Initio® and Zyprexa Relprevv® (Table S1).

Other administration routes

This section gathers the main administration routes that have been reported to deliver NCs. Many other routes have been investigated using nanocrystals and can be found in these reviews [29], [38].

Transepidermal and trans-appendageal routes

The transepidermal route involves drug delivery through or between skin cells, while trans-appendageal route involves the absorption of drugs through hair follicles or sweat glands within the skin [29]. These two routes are widely used for delivering cosmetic agents. NCs show potential for passive penetration after topical application and can penetrate skin pores due to their size. In a cosmetic product using rutin, a naturally occurring bioflavonoid found in plants, smart NCs have shown a bioactivity 500 times superior in terms of sun protection than a conventional rutin cream [39].

Ocular route

The ocular route is a major challenge for efficient drug delivery due to the anatomy and physiology of the eye. Despite this, it is commonly used for treating glaucoma or other inflammatory diseases [40], [41], [42]. However, numerous obstacles must be considered including: the small volume that can be administered due to the conjunctival sac, nasolacrimal drainage, eye barrier, blinking, lacrimal reflexes, irritation and the tolerability of NC formulations [1]. Some of these issues could be overcome with NC technologies. In 1998, brinzolamide was approved as eye drops to treat glaucoma [9].

Intranasal route

The intranasal route is interesting for NC delivery because the drug deposited on the nasal mucosa can exert a local effect and be progressively absorbed into the bloodstream. Indeed, absorption via the nasal mucus layer is facilitated by a highly vascularized surface area with a poor enzymatic activity. For instance, it was shown that intranasal delivery of loratadine resulted in a 5.5-fold increase in the bioavailability compared to oral delivery [43]. Integrating NCs in a bioadhesive gel or using bioadhesive polymers to stabilize the NCs could prolong the residence time of the NCs into the highly vascularized mucosa and allows for better systemic passage. This route has also been investigated as a potential transport route to the brain [44] via the so-called *nose-to-brain* delivery, which takes advantage of the olfactory nerves connecting the olfactory area and the brain.

New applications in the NC R&D using a bottom-up approach

Monocrystals

Out of the 31 research articles we selected for their biomedical applications, 12 reported the use of mono-crystals in cancer, 7 in inflammatory diseases, and 12 in other diseases such as HIV, psychiatry or obesity (Table S2).

For cancer applications, oral and parenteral delivery have been proposed using NCs mainly obtained through solvent antisolvent precipitation. Twenty-six articles out of 31 followed this

method, with four being followed by HPH and five by ultrasonication.

Paclitaxel is the most documented drug due to its low water solubility, which makes it readily form NCs. We found that drugs with a log P below 3 are the most prone to form NCs. However, achieving supersaturation is necessary to obtain NCs using a bottom-up approach, and stability should be fixed to prevent uncontrolled crystal growth, as schematized in Figure 1. The difficulty in obtaining reproducible NCs through the solvent-antisolvent precipitation method was described by Ren et al. [13]. They determined the metastable zone of paclitaxel by quantifying its solubility by HPLC. The group obtained nucleation by evaluating various formulations within this metastable zone. They managed to obtain rather monodisperse NCs of paclitaxel as observed by SEM. Moghaddam et al. also adapted the solvent-antisolvent nanoprecipitation approach using a microfluidic device to obtain chitosan-coated paclitaxel NCs. This is interesting because microfluidics allow for better control of mixing conditions of the two phases, but it can be limited by the amount of solvent used in microfluidic devices, which can itself be a limitation for poorly soluble drugs [45].

Apart from nanocrystallization, another means to control crystal growth NC and limit aggregation, is the use of stabilizers. These molecules, usually polymers, form a hydrophilic coating around NCs making them more prone to remain suspended in an aqueous medium via steric stabilization. The interaction of hydrophilic polymer with circulating proteins can also influence their biodistribution and cell uptake. For paclitaxel, several coatings have been proposed, such as hydroxypropyl methylcellulose (HPMC), pluronic F68, PVA, Poloxamer 407 (Pluronic® F407), Poloxamer P188 (Pluronic® F68), Tween 80, polymer poly(allylamine hydrochloride), polysodium styrenesulfonate, D-α-tocopheryl polyethylene glycol$_{1000}$ succinate (TPGS) or chitosan [46]. Most NCs reported in the literature have been coated with poloxamer, particularly P407 (Table S2). There is no “best coating”; the interaction with the drug may guide the choice of polymer, which is usually demonstrated via NMR or/and FTIR studies.

Albumin associated with P407 has also been proposed for paclitaxel and showed a reduced crystal growth rate [47]. We also evaluated albumin in association with poloxamer P407 to stabilize etoposide NCs, but did not find additional benefit in terms of pharmacokinetic [15]. In contrast, albumin associated with F127 to coat docetaxel NCs showed potential to overcome multidrug resistance in SKOV-3, B16F10, and NCI/ADR-RES cells [48]. Moreover, albumin associated with P407 was the most efficient to stabilize and induce antitumor efficacy for carfilzomib on a model of breast cancer [47].

Apart from polymers and proteins, lipidic membrane surrounding NCs can also be used to stabilize them. Although not obvious due to different solubilities between drugs and lipids, or solvent used in the methods, it cannot be applied to all combinations, but few have been reported, such as lipid membrane surrounding etoposide NCs or the addition of DSPE-PEG on paclitaxel NCs which did not drastically improve pharmacokinetics [49]. Combination of methods had to be applied to obtain them, sequentially using sonoporation for the lipids, solvent-antisolvent precipitation for the drug, both followed by HPH [50].

The polymer coating the NCs can also play a role in the migration of the NCs. A recent example described various degrees of PEG polymerization at the surface of curcumin NCs to increase the passage across mucosal barrier. They showed that hydrophilicity was a main driver of mucin interaction resulting in tunable passage of NCs across a mucin barrier model [51].

Oral bioavailability of anti-inflammatory APIs has also been improved with nanocrystals, but it depends on the crystallinity of the NCs; amorphous will result in different bioavailability as regard to crystalline forms, as shown for instance with fenofibrate [52].

Co-nanocrystals

The emergence of organic therapeutic nanocrystals over the last two decades for therapeutic indications and various routes of administration has led to more complex NC-based pharmaceuticals. The first proofs of concept for pharmaceutical co-nanocrystals have been established with nanosized co-crystals prepared from API/Co-former excipient cocrystals [53],

[54]. The co-former in a co-crystal improves the apparent solubility of the API. It is associated with menthol [55], which may represent a breakthrough by combining two main characteristics, namely the nanosize distribution, and co-crystal dissolution properties. In 2019, a step forward has been achieved with the baicalein/nicotinamide [56] and the paclitaxel/disulfiram [57] co-formulation, which showed potential synergistic effects [58]. For this review, we will focus on API/API co-nanocrystals (Table S3). However, due to limited techniques for ensuring co-crystal evidence, we will not classify them as nano-cocrystals but rather as co-nanocrystals. To date, only four API/API co-nanocrystals have been reported in the literature. The main challenge, being the stability issue as it has been encountered with the Cabenuva formulation. Indeed, the cabotegravir and rilpivirine nanocrystals have been stored in two different primary packagings for co-administration of the two nanocrystals [59]. The combination of paclitaxel and disulfiram or paclitaxel and lapatinib stabilized by lactoglobulin or polydopamine/PEG respectively have shown enhanced in vitro efficacy, in particular paclitaxel/disulfiram NCs have shown a 6 fold enhancement in tumor cells apoptosis in vitro [60], [61].

Targeting

Few examples are available in the literature regarding the feasibility of NCs targeting. Several strategies have been proposed for coupling a ligand to the surface of the NCs (Table S4). These include non-covalent interactions, functionalizing a stabilizer that is then grafted with the ligand, or using a lipid or cell membranes to stabilize the NCs and grafting the ligand onto them. For instance, a modified T7 peptide targeting the transferrin receptor was coupled by catechol chemistry to polydopamine which was used to stabilize camptothecin NCs [62]. Comparing paclitaxel-NCs coated with hyaluronic acid or transferrin on CD44 MCF-7 cells expressing CD44 and transferrin receptors, Sohn et al. showed that targeting NCs were taken up more efficiently by the cells compared to the non-targeting NCs and that targeting NCs inhibited cell growth more efficiently [63]. These studies were solely conducted in vitro and did not lead to further reports. Interestingly, hyaluronic acid-coated paclitaxel NCs were shown to be as effective in vivo as Taxol on an LA-7 mammary gland cancer model, but these NCs were not compared to untargeted NCs [64].

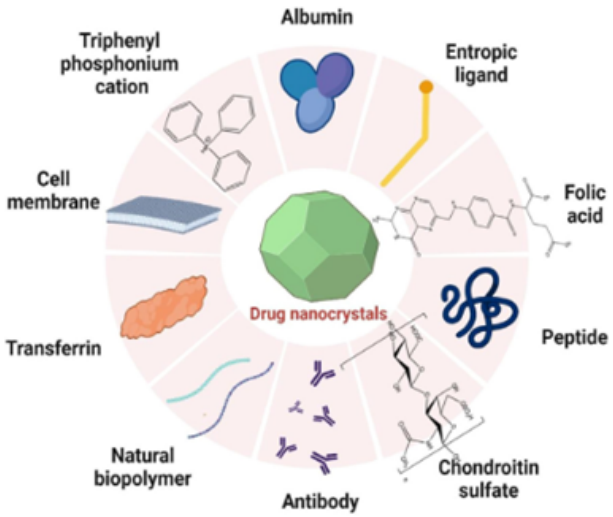

Figure 4 : Targeting approaches reported for nanocrystals from Lhaglham et al. [67] Copyright 6034870717260.

Grafting trastuzumab as a targeting ligand onto F127 and membrane-stabilized paclitaxel nanocrystals, Wu et al. reported a higher accumulation of labeled membrane-wrapped NCs in SK-BR-3 based-tumor tissue when trastuzumab was present [65]. It is worth noting that in this study, trastuzumab was not directly grafted to the poloxamer, but rather to the cell-extract

membrane which served as NC coating. The same group also showed that a folate ligand coupled to cell-derived membrane wrapped paclitaxel nanocrystals led to specific distribution and efficacy [66]. This approach may be more complex but could be necessary to stabilize the NCs and maintain the ligand at their surface. Figure 4 illustrates the various targeting approaches reported so far for nanocrystals [67]

Conclusion and perspectives

In terms of production, most approved nanocrystals have been obtained by the top-down approach since they aimed to be taken orally. The parenteral administration requires smaller and more controlled particle size, which is why the bottom-up approach has been proposed to produce the nanocrystals. This requires determining the solubility of the compound and determine precisely the solvent-antisolvent ratio to control crystal growth. Nevertheless, that approach successfully allowed forming smaller nanoparticles. Unfortunately, while preparing this review, one of the challenges was the selection of articles that provided robust evidence of NCs formation. The term is sometimes misused, and the crystalline form is not adequately demonstrated. A key issue is verifying the presence of nanocrystalline structures rather than partial or complete amorphous nano-aggregates, especially in aqueous suspensions. Obtaining clear Bragg diffraction peaks from XRD measurements is challenging because the aqueous continuous phase is amorphous. Other solid-state characterization techniques, such as DSC for crystallinity quantification and SEM for morphology and size determination, are not suitable for use in solution. Therefore, the lack of convenient techniques to prove the presence of NCs in aqueous suspension remains a significant issue. Cryo-TEM is emerging as a technique of choice for visualizing suspensions in their buffer and characterizing the crystalline shape, addressing some of these challenges.

However, many studies in the literature may refer to both amorphous and crystalline forms when discussing "nanocrystal" suspensions, which can significantly impact the pharmacokinetics of the nanodrug. While many reports highlight improved biological efficacy with NCs, the pharmacokinetic improvements are not always consistent. This discrepancy may stem from the presence of a mixture of amorphous and crystalline forms, leading to an average pharmacokinetic profile that does not accurately represent the pure crystalline form. Therefore, it is crucial to enhance both the characterization of nanocrystals and the development of more accurate pharmacokinetic models.

Several studies have attempted to demonstrate targeting effects using NCs in cellular and in vivo models. However, a critical question arises regarding the fate of targeting ligands when NCs dissolve upon contact with aqueous media. This dissolution can affect the availability of the ligand for target interaction. To address this, researchers have proposed stabilizing NCs within polymers that can provide cell interactions, such as hyaluronic acid, or using lipidic membranes that can be functionalized to stabilize the NCs and facilitate cell interaction.

Novel approaches, such as the use of films or hydrogels to locally deliver stabilized NCs, hold promise for future developments. These strategies could enhance the stability and targeting efficiency of nanocrystals, leading to more effective therapeutic outcomes.

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