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REVIEW

Nanocrystalline Drug Delivery Systems for Natural Compounds: Progress, Challenges and Future Opportunities

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Abstract: Herbal medicines, under the guidance of Traditional Chinese medicine (TCM) theory, have played an irreplaceable role in treating and controlling various diseases for centuries. However, both traditional and contemporary TCM formulations are plagued by drawbacks such as complex preparation processes, poor stability, and the inconvenience of water decoction. Moreover, natural active ingredients derived from TCM, despite their definite physicochemical properties and significant therapeutic potential—exemplified by the anticancer effects of terpenoids like paclitaxel and tretinoin, and the antihypertensive properties of flavonoids including artemisinin and quercetin—face substantial hurdles in clinical translation due to poor aqueous solubility, low bioavailability, and potential toxicity. Nanocrystalline drug delivery systems (NCDDS) have emerged as a versatile strategy to address these limitations, leveraging the unique properties of nanocrystals to enhance drug dissolution, improve bioavailability, and enable targeted delivery. This review synthesizes recent advancements in NCDDS for natural compounds, elaborating on the current cutting-edge status of preparation techniques and characterization methods, as well as key progress in enhancing the in vitro and in vivo efficacy of natural agents, including terpenoids, flavonoids, and polyphenols. Despite these accomplishments, several challenges persist, such as inadequate colloidal stability, obstacles in scaling up production, and potential long-term toxicity concerns. Future opportunities are centered on the development of advanced nanocrystal preparation technologies, integration with multifunctional modification techniques, and exploration of interdisciplinary cross-applications. The objective of this review is to offer insights into the current landscape of NCDDS for natural compounds and to guide further research efforts toward addressing existing challenges, thereby expediting their clinical translation.

Keywords: herbal medicine, chinese medicine, natural compounds, drug delivery systems, nanocrystal technology

Introduction

Role and Limitations of Herbs in Traditional Medicine

Herbal medicines have a long-standing presence in numerous traditional medical systems worldwide, and their therapeutic efficacy has been demonstrated over an extended timeframe. Plant extracts and their active ingredients have a long history of use in the treatment of a wide range of diseases, including inflammation, respiratory disorders, metabolic disorders, and even cancer. These extracts have been utilized in various systems of medicine, such as TCM, Ayurvedic Medicine, Siddha Medicine, and Unani Medicine, reflecting their diverse applications in healthcare.[1] For example, in Ayurvedic medicine, Divya-Swasari-Vati (DSV) is a calcium-rich Ayurvedic prescription medicine consisting of a finely ground powder of nine botanical medicines from the Ayurvedic system of medicine and ash of seven minerals known as Bhasmas. It is used to treat respiratory diseases and pneumonia.[2] In TCM, the use of herbs such as turmeric, ginkgo biloba, and safranin is a well-established practice for combating inflammation, enhancing circulation,

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and regulating metabolism.[3–5] According to statistical data, approximately one-third of the most prevalent pharmaceuticals in current use are derived from plant or natural sources, underscoring the pivotal role of herbal remedies in the realm of drug development.[6]

Despite their considerable medicinal potential, herbal medicines confront a series of obstacles in terms of clinical transformation and widespread application. On one hand, traditional drug delivery systems commonly employed in herbal preparations in both traditional and modern Chinese medicine have numerous drawbacks. For instance, conventional dosage forms of herbal medicine—including soups, pills, pastes, and dispersions—are constrained by conventional processes and technological conditions. On the another hand, these forms are deficient in modern quality standards and are challenging to standardize on an industrial scale.[7] Furthermore, the active ingredient content of herbs is significantly affected by factors such as geography, climate, and harvesting season. For instance, the flavonoid content of ginkgo biloba can fluctuate by more than 30% due to regional differences in growth, which complicates the control of consistency in preparations from batch to batch.[8] Conversely, as research into herbal medicines progresses, their active ingredients are increasingly characterized by clear physicochemical properties. However, the bioavailability of most active herbal ingredients is limited due to their physicochemical properties, such as high fat solubility or insufficient water solubility, and poor membrane permeability.[9] Consequently, their bioavailability is extremely low, as evidenced by the fact that less than 10% of quercetin, a flavonoid compound, is bioavailable after oral intake.[10] In addition, polyphenols and terpenoids, which are the active ingredients, exhibit suboptimal stability. These compounds are sensitive to light, heat, oxidation, and undergo facile degradation during storage, resulting in a loss of biological activity.[11,12] For instance, the degradation rate of polyphenolic compounds, such as curcumin, can reach up to 50% within three days in light.[13] In the presence of oxygen, tetracyclic diterpenes, including andrographolide, undergo auto-oxidation through the process of andrographolide glycoside and other inactive product degradation.[14]

The Revolutionary Impact of Nanotechnology on Herbal Medicine

The advent of nanotechnology has furnished a pivotal solution to the constraints imposed by herbal medicines by means of the formulation of nanoscale drug delivery systems (eg, herbal nanomedicines) that substantially augment the therapeutic potential of herbal medicines. A wide array of herbal medicines and their bioactive components have been utilized in the development and enhancement of diverse nanoformulations.[15] Some of the common nano-formulations including liposomes, dendritic polymers, polymeric micelles, nanoparticle solvents, nanocrystals, and polymer-based multi-drug couplings are illustrated in Figure 1.

These nano-formulations are not only powerful and promising strategies to improve the delivery problem of active ingredients in HNMs (like Solid lipid nanoparticles (SLN) loaded with tretinoin[16] reduced mucosal irritation, and SLN loaded with geranylgeranyl increased bioavailability by more than three times), but also play a significant role in improving the stability of the drugs (eg, glycyrrhetinic acid,[17] resveratrol,[18] and curcumin,[19] as well as the active ingredients that are prone to degradation under physiological conditions).

Nanocrystal technology is a key tool for improving the bioavailability of insoluble drugs. This technology takes advantage of nanoscale surface effects, quantum-limited domain effects, and the high specific surface area of particles to refine drug particle size down to 10–1000 nm. These properties help overcome the dissolution and absorption bottlenecks of conventional drugs. As illustrated in Figure 2, drug nanocrystals produced with nanocrystal technology have several advantages over other nanosystems. These advantages include relatively low manufacturing costs, ease of scaling up to commercial levels, simple particle size control, and multiple delivery methods (eg, oral,[20] injectable,[21] transdermal,[22] pulmonary,[23] and ocular,[24] among others). Additionally, drug nanocrystals require only a small amount of stabilizer or protectant and have a theoretical drug loading capacity close to 100%. This reduces physicochemical interference between the excipient and the drug, decreasing the probability of adverse reactions in the body.[25]

Therefore, this review is based on the advantages of nanocrystalline technology in the application of natural compound formulations and revolves around the nanocrystalline technology, summarizing the techniques used to prepare natural compound components into nanocrystalline drugs using nanocrystal technology, factors affecting the preparation of nanocrystalline drugs, and the characterization methods for determining the level of quality of nanocrystalline drugs.

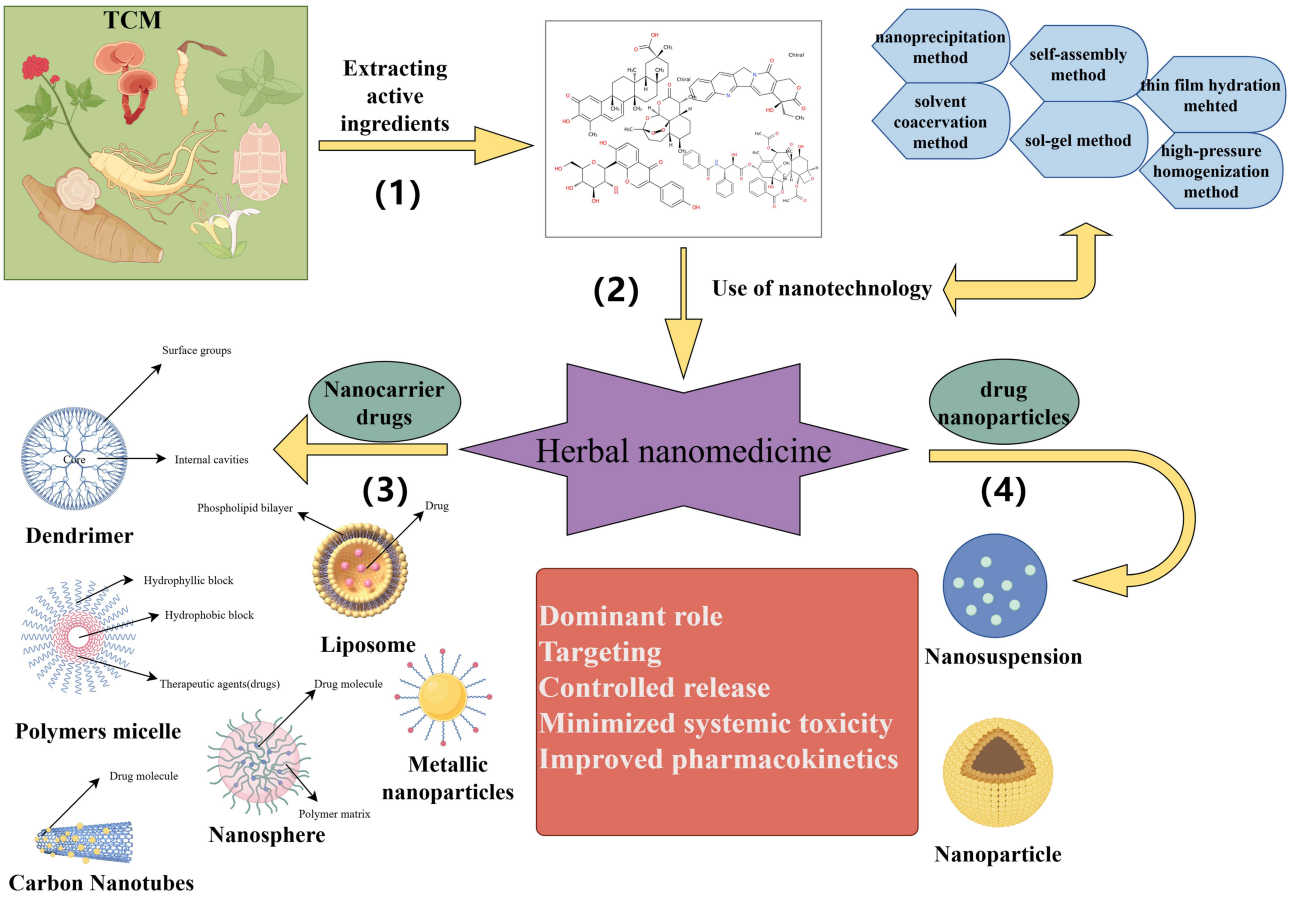

Figure 1 Structural illustration of applications in nanodrugs of TCMs. Firstly, medicinally active compounds are extracted from herbs through (1) and then (2) various types of nanotechnology are applied to obtain nano-herbal preparations, which are categorized into (3) nano-delivered drugs and (4) nano-molecular drugs.

The paper also outlines and analyzes which natural compounds are suitable for preparation into nanocrystalline drugs as well as future trends and challenges facing nanocrystalline technology in the field of natural compounds.

Common Methods for Preparing Drug Nanocrystals

Preparation technology is an important tool for successfully converting natural ingredients into nanocrystals for use in drug delivery systems. Nanocrystal technology for preparing drug nanocrystals is divided into three main categories: bottom-up, top-down, and combinatorial techniques. These techniques reduce the size of drug particles to the nanoscale using physical or chemical means to improve the delivery properties of insoluble drugs. Figure 3 briefly shows representative preparation methods of the two techniques, which can be compared to see the differences, as detailed below.

Top-Down Approach

The top-down technique uses specific mechanical processes to compress active pharmaceutical ingredients (APIs) down to the nanoscale. The two most commonly used methods are wet media milling (WMM)[26] and high-pressure homogenization (HPH).[27] In the WMM method, the pharmaceutical ingredients are dispersed in a liquid medium (usually aqueous), grinding media (beads made from various materials) are added, and the coarse particles are broken into nanocrystals using mechanical forces generated by the milling process (eg, rotational motion, collisions between the media and particles, and shearing). Key parameters affecting the outcome (eg, particle size and dissolution kinetics) include grinding time, rotational speed, grinding media volume, and mass loading of the APIs. A study on the production of nanocrystals (NCs) by wet milling using a dual asymmetric centrifugal (DAC) mixer, which can vary the rotation

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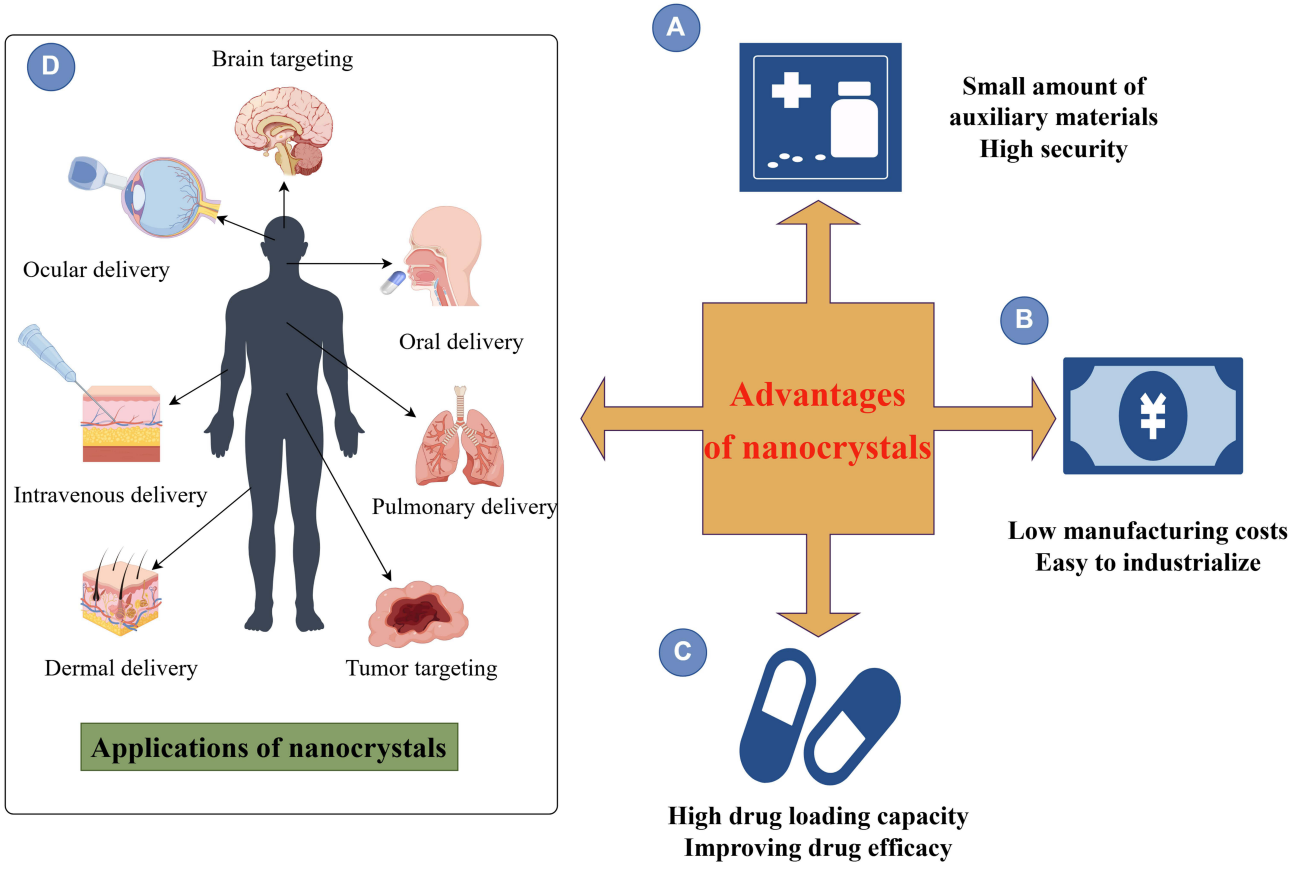


Figure 2 Advantages of nanocrystalline technology over other nanotechnologies. The advantages of pharmaceutical nanocrystals are mainly the following four points: (**A**) low amount of excipients, high safety; (**B**) low preparation cost, easy to industrialize; (**C**) high drug loading, good drug efficacy; (**D**) application of a variety of dosage forms.

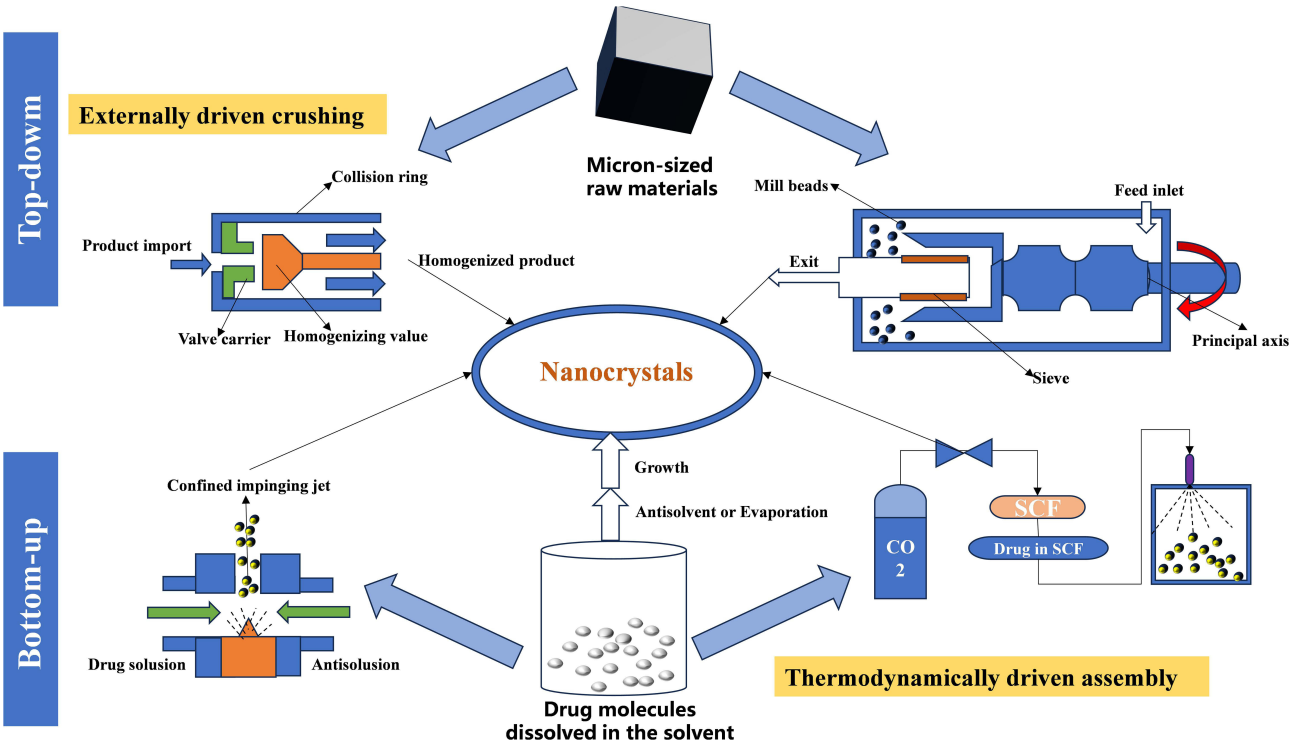


Figure 3 A schematic comparing Top-Down vs Bottom-Umethods.

speed, found that the DAC method had the highest milling efficiency compared to conventional wet media milling. All drugs exhibited crystalline properties, confirming that the DAC method can successfully prepare NCs.[28] In the HPH, the drug suspension is placed under high pressure and passes through a homogenization cavity or interstitial structure at high speed. The coarse particles are crushed into nanocrystals using comprehensive mechanical effects, such as the cavitation and impaction effects and the shear force generated during the process. There are two types of HPH: the microfluidization technique and Piston-gap homogenizers, which differ based on the homogenizing equipment and parameters used.[29] Although its particle size reduction is less effective than wet milling, the impurity content of drug nanocrystal suspensions prepared by the HPH process is much lower.

Both methods are simple, low-cost technologies that can easily be converted from laboratory scale to mass production. Many marketed nanocrystalline drugs are prepared using these methods. Examples include Emend®, an antiemetic drug manufactured by Merck; Focalin XR®, an ADHD drug manufactured by Novartis; and Invega Sustenna®, an antipsychotic drug manufactured by Johnson & Johnson. These nanocrystalline drugs all have improved bioavailability compared to traditional dosage forms. They are also easy to administer as needed, thus improving patient compliance.[30–32]

Bottom-up Methods

The bottom-up method for producing drug nanocrystals is predicated on the principle of precipitating drug nanocrystals from a supersaturated solution of a drug, also known as precipitation. Precipitation can be induced by processes that further increase the degree of supersaturation in the system, such as solvent evaporation, lowering the temperature, or mixing it with a counter-solvent. Depending on the process, they can be systematically categorized into different sub-methods, including solvent-counter-solvent precipitation, supercritical fluid methods, solvent evaporation, and freeze-drying.[33] Among the various precipitation techniques, the production of drug nanocrystals by liquid solvent-anti-solvent addition has been most reported. This is due to the fact that it is the simplest and most cost-effective method. In this process, the counter-solvent—which is miscible with the solvent but does not dissolve the drug—is added to the drug solution and thoroughly mixed to create a supersaturated condition. This leads to the nucleation and precipitation of the drug molecules, and ultimately, the formation of nanoscale drug nanocrystals. Furthermore, a substantial body of research has evidenced that incorporating specific external factors, such as ultrasound, high gravity, evaporation, microfluidics, and others, into the solvent-counter-solvent process not only facilitates the precipitation of nanocrystals but also significantly reduces the particle size of the crystals.[34] However, this method is associated with several drawbacks, including the complexity of regulating the nucleation process, the challenge of selecting suitable solvents and stabilizers, and the presence of significant solvent residues. This has caused it to not receive much attention in industrialized production.[35]

The emergence of supercritical fluid methods has addressed these issues. These methods utilize supercritical fluids (SCFs) as solvents or anti-solvents, leveraging their unique properties under high pressure. Upon depressurization, SCFs can rapidly vaporize and completely separate from the system, thereby avoiding organic solvent residues that are problematic in traditional solvent-based approaches. The resulting nanocrystals exhibit high purity, which better meets the stringent standards for pharmaceutical formulations.[36] Supercritical technologies for nanocrystal preparation, including RESS (Rapid Expansion of Supercritical Solutions), RESOLVE (Rapid Expansion of Supercritical Solutions into a Liquid Solvent), and SAS (Supercritical Anti-Solvent), are applicable not only to heat-sensitive drugs but also to other pharmaceutical substances.[37]

Freeze-drying and spray drying are two techniques based on the principle of physical solvent removal. They eliminate solvents from drug solutions, causing the drug to crystallize into nanocrystals due to supersaturation. During the preparation process, careful selection of solvents, drying protectants, and stabilizers is crucial; otherwise, issues such as solvent residues, particle agglomeration, or crystal form transformation may occur.[38]

In summary, due to differences in their principles and process characteristics, these four categories of methods have distinct focuses in terms of applicability, scaling potential, and product performance. They demonstrate the versatility of tailoring nanocrystal properties through solution chemistry and process kinetics.

Combination of Bottom-up and Top-Down Approaches

The typical process of preparing nanocrystals via combined technologies involves first synthesizing coarse crystals using bottom-up approaches, followed by regulating their particle size and morphology through top-down methods, ultimately obtaining

nanocrystals with small particle sizes and uniform distribution. In 2003, Baxter launched the Nanoedge technology, which stands as the first combined technology in the field of nanocrystal preparation.[39] It initially generates micron-sized crystal particles via precipitation, then employs high-pressure homogenization to enhance the uniformity of crystal size and product stability.[40] The H69 technology, jointly developed by Muller and MasChwitter, shares a similar principle with Nanoedge, with the key difference being that the precipitation of drug particles occurs in the high-pressure region of the homogenizer.[41]

Studies have shown that high-pressure homogenization is the most widely used top-down technique in combined processes, which can be combined with various bottom-up methods to form technologies such as H96 (freeze-drying combined with high-pressure homogenization), H42 (spray drying combined with high-pressure homogenization), and CT (media milling combined with high-pressure homogenization).[41–43] Additionally, PLH technology and ARTcrystals technology are also typical representatives.[44] The core advantage of such multi-process synergistic systems lies in their ability to prepare drug nanocrystals with smaller particle sizes. Zhao et al conducted a study on the drug NC of clonidine using a combination of techniques (antisolvent precipitation-rotary evaporation-HPH). The study yielded NC with sizes between 140 and 180 nm and polydispersity indices (PDI) of 0.1 to 0.25. Lyophilization also improved the stability of the suspension and increased the drug loading capacity.[45]

However, combined processes are rarely applied in industrial practice, mainly due to the significant cost increase caused by the two-stage preparation mode, specifically reflected in prolonged operation time, increased energy consumption, and aggravated potential equipment wear. Therefore, this method is only suitable for scenarios with extreme requirements for particle size reduction.

Finally, the advantages and insufficient of all nanocrystalline preparation technologies and the characteristics of relevant application components are summarized in Table 1.

Table 1 Advantages and Insufficient of Different Preparation Techniques and Representative Nanocrystalline Drugs

Preparation Method		Advantage	Insufficient	Composition and Dosage Form	Refs.
Top-down approach	Wet media milling	Simple and stable preparation, high drug loading, and the use of water as a dispersing medium, thus avoiding the use of organic solvents.	Low efficiency, high risk of microbial growth and grinding media residue, slow process	Cyclosporine A Nanosuspension; Agomelatine Nanocrystals; Aprepitant Nanocrystals; Nanosuspension;	[46–49]
	High-pressure homogenization	Smaller average particle size and narrower particle size distribution, good reproducibility, and less product contamination.	Special equipment is required, the process is energy-intensive and requires operating experience.	Valsartan nanosuspension; Paclitaxel nanosuspension; Quercetin nanosuspensions; Self-dispersible nanocrystals of albendazole	[50–53]
Bottom-up methods	Solvent-antisolvent precipitation	Simple operation, common means for laboratory preparation of drug nanocrystals	Difficulty in controlling the nucleation process, selection of suitable organic solvents and stabilizers, residual organic solvents, and stabilizers, and the presence of residual organic solvents.	Amphotericin B nanosuspensions; Venetoclax nanocrystals; Icaritin Nanoparticles; Naproxen Nanoparticles	[54–57]
	Supercritical fluid technology	The technology is simple and low-cost and uses harmless solvents without leaving any organic solvent residue.	Excessive consumption of supercritical fluids; Uniform distribution of particle size.	Apigenin nanocrystals; 10-hydroxycamptothecin nanoparticle; Sirolimus nanoparticles	[58–60]
	Solvent evaporation and spray drying	Simple equipment and operation, wide range of applications, high crystallinity	Stabilizers must be added to avoid crystal agglomeration and the use of cyclones to collect nanocrystals is also a challenge.	Cellulose Nanocrystals; Resveratrol Nanocrystal; Spray-dried nanocrystals;	[61–63]

(*Continued*)

Table 1 (Continued).

Preparation Method		Advantage	Insufficient	Composition and Dosage Form	Refs.
Combinative technology	Nanoedge technology	Small particle size; good product stability	Organic solvent residues; are complex and expensive to prepare	Avanafil nanoparticles; Dipyridamole nanocrystalline solid dispersions; Ibuprofen nanocrystals	[40, 64, 65]
	H69 technology	Good crystal stability	Organic solvent residue	Ursodeoxycholic acid Nanocrystals	[29, 66]
	H96 technology	Low organic solvent residue	The freeze-drying process is time-consuming.	Curcumin nanoparticles; Glibenclamide Nanocrystals; Meloxicam Tablets	[67–69]
	H42 technology	Spray drying is time-consuming; there are no intermediates	The yield is not high, the smaller the batch, the lower the yield, not suitable for small-scale production	Hydrocortisone acetate Nanocrystals, Resveratrol nanosuspensions, Glibenclamide tablets	[43, 70, 71]
Other techniques	Ultrasonication combined with anti-solvent precipitation	Precise particle size control, high preparation efficiency, high crystallinity	High equipment and operating costs, organic solvent residues	Glycyrrhetinic acid Nanocrystal; Lutein nanocrystals; Luteolin Nanocrystals	[72–74]
	Precipitation-lyophilization-homogenization method (PLH)	More pronounced particle size reduction, low organic solvent residue	Complex preparation, high energy consumption, time-consuming lyophilization process	Clarithromycin nanocrystals, Cryptotanshinone; nanocrystals	[44, 75, 76]
	ARTcrystals technique	Reduces the pressure of high-pressure homogenization, improves homogenization efficiency, and significantly improves the stability of nanocrystals.	Difficulty in production scale-up and strict system requirements	Industrial nanocrystal; Rutin, hesperidin and apigenin Nanocrystal	[77, 78]

Characterization Techniques for Drug Nanocrystals

The development of nanocrystalline drugs as key formulations to enhance the bioavailability of difficult-to-solve drugs is contingent upon systematic characterization technologies for quality control, safety, and efficacy. In this chapter, the core technical scope of nanocrystal drug characterization is systematically delineated. The principles, applications, and limitations of various characterization methods are described from the three dimensions of physicochemical properties, biological properties, and stability. This provides technical references for the optimization of research and development of nanocrystalline drugs and the quality control of nanocrystalline drugs. Table 2 offers a concise exposition of the primary advantages and disadvantages associated with the diverse methodologies employed for the characterization of the physicochemical properties of drug nanocrystals. A thorough exposition of these methodologies is provided in the ensuing subsections.

Characterization of Physicochemical Properties of Nanocrystalline Drugs

Particle Size and Distribution, Surface Charge Measurement

The physicochemical properties of nanocrystals determine their formulation performance. Key parameters include particle size distribution, surface charge, crystalline structure, surface features, and drug loading capacity. These properties must be characterized using multiple technologies.

Dynamic Light Scattering (DLS) has emerged as a routine screening technique for determining nanocrystal size and size distribution, owing to its speed and convenience. It enables the measurement of hydrodynamic diameter and polydispersity index (PDI), where a lower PDI indicates better long-term stability of the crystals.[79] However, DLS

Table 2 Properties of Nanosystems and Most Relevant Characterization Techniques

Quality Attribute	Methods	Advantages	Shortcomings
Particle size and distribution	Dynamic light scattering (DLS), Static light scattering (SLS)	Fast, non-destructive, particle size distribution information available	Decreased accuracy for highly concentrated or polydisperse systems
	Laser particle size analyzer	Wide measuring range, accurate results	Biased measurement of irregularly shaped particles
Surface charge	Dynamic light scattering (DLS), Zeta potential analyzer	Direct determination of particle surface charge properties and potentials	Highly affected by solution conditions
Morphology	Scanning electron microscopy (SEM)	Easy sample preparation by providing surface morphology and dimensions	Lower resolution than TEM requires sample conductivity
	Transmission electron microscopy (TEM)	High resolution for viewing internal structures	Complex sample preparation and expensive instrumentation
	Environmental scanning electron microscopy(ESEM)	Wet samples can be observed, reducing charging effects	Complex and expensive instrumentation
Solid state properties	Thermal analysis differential scanning calorimetry (DSC)	Quantitative analysis, High sensitivity, Low sample volume	High environmental impact and sample requirements
	Thermogravimetric analysis (TGA)	Widely applicable to a variety of systems, good interoperability with other methods	Limited resolution, single message
	X-ray diffraction (XRD)	Accurate crystal structure analysis and physical phase identification are possible. No damage to nanocrystalline samples	Expensive instruments, shallow depth of analysis
	Fourier transform infrared spectroscopy (FTIRS),	Determinable surface functional groups, easy to operate	Difficult to analyze complex mixtures
Chemical structure and degradation	Liquid chromatography like high-performance liquid chromatography (HPLC)	Good separation effect, wide range of applications, accurate quantification	Complex sample preparation and long analysis time
Stability study	Accelerated test, Long-term test, Impact factor test	Predictable stability of drugs under different conditions	It is time-consuming and uncertain to extrapolate results
Vitro release assay	Dialysis method	Simple, simulates in vivo environment	Time-consuming, possible drug adsorption
	Sample separation method	Relatively simple to operate, wide range of applications, offline analyzable	Cannot be monitored in real-time, large errors
	Flow cell method	Real-time monitoring, good simulation of in vivo environment	Complex instrumentation and high analytical costs
Drug load or entrapped efficiency	High-Performance Liquid Chromatography (HPLC)	Good separation effect, high accuracy, wide range of application	Complex sample pre-treatment and long analysis time
	Ultraviolet-Visible Spectrophotometry (UV - Vis)	Easy and fast operation, low instrument cost	Poor specificity and limited sensitivity

results are susceptible to interference from the medium's refractive index and particle agglomeration, thus requiring verification of particle morphology by complementary techniques such as transmission electron microscopy (TEM) or scanning electron microscopy (SEM). With sub-nanometer resolution, TEM allows observation of crystal lattice structures, while SEM is more suitable for analyzing surface topographies. Both techniques effectively compensate for DLS's bias in detecting large particles, typically through size distribution analysis based on counting at least 200 particles.[80] Nanoparticle Tracking Analysis, a recently developed technique, calculates particle size by directly tracking the movement of individual particles and exhibits higher accuracy than DLS in low-concentration systems.[81]

Additionally, zeta potential determination, which assesses surface charge based on the principle of electrophoretic light scattering, often shares instrumentation with DLS. The zeta potential is associated with the colloidal stability of nanoparticles (NPs). According to guidelines for nanodelivery systems, NP dispersions with zeta potential values of ±0–10 mV, ±10–20 mV, ±20–30 mV, and >±30 mV are classified as highly unstable, relatively stable, moderately stable, and highly stable, respectively.[82] Therefore, when evaluating the surface charge of NPs, only the magnitude (regardless of positive or negative polarity) matters: a higher absolute value of zeta potential indicates stronger electrostatic repulsion between particles, which helps maintain the uniform dispersion of nanocrystals in the dispersion medium and keeps the nanocrystalline drug system in a stable state. Recently, Zong et al[83] successfully developed curcumin nanocrystals with adjustable surface zeta potential. Their study not only revealed that curcumin NCs could enhance the water solubility, stability, and dissolution rate of curcumin, but also found that curcumin NCs with high positive surface charge exhibited excellent antibacterial activity against both *Escherichia coli* and *Staphylococcus aureus*, and that the antibacterial activity depended on the high value of its zeta potential.

The Analysis of Surfaces and Crystal Structures

Analyzing the surface features and crystalline structure of nanocrystals is crucial not only for determining the solubility, stability, and biocompatibility of drug nanocrystals but also for understanding their functional mechanisms. The analytical methods can be primarily categorized into two types: One type includes X-ray diffraction (XRD) and Fourier transform infrared (FTIR) spectroscopy, which explore the interaction between electromagnetic waves (eg, X-rays, infrared rays) and substances to resolve their crystalline structures, chemical compositions, or functional group information. The other type comprises differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA), which reveal thermal stability, phase transition behavior, or compositional evolution by monitoring changes in physical or chemical properties during temperature variation.

Both types of methods are often used together in specific practices. In the experiment on esterification of starch nanocrystals (SNCs) with oleic acid, the successful synthesis of oleic acid-modified SNCs (SNCs-OA) was confirmed by FTIR spectroscopy—through identifying changes in functional group peaks—and XRD—via analyzing crystalline structure alterations. Meanwhile, TGA and DSC curves demonstrated that oleic acid modification reduced the thermal stability of SNCs. These results indicate that the combination of these multi-technical analyses ensures the reliability and comprehensiveness of experimental findings, thereby facilitating a deeper understanding of nanocrystal properties.[84]

Drug Load or Entrapped Efficiency

Although making nanocrystals of insoluble natural drug components can increase the solubility and bioavailability of the drug, in actual clinical trials, drug nanocrystals are usually made into formulations with different delivery forms, taking into account the type of patient and compliance, as well as therapeutic requirements. Therefore, another major parameter of nanocrystal drug characterization analysis is to calculate the encapsulation rate or drug loading capacity by determining the free or bound drug content. A high drug loading capacity indicates that more active drugs can be carried; a high encapsulation rate means less loss of drug and high utilization. Determination of their total drug content or encapsulation rate is usually based on disruption of the nanomedicine, such as separation of a free and encapsulated drug by freeze-drying and addition of surfactants or organic solvents, and separation methods include dextran gel column method, ultracentrifugation method, and ultrafiltration method. Followed by quantification of the drug or the active ingredient using high-performance liquid chromatography (HPLC) and an appropriate detector (UV-visible or fluorescent).[85]

Characterization of Biological Properties of Nanocrystalline Drugs

In assessing the biological behavior of nanocrystals, the in vitro dissolution test is of primary importance. The methods for determining the in vitro dissolution of nanocrystalline drugs include the paddle method, dialysis bag method, and flow cell method, among which the dialysis bag method is most commonly used for testing the dissolution of nanocrystalline formulations.[86] Based on Fick's law of diffusion, this method operates under conditions simulating the human physiological environment. Utilizing the semipermeability of the dialysis membrane, the drug is placed in a specific dissolution

medium, allowing the drug to dissolve from the formulation and diffuse through the dialysis membrane into the receiving solution. The in vitro dissolution rate and extent of the drug are evaluated by measuring the time-dependent changes in drug concentration in the receiving solution. This method reflects the in vivo behavior of nanomedicines to a certain extent, thereby ensuring the effectiveness and safety of clinical drug use.

Nanocrystal Drug Stability Characterization Techniques

Stability Study

The stability of nanocrystals is a key bottleneck in formulation industrialization. As an important part of quality control for APIs or formulations, stability studies require assessing physicochemical stability changes via accelerated and long-term tests—simulating actual storage or accelerated degradation conditions to monitor short- and long-term drug changes and predict long-term storage stability.

For physical stability, DLS is used periodically to monitor particle size and PDI changes in sample suspensions; It is instability when particle size increases by over 20% or visible precipitation occurs.[87] To avoid agglomeration artifacts during routine sample preparation, cryogenic transmission electron microscopy can capture the true morphology of nanocrystals in the frozen state.[88] For chemical stability, HPLC measures changes in drug content to calculate the degradation rate constant (k) and expiration date (t_{90}).

Additionally, the stability characterization has enabled researchers to more deeply explore the factors affecting nanocrystal stability and improvement measures. Figure 4 provides a concise synopsis of the predominant factors influencing the stability of nanocrystalline drugs and the corresponding strategies for their mitigation.

Instability Principles and Improvement Strategies

As shown in the figure, drug nanocrystals exhibit instability due to aggregation, sedimentation, Ostwald ripening, and other factors. Common approaches to improve the stability of drug nanocrystals include controlling particle size,[89]

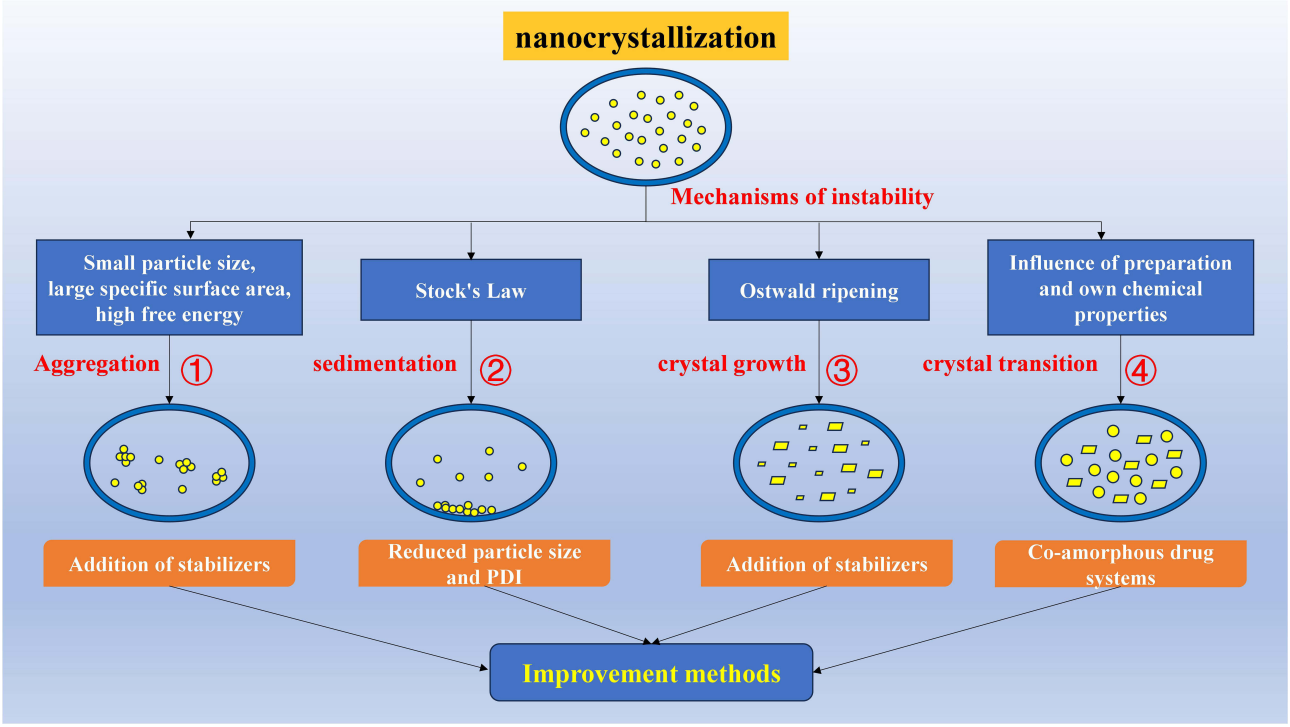


Figure 4 Instability phenomenon of nanocrystals and improvement methods. (1) The crystal aggregation due to small particle size and large specific surface area of high free energy nanocrystals can be solved by the addition of an appropriate amount of stabilizers; (2) Reduction of particle size and its distribution can help to improve nanocrystal settling problems; (3) The Ostwald ripening phenomenon can lead to nanocrystalline drug instability and even aggregation, and the use of stabilizers can help improve the situation; (4) The drug itself is chemically unstable or improper preparation and storage conditions can lead to crystalline transformation of drug nanocrystals. This can be improved by using co-amorphous drug systems.

rational selection of stabilizers,[90] and crystal form regulation.[91] Among these, stabilizers demonstrate multi-dimensional academic advantages in addressing the stability issues of nanocrystalline drugs. Zhang et al[92] prepared naringenin NCs using different stabilizers, respectively. The naringenin nanocrystals stabilized by PVP showed optimal performance in terms of dissolution behavior, cellular uptake, permeability, oral bioavailability, and in vitro and in vivo anti-inflammatory effects. The underlying mechanism is that the stabilizer inhibits nucleation by preventing the dimerization of naringenin, thereby enhancing the stability of the supersaturated solution when the nanocrystals dissolve. This further indicates that stabilizers not only improve the stability and oral bioavailability of naringenin nanocrystals but also that their types affect the "stabilization-synergistic enhancement" effect. In addition, the multi-functionality of stabilizers has expanded their application value and promoted the development of natural-source stabilizers. Liu et al[93] innovatively used arbutin as a multifunctional stabilizer for novel nanocrystal-based solid dispersions (NSDs) with high drug loading, successfully preparing AP-NSDs by combining homogenization and spray drying. The results showed that the in vitro dissolution rate of the insoluble drug apigenin (AP) was improved, and the AP-NSDs stabilized by 20% arbutin had high drug loading, good redispersibility, and stability.

In summary, the characterization of nanocrystalline drugs necessitates the establishment of a multifaceted technical system. This system is achieved through the systematic correlation analysis of physicochemical properties, biological properties, and stability. The implementation of this multifaceted system is essential to ensure the quality control of drugs from the laboratory research and development phase to the industrial production phase.

Natural Ingredients for Successful Preparation of Nanocrystals And Applications

Natural ingredients have attracted much attention in the research and development of modern drug delivery systems due to their advantages such as multi-targeting and low toxicity. Meanwhile, nanocrystal technology provides an effective approach to solving problems like low solubility and poor bioavailability of natural ingredients. As the core material basis of nanocrystal drug delivery systems, natural ingredients directly determine the efficacy of the delivery systems through their selection and application. This chapter focuses on natural ingredients that have successfully been used to prepare nanocrystals (Table 3), exploring their application value in drug delivery systems. It not only concretely presents the progress of natural compound nanocrystal drug delivery systems, but also provides a practical basis for the subsequent analysis of challenges and opportunities.

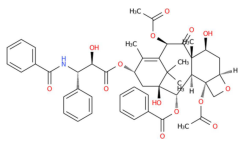
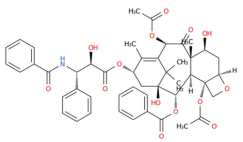
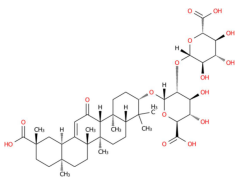
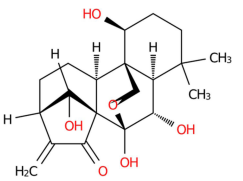
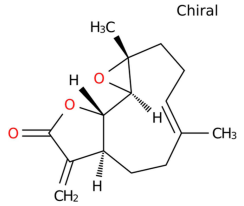
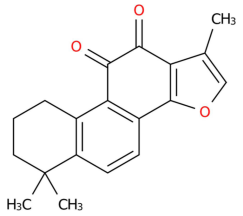
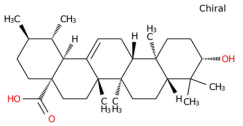
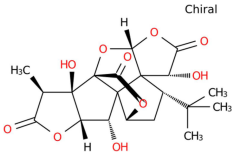
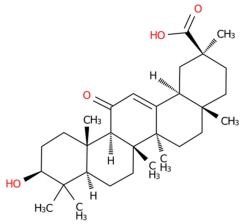
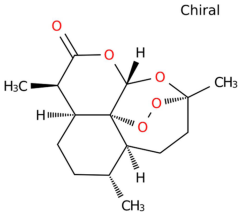
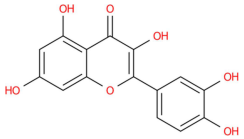
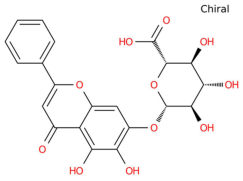
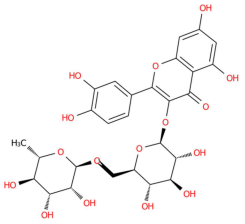
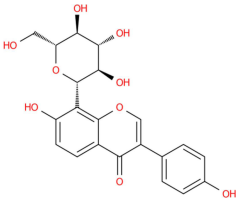
Terpenoids

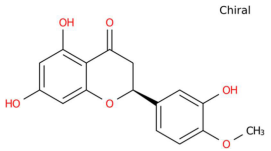
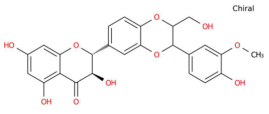
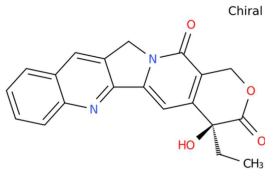
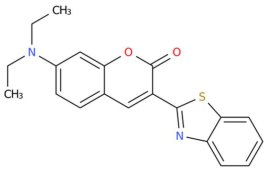
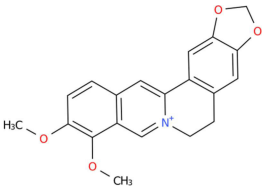
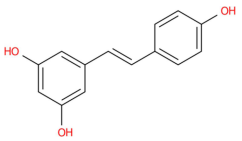
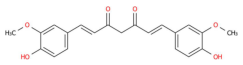
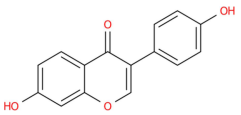
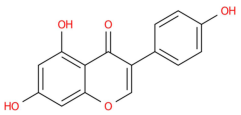
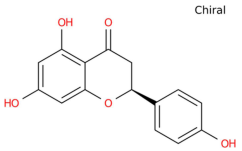
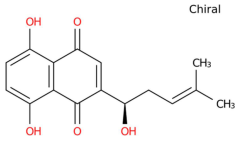
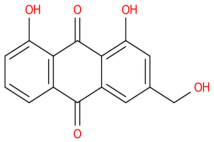
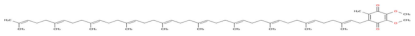
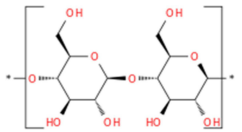
Terpenes are found in nature as secondary metabolites of plants (essential oils, resins, waxes and latex), bacteria, fungi and algae.[94] A multitude of studies have demonstrated that terpenoids manifest a diverse array of pharmacological activities, including anti-inflammatory, antimicrobial, anticancer, and antiparasitic properties. This characteristic renders them promising candidates for the development of novel pharmaceutical agents.[95–97]

A typical example is paclitaxel, an anticancer drug extracted from the bark of Taxus chinensis and a naturally occurring diterpenoid compound for oral administration. Firstly, its encapsulation with albumin to form nanocrystals improves the formulation limitations of poor water solubility and low bioavailability of paclitaxel, while also enhancing tumor targeting.[98] Secondly, paclitaxel nanocrystals, as the core of high-dose drugs, are used to construct a biomimetic platelet membrane-camouflaged paclitaxel nanocrystal system, which not only breaks through the dose limitation of intravenous chemotherapy but also enhances the efficacy of postoperative chemotherapy.[99] Recently, a new method for preparing carrier-free paclitaxel nanocrystals has been developed: by exploiting a wide metastable zone applicable to the preparation of carrier-free nanocrystals, ultrasonic treatment within this zone triggers nucleation, forming small and uniform nanocrystals.[100] Other natural terpenoids with similar formulation limitations, such as artemisinin, tanshinone IIA, andrographolide, triptolide, and ginsenosides, etc., can also benefit from nanocrystal formulations as an effective approach to improve the aforementioned limitations, with specific examples provided in Table 4.

https://doi.org/10.2147/IJN.S536383

Table 3 Summary of Nanocrystalline Drugs of Various Natural Compounds

Terpenoids	 **Paclitaxel**	 **Celastrol**	 **Glycyrrhizic acid**	 **Oridonin**
	 **Parthenolide**	 **Tanshinone IIA**	 **Ursolic acid**	 **Ginkgolide B**
	 **18α-Glycyrrhetinic acid**	 **Artemisinin**		
Flavonoids	 **Quercetin**	 **Baicalon**	 **Rutin**	 **Puerarin**

	 **Hesperetin**	 **Silybin**		
Alkaloids	 **Camptothecin**	 **Coumarin 6**	 **Berberine**	
Polyphenols	 **Resveratol**	 **Curcumin**	 **Daidzein**	 **Genistein**
	 **Naringenin**			
Quinones	 **Shikonin**	 **Aloe-emodin**	 **Coenzyme Q10**	
Polysaccharides	 **Cellulose**			

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Flavonoids

Flavonoids, as natural compounds, hold promising applications in medicine due to their multiple therapeutic targets and low toxicity. Among their diverse pharmacological activities, antioxidant, anti-inflammatory, wound-healing, depigmenting, photoprotective, and anti-aging effects are beneficial to the skin, showing potential in the treatment of various skin diseases.[129] However, their lipophilicity, low solubility, and poor skin permeability limit therapeutic efficacy. Nanocrystals may serve as a promising technological platform to enhance the overall therapeutic properties of flavonoids when administered via the dermal route.[130]

Currently, the main flavonoids prepared using nanocrystal technology include quercetin, baicalin, apigenin, lignans, rutin, and hesperidin. In experiments evaluating the effects of quercetin and titanium dioxide nanocrystal gel (nanogel) on skin cancer and chemoprevention, in vitro studies demonstrated increased drug deposition in the skin, attributed to the nanocrystals' small particle size and large surface area. In vivo studies on SKH-1 mice also showed that the nanogel-pretreated group had significantly reduced tumor size and volume compared to the UV-exposed group.[131]

Another study utilized nanosuspensions prepared by the SmartCrystal® process to enhance rutin's antioxidant activity and skin permeability. In vivo permeation tests on pig ear skin, rutin nanocrystals achieved 4 to 5 times higher concentrations in the deeper layers of the stratum corneum than the normal form, confirming their superior permeability.[132] Additionally, baicalin can be combined with other natural products such as glycyrrhetinic acid and berberine to form composite nanocrystals, improving the solubility and in vitro release profiles of the individual components.[133–135]

Alkaloids

Alkaloids are a class of natural compounds containing primarily basic nitrogen atoms. Based on their main carbon-nitrogen backbone structures, they can be divided into several subclasses, including pyrrole, pyridine, quinoline, isoquinoline, and indole alkaloids. The natural alkaloid components that can be formulated into nanocrystals are limited. Compared with quinoline antitumor drugs—whose hydrophobicity, lactone ring instability, and high toxicity have been addressed by nanocrystal preparation (As seen in Table 4)—coumarin nanocrystals have more specific applications.

Table 4 Summarizing Natural Compound Nanocrystal Types, Preparation Techniques and Pharmacological Results

Category	Representative Compounds	Type of Nanocrystalline Formulation	Preparation Related Technologies	Main Pharmacological Results/Application Advantages	Refs.
Terpenoids	Paclitaxel	Lipid-coated nanocrystals of paclitaxel	Anti-solvent crystallization by combined probe sonication	Increased drug loading, dissolution enhancement, and aerosolization stability	[101]
	Celastrol	Carrier-free celastrol and doxorubicin nanocrystals	Solvent-antisolvent precipitation	Improvement of the water solubility of tretinoin, reduction of adriamycin dosage, and enhancement of cellular drug accumulation	[102]
	Glycyrrhizic acid	Colon-targeted piperine-glycyrrhizic acid nanocrystals	Solvent-antisolvent precipitation	Ultra-high drug loading and colon-specific drug release	[103]
	Oridonin	Oridonin nanocrystals	Solvent-antisolvent precipitation	Increased dissolution rate, drug internalization, and transmembrane volume	[104]
	Parthenolide	Parthenolide nanocrystals	Nanoedge technology	Improved poor water solubility of PTL and enhanced synergistic therapeutic effect with sorafenib	[105]
	Tanshinone IIA	The nanocrystal-loaded liposome of tanshinone IIA	Ultrasonication combined with anti-solvent method	High colloidal stability, high drug loading capacity, high safety; significant therapeutic effects	[106]

(*Continued*)

Table 4 (Continued).

Category	Representative Compounds	Type of Nanocrystalline Formulation	Preparation Related Technologies	Main Pharmacological Results/Application Advantages	Refs.
	Ursolic acid	Ursolic Acid Nanocrystals	High-pressure homogenization	The dissolution rate of the nanocrystals was significantly increased and the relative bioavailability was higher than that of the UA crude suspension, along with an increase in peak concentration and prolonged retention time.	[107]
	Ginkgolide B	Highly stabilized Ginkgolide nanocrystals	Solvent-antisolvent precipitation	Smaller size, higher dissolution rate, enhanced cellular uptake and permeability	[108]
	18α-Glycyrrhetinic acid	18β-glycyrrhetinic acid nanocrystals	High-pressure homogenization	Significantly increased solubility, higher skin permeability, and anti-edema capacity.	[109]
	Artemisinin	Artemisinin nanocrystals	High-pressure homogenization and sedimentation methods	Improve bioavailability, personalization, and efficacy.	[110]
Flavonoids	Quercetin	Quercetin Nanocrystals in Nanosuspension	Microfluidic technology	Significant improvement in dissolution properties and oral bioavailability	[111]
	Baicalon	Hyaluronic acid based Baicalon nanocrystals hydrogels	Nanoedge technology	Improved solubility and in vitro release characteristics of baicalin monomer drug, resulting in faster drug release and higher release rate	[112]
	Rutin	Rutin nanocrystals	Ultrasound-assisted freeze-drying method	Ultrasonically treated rutin (UTR) nanobundles with a diameter of <820 nm offer low cost and high efficiency in nanomedicine productionUltrasonication enhances the properties of rutin delivered orally	[113]
	Puerarin	Oral Delivery of Puerarin Nanocrystals	High-pressure homogenization	Improves drug dissolution in the gastrointestinal tract and enhances bioavailability	[114]
	Hesperetin	Hesperetin Nanocrystals	Wet media milling	Improve Mitochondrial Function in a Cell Model of Early Alzheimer Disease	[115]
	Silybin	Albumin-Based Silibinin Nanocrystals	Acid-base neutralization precipitation	The prepared SLB-HSA NCs showed uniform particle size distribution of approximately 60 nm with PDI < 0.15 and high loading efficiency up to 49.4%. In addition, SLB-HSA NCs significantly improved the bioavailability compared with free SLB in pharmacokinetic study	[116]
Alkaloids	Camptothecin	Hyaluronic Acid-Coated Camptothecin Nanocrystals	Solvent-antisolvent precipitation	High drug loading efficiency, improved aqueous dispersion, extended cycling, and enhanced stability.	[117]
	Coumarin 6	Coumarin 6 Nanocrystals	Solvent-antisolvent precipitation	Improvement of oral bioavailability by enhancing the drugability of insoluble drugs and increasing the solubility of poorly water-soluble drugs	[118]
	Berberine	Baicalin-berberine complex nanocrystals	High-Pressure Homogenization Method	Enhance the passive diffusion ability of the drug and weaken the efflux effect, thus improving oral absorption and bioavailability.	[119]
Polyphenols	Resveratol	Resveratrol nanocrystals based dissolving microneedles	Wet media milling	Improved therapeutic outcomes in rheumatoid arthritis by improving the shortcomings of long-term oral drug delivery	[120]

(*Continued*)

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Table 4 (Continued).

Category	Representative Compounds	Type of Nanocrystalline Formulation	Preparation Related Technologies	Main Pharmacological Results/Application Advantages	Refs.
	Curcumin	Skin permeation of curcumin nanocrystals	Solvent-antisolvent precipitation	Improve the disadvantage of low oral bioavailability, with high drug loading, low toxicity, and good stability.	[121]
	Daidzein	Daidzein nanosuspensions	Saturated aqueous method	The resulting daidzeins NS are physically stable and biocompatible, with regular shape, uniform particle size of 360–600 nm and reduced crystallinity. Due to the increased solubility and dissolution rate, the oral bioavailability of soy sapogenins NS in rats was 1.63–2.19 times higher than that of crude soy sapogenins.	[122]
	Genistein	Transferrin-modified genistein nanocrystals	Wet media milling	5.8-fold increase in solubility and significant enhancement of dissolution kinetics	[123]
	Naringenin	Naringenin nanocrystals	Wet media milling	Exhibited excellent lysis behavior, increased cellular uptake, and enhanced transcellular spreading in addition; effectively improved rheumatoid arthritis treatment in rats with collagen-induced arthritis	[124]
Quinones	Shikonin	Shikonin nanoparticle	Solvent evaporative method	Increased bioavailability, improved tissue distribution, enhanced biostability, prolonged in vivo residence time and reduced adverse effects.	[125]
	Aloe-emodin	Aloe-emodin nanocrystals	Nanoemulsion method	Enhances its water solubility makes it useful for anti-cancer purposes and increases the serum stability of nanoparticles	[126]
	Coenzyme Q10	Coenzyme Q_{10} nanosuspensions	High-pressure homogenizer	The formulations tested show an average particle size well below 100 nm and good aerosolization	[127]
Polysaccharides	Cellulose	Cellulose nanocrystals	Ultrasound-assisted maleic acid hydrolysis method	Ultrasound-assisted maleic acid hydrolysis has great potential to realize the industrialization of CNCs.	[128]

Coumarin 6 (C6), a naturally occurring indole alkaloid, exhibits high photostability, structural diversity, low toxicity, and biological activity, making it one of the classic fluorescent dyes.[136] Both coumarin and boron dipyrromethene systems have been effectively used as fluorescent probes, chemosensors, and energy transfer carriers, finding wide applications in molecular sensing, bioimaging, and photothermal cancer therapy.[137,138] Recently, a study prepared NCs using C6 as a model drug and utilized its fluorescent properties to investigate the absorption mechanism of NCs. The results showed that NCs enhance oral bioavailability mainly by improving the solubility of poorly water-soluble drugs.[118] This finding is of great significance for the extensive application of NCs in improving the druggability of insoluble drugs and also provides a universal technique for tracking the distribution, trans-epithelial transport, and intracellular fate of nanocrystals.

Polyphenols

Polyphenolic natural compounds have emerged as a vital resource for drug discovery and development, owing to their structural diversity and pleiotropic effects. Their applications have expanded from traditional Chinese medicine to modern precision medicine. In recent years, nanomedicines containing polyphenolic compounds have garnered extensive research interest due to their potent anticancer activity and multifunctionality, with resveratrol, curcumin, and puerarin being typical examples.

Resveratrol exhibits various bioactive effects, including anti-inflammatory, antiviral, antioxidant, anti-cardiovascular disease, and antitumor properties. Notably, its excellent antitumor activity has established it as a natural antitumor agent following paclitaxel. The preparation of resveratrol into nanocrystals using nanocrystal technology has overcome limitations related to its physicochemical properties (such as poor solubility and photoinstability) and pharmacokinetic characteristics (rapid metabolism, quick elimination, and low bioavailability), thereby improving its bioavailability.[139]

This makes it a promising therapeutic approach for cancer and Parkinson's disease. Additionally, its integration with soluble transdermal drug delivery system microneedles has emerged as a novel therapy for cutaneous melanoma.[140] In pulmonary delivery studies, microparticulate formulations based on curcumin (CUR) acetate NCs enhanced the local bioavailability of transformed CUR and demonstrated better therapeutic efficacy in a rat model of pulmonary arterial hypertension.[141]

Another study revealed that puerarin nanocrystals can adsorb onto the surface of micrometer-sized oil droplets, forming a "micro-nano" synergistic microstructure. This not only improves the physical stability of the emulsion but also facilitates cellular uptake and translocation of components, holding promise as a potential new oral dosage form for traditional Chinese medicine compounds.[142]

Quinones

According to the prevailing taxonomy, quinones can be classified into five distinct classes: benzoquinones, naphthoquinones, phenanthrenequinones, and anthraquinones. This classification system is based on the parent structure. Anthraquinones represent a prominent class of natural quinones that has been extensively researched. These compounds are found in various plants, including rhubarb, crocus sativus, and cassia seeds. Examples of anthraquinones include rhodopsin,[143] rhodopsinol,[144] and aloe rhodopsin.[145] Recent studies have shown that aloe-emodin (AE) has unfavorable pharmacokinetic properties as an iron death inducer and photosensitizer for specific surface diseases. However, aloe-emodin nanocrystals can evade immune clearance, significantly increase tumor accumulation in vivo, and achieve superior therapeutic efficacy compared to free AE.[126] Benzoquinones have a relatively limited distribution in the natural world, and representative compounds such as coenzyme Q10 (ubiquinone), although not strictly a natural phylloquinone, have a wide range of sources (eg, plant and animal cells), and have antioxidant and cellular energy metabolism-enhancing functions.[146] The nanocrystalline form has been demonstrated to enhance the water solubility and bioavailability of coenzyme Q10, thereby facilitating its absorption by the human body.[127] This form is frequently utilized in health supplements, food additives, and skin care products to augment the antioxidant effect.[147]

Polysaccharides

Polysaccharides are a class of important organic compounds widely distributed in nature and serve as the primary source of energy for all living organisms to maintain life activities. Based on their natural sources, polysaccharides can be categorized into plant-derived, animal-derived, and microbial-derived types. Cellulose, as the most abundant plant polysaccharide on Earth, is a crucial source for the preparation of nanocrystals. Through enzymatic/acid hydrolysis, mechanical treatment, oxidation, or other means, amorphous chains are separated from cellulose fibers, and the crystalline components (cellulose nanocrystals, CNCs) are extracted.[148]

CNCs possess unparalleled properties, including excellent mechanical strength, high surface area, low density, and biodegradability, making them attractive materials for various fields such as biomedical engineering, renewable energy, and nanotechnology—for instance, as lubricant additives,[149] biopolymer films,[150] and sensors.[151] Compared with the application of nanocrystal technology in improving the pharmacological effects and properties of other types of compounds, polysaccharide nanocrystals tend to act as one of the auxiliary tools facilitating the successful application of nanocrystal formulations.[152]

Meanwhile, significant progress has been made in the surface modification/functionalization methods of CNCs, expanding their potential applications. Particularly in Pickering emulsion drug delivery systems, Pickering agents stabilized by acylated cellulose nanocrystals are used for the oral co-delivery of macromolecules and penetration enhancers;[153] cellulose nanocrystals with optimized lengths can enhance curcumin delivery in Pickering emulsions;[154] and clove oil Pickering emulsions based on sodium carboxymethyl cellulose-modified CNCs exhibit enhanced antibacterial activity.[155]

Current Challenges and Future Opportunities

The application of natural ingredient nanocrystals in drug delivery systems, despite showing significant potential, still confronts multiple challenges. The complexity of natural ingredients complicates purification and renders their activity

vulnerable to the preparation environment. Additionally, the instability of nanocrystals during storage and in vivo transport, coupled with delays in scaled-up production and in vivo behavioral studies, hinders their clinical translation.[156] Moreover, regulations governing nanopharmaceuticals—encompassing stability, manufacturing, and toxicology—and the stringent control measures imposed on these aspects present the most notable barriers to the development of pharmaceutical or API nanocrystalline drugs. Nevertheless, these challenges also give rise to distinct development opportunities:

To tackle the issues of compositional complexity and stability, nanocrystals can be endowed with properties like targeting and smart responsiveness through multifunctional modifications, thereby enhancing their specificity and stability. In one study, folic acid was employed as a ligand to stabilize andrographolide nanocrystals, leveraging the stabilizing effect of serum proteins and the modifying role of ligand conjugation. These nanocrystals were co-loaded with imatinib into the hydrophobic domains of bovine serum albumin. Experiments demonstrated that the resulting nanocrystals achieved high drug-loading capacity and excellent colloidal stability, while folic acid modification enhanced tumor targeting.[157] Several other studies have indicated that parameters such as the molecular weight, hydrophilic-hydrophobic properties, and concentration of stabilizers influence the adsorption efficiency and stability of nanocrystal formulations.[158] Establishing key criteria for the initial evaluation of stabilizers can thus help optimize stabilization strategies, thereby improving the formulation of poorly water-soluble drugs.

To address the challenges in large-scale production of nanocrystalline drugs—such as difficulties in controlling particle size uniformity, significant batch-to-batch variation, and complex optimization of process parameters—artificial intelligence (AI) offers solutions through multi-dimensional technical approaches.[159] For instance, machine learning algorithms (eg, random forests, artificial neural networks) are used to model correlations between key production parameters (eg, dispersant concentration, milling time, temperature) and quality attributes (eg, nanocrystal particle size distribution, zeta potential).[159,160] This enables accurate prediction and optimization of process parameters. Ze et al[161] for example, innovatively replaced traditional reactors with impinging jet crystallizers. By combining computational fluid dynamics simulations with experimental studies, they determined optimal process parameters for the crystallizer, successfully preparing baicalin nanocrystals with an average particle size below 300 nm and spherical morphology—conducive to improving baicalin's bioavailability and stability. Additionally, digital twin models, integrating historical production data, raw material properties, and quality testing results, can simulate process stability under different scale-up scenarios, reducing trial-and-error costs and enhancing batch consistency. Buket Aksu et al[162] demonstrated this by applying AI to control critical quality attributes in ramipril tablet production via wet granulation. They designed experiments using response surface methodology and AI-based artificial neural network modeling, and utilized an AI-driven multidimensional design space to produce ramipril tablets with consistent quality.

Finally, the development of new preparation techniques characterized by high efficiency, environmental friendliness, and low cost—such as green synthesis methods and microfluidics—has also emerged as a key breakthrough. For example, Zhu et al[163] utilized microfluidics to fabricate curcumin-soy protein isolate-rhamnolipid ternary complex nanocrystals through a simple, controllable one-step assembly process, with no risk of solvent residue. The results showed that the solubility and bioaccessibility of curcumin in these nanocrystals increased by 664.67 and 6.49 times, respectively.

Conclusions and Perspectives

In summary, the following points can be concluded: First, although nanocrystalline technology has a relatively short development history, both its preparation methods and characterization techniques are relatively mature in the application of natural compound formulations. We can not only select appropriate preparation methods based on the properties and particle size requirements of natural active compounds but also use various characterization techniques to evaluate and analyze the material properties, composition, structure, and performance of nanocrystalline drugs. This provides a basis for optimizing drug preparation processes, dosage forms, and quality control.

Second, research on the factors affecting the stability of nanocrystalline drugs has yielded certain results. These findings can guide the research, development, and production of nanocrystalline drugs, helping researchers select suitable

drug carriers, stabilizers, and preparation processes at an early stage. This improves the success rate of research and development, shortens the research cycle, and reduces costs.

Third, nanocrystalline technology offers new solutions to the clinical application bottlenecks of natural active ingredients in traditional Chinese medicine. Its potential in improving drug solubility, enhancing bioavailability, strengthening targeting, and reducing toxicity lays an important foundation for the modernization and clinical translation of natural drugs. The challenges in the application of natural ingredient nanocrystals also provide continuous impetus for the development of nanocrystalline drug delivery systems.

It is reasonable to believe that the application prospects of nanocrystalline technology in the field of natural compound formulations will become increasingly promising.

Abbreviations

NCDDS, Nanocrystalline drug delivery systems; TCM/TCMs, traditional Chinese medicine/medicines; DSV, Divya-Swasari-Vati; SLD, Solid lipid nanoparticles; WMM, wet media milling; HPH, High-Pressure Homogenisation; DAC, dual asymmetric centrifugal; NC/NCs, nanocrystals; ADHD, Attention deficit disorder; SCFs, supercritical fluids; H69 technology, High Pressure Cavitation Precipitation-Homogenisation Combined Technology; H42 technology, Spray Drying - High Pressure Homogenising Combined Technology; H96 technology, Freeze Drying - High Pressure Homogenising Combination Technology; PLH, precipitation-lyophilization-homogenization method; SLC, static light scattering; DLS, dynamic light scattering; PDI, Polymer dispersity index; SEM, scanning electron microscopy; TEM, transmission electron microscopy; DSC, differential scanning calorimetry; TGA, thermogravimetric analysis; FTIRS, fourier transform red spectroscopy; PXRD/XRD, powder x-ray diffraction/ x-ray diffraction; HPLC, high-performance liquid chromatography; API/APIs, active pharmaceutical ingredient/ingredients; SNCs, starch nanocrystals; PVP, k; AP, apigenin; NSD, nanocrystal-based solid dispersions; CUR, curcumin; AE, aloe rhodopsin; CNCs, cellulose nanocrystals.

Data Sharing Statement

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Disclosure

The authors report no conflicts of interest in this work.

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