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Nanocrystal Technology for Preparation of Natural Product Formulations: Processes, Formulation, Limitations and Challenges

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Abstract. Natural products often contain multiple coexisting constituents. Their therapeutic effects are limited by poor aqueous solubility, rapid in vivo metabolism, limited absorption, and inadequate formulation stability. Drug nanocrystals are composed primarily of active ingredients and small amounts of stabilizers. In drug nanocrystals, reduction of crystal particle size and increase in specific surface area enhance drug saturation solubility and dissolution rate; they also offer high drug loading, low excipient requirements, and flexible routes of administration. This article reviews top-down processes, such as wet media milling and high-pressure homogenization, and bottom-up processes, including antisolvent precipitation, electrohydrodynamic atomization, and spray drying, and summarizes applications to natural products such as terpenoids, flavonoids, alkaloids, and polyphenols. Existing studies indicate that nanocrystals not only improve the dissolution and oral absorption of natural active constituents but also enable pulmonary inhalation, colon targeting, transdermal delivery, and tissue targeting through surface modification, composite nanocrystals, and integration with delivery systems such as microneedles. Nevertheless, this technology still faces challenges including variability in the composition of natural raw materials, difficulties in controlling crystal form and particle size, inadequate long-term stability, unclear in vivo fate, and poor consistency during process scale-up. Future studies should integrate smart stabilizers, continuous manufacturing, process monitoring, in vivo tracing, and physiologically based pharmacokinetic models to establish a systematic evaluation framework linking raw materials, processes, formulation attributes, and in vivo effects, thereby advancing the clinical translation of natural-product nanocrystal formulations.

Keywords: natural products, drug nanocrystals, preparation processes, bioavailability, targeted delivery

1. Introduction

Natural products are chemical constituents biosynthesized by organisms in nature over the course of evolution. Natural products come from many sources, such as animals, plants, and microorganisms, and some are used in traditional Chinese medicine, and they have complex structures and exhibit

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diverse pharmacological activities. Multicomponent mixtures generally have problems of formulation instability and low bioavailability, as manifested by poor aqueous solubility, rapid in vivo metabolism, considerable barriers to oral absorption, and inadequate physicochemical stability of the injectable form. Consequently, they are not suitable for clinical application development. The immediate problems in natural product formulations are how to enhance bioavailability, how to efficiently extract therapeutic components, and how to improve formulation stability. Although the above problems have been studied by others, several limitations remain unaddressed. Through inclusion and emulsification technologies, Zhang and others have used cyclodextrins to improve the stability of volatile oil processing for traditional Chinese medicine. However, batch-to-batch consistency is not guaranteed, and industrial-scale production of cyclodextrin-based formulations has also been limited [1]. Lu and others have employed nanocrystalline liposomes to enhance the aqueous solubility and bioavailability of natural products. However, the safety of these liposomes has not been fully verified, and thus these liposomes are currently used only on a small scale [2].

Nanocrystal technology reduces the size of the drug to the nanoscale, does not require a carrier, and requires only a small amount of stabilizer to obtain a formulation with high drug loading. The nanocrystals have a small particle size and are thus more soluble; their dissolution rate and saturation solubility increase, which extends the scope of oral administration, improves absorption, and enables dose reductions while maintaining equivalent effectiveness. This approach can increase effectiveness and safety. It involves a relatively simple process, requires few excipients, is easily scalable, and provides a practical new path for the development of formulations for many poorly soluble active ingredients in natural products. On the basis of the above analysis, this paper will systematically review progress in applying the two main nanocrystal preparation approaches (top-down and bottom-up) to representative natural products, including terpenoids, flavonoids and alkaloids. Particular attention is paid to experimental evidence of nanocrystal enhancement of dissolution and release for improved oral bioavailability and simplified formulation. The above problems in quality control, in vivo fate, and translational prospects are also discussed. This review provides a reference for the modern development of natural product formulations.

2. Nanocrystal preparation processes

Nanocrystal preparation technologies are broadly classified into top-down and bottom-up approaches. Top-down approaches use mechanical forces to break drug crystals. Wet media milling (WMM) and high-pressure homogenization (HPH) represent the principal processes. Bottom-up approaches create a supersaturated system by altering the solvent environment, thereby inducing drug nucleation and growth into nanocrystals. The bottom-up approaches mainly include anti-solvent precipitation, electrohydrodynamic atomization, and spray drying.

2.1. Top-down approaches

Wet media milling involves dispersing coarse drug powder in a liquid phase containing a stabilizer and reducing crystal particle size through collision, shear, and friction generated by milling beads. The process is simple, affords high drug loading, and is readily scalable. However, product quality is affected by milling-bead size, bead loading, rotational speed, processing time, and stabilizer type, and excessive milling may also cause heating, equipment wear, and particle aggregation. López-Vidal et al. used wet media milling driven by dual asymmetric centrifugation to mill 100 mg of drug for 1 min at 3,000 rpm. Nanocrystals were successfully formed for 9 of the 10 model drugs, with a minimum particle size of 174 nm. The polydispersity index (PDI) of most formulations was below

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0.30, and processing was approximately 120 to 1440 times faster than with conventional methods. The study also found that several short 1-min cycles were more effective than continuous milling for 5 min in reducing particle size and suppressing temperature increases [3]. This method is suitable for high-throughput screening during early formulation development, but temperature, vessel wear, and the cost of specialized equipment remain important considerations.

High-pressure homogenization passes a drug suspension through a narrow channel under high pressure and uses cavitation, shear, and particle collisions to break the crystals. This method requires no milling beads and offers good containment and reproducibility, but it consumes considerable energy and generally requires multiple cycles. In a review of marketed products, Möschwitzer noted that wet media milling and high-pressure homogenization are the most industrially mature top-down processes [4]. At the time of publication, six nanocrystal formulations had been approved by the United States (U.S.) Food and Drug Administration, indicating that these technologies already provided a basis for translation from milligram-scale screening to large-scale manufacturing [4].

2.2. Bottom-up approaches

In antisolvent precipitation, the drug is first dissolved in a good solvent, and then an antisolvent is added to rapidly supersaturate the system and form nanocrystals. Drug concentration, solvent ratio, addition rate, mixing intensity, temperature, and stabilizer concentration are the principal factors affecting particle size and crystal form. This method has low energy requirements and facilitates control of crystal form and morphology, but batch production is susceptible to nonuniform mixing, batch-to-batch variability, and residual organic solvents.

Costa and Padrela summarized advances in the transition of bottom-up processes from batch production to continuous manufacturing [5]. Continuous mixing devices, such as microfluidic and impinging-jet systems, can shorten mixing time, render nucleation conditions more uniform, and support online monitoring and scale-out. However, pipeline clogging, solvent recovery, solid-liquid separation, and drying remain major obstacles to industrial application [5].

Electrohydrodynamic atomization uses a high-voltage electric field to disperse a drug solution into charged microdroplets and rapidly removes the solvent at relatively low temperatures, and spray drying uses a hot gas stream to atomize and dry the droplets. Arzi and Sosnik noted that both methods can produce pure-drug nanocrystals or cocrystal dry powders in a single step, thereby reducing postprocessing and improving storage stability [6]. Electrohydrodynamic atomization is suitable for heat-sensitive constituents but has a relatively low throughput. Spray drying is better established for continuous operation and scale-up but may cause degradation of heat-sensitive natural products.

In summary, top-down approaches have a broad scope of application and extensive industrial experience, but they entail risks related to energy consumption and contamination. Bottom-up approaches provide greater flexibility in controlling particle size and crystal form but depend on solvents and precise mixing. In the future, combination processes such as antisolvent precipitation coupled with high-pressure homogenization and media milling coupled with high-pressure homogenization may be used together with continuous manufacturing and online quality monitoring to improve the production efficiency and quality controllability of natural-product nanocrystals.

3. Applications of nanocrystals in common natural product formulations

Most natural active constituents fall into the low-solubility, low-permeability category of the Biopharmaceutics Classification System, although the extent of these limitations varies with the core

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scaffold. Terpenoids frequently crystallize readily and are highly lipophilic. The polyphenolic structures of flavonoids confer some hydrophilicity but are associated with poor chemical stability. Alkaloids are often weakly basic, with dissolution behavior that is strongly pH-dependent. These differences result in category-specific requirements for crystal breakage efficiency, stabilizer selection, and particle-size control during nanocrystal preparation, which makes a single formulation strategy unsuitable for all constituents. Accordingly, this section reviews studies of emerging nanocrystal technologies for major categories, including terpenoids, flavonoids, and alkaloids, with particular emphasis on the relationships among process parameters, particle-size distribution, the degree of dissolution enhancement, and improved oral absorption, aiming to provide category-specific design guidance for the development of nanocrystal formulations containing similar constituents.

3.1. Terpenoids

Paclitaxel is a diterpenoid anticancer agent with extremely low aqueous solubility. Its conventional injectable formulation commonly uses polyoxyethylated castor oil as a solubilizer, which can induce severe hypersensitivity reactions in clinical use. Consequently, a high-drug-loading delivery system free of this excipient is urgently needed. Kumar et al. prepared fucoidan-stabilized paclitaxel nanocrystals, coated their surfaces with phospholipids, and converted them by lyophilization into a dry powder for pulmonary inhalation. The formulation exhibited good powder flowability and aerosolization performance and could be deposited in the deep lung. The phospholipid layer also delayed drug release, increased retention in lung tissue, and reduced systemic distribution, offering a new approach to the local treatment of lung cancer (Table 1) [7].

The development and progression of ulcerative colitis are closely associated with dysregulated inflammatory responses, abnormal macrophage polarization, and damage to the intestinal mucosal barrier. Piperine has anti-inflammatory and immunomodulatory effects, whereas glycyrrhizic acid suppresses inflammation, modulates immunity, and protects the mucosa; their combined use may therefore produce synergistic effects by acting at different stages, including the control of inflammatory responses and the promotion of mucosal repair. However, piperine has poor aqueous solubility and limited oral absorption, while constituents such as glycyrrhizic acid may be affected by gastric acid or may be released and absorbed prematurely before reaching the colon, making it difficult for both constituents to reach the lesion site simultaneously at sufficient concentrations. In addition, conventional nanocarriers have limitations such as low drug loading and premature drug release. On this basis, Wu et al. prepared piperine-glycyrrhizic acid composite nanocrystals and surface-modified them with the enteric material Eudragit S100 so that the formulation remained relatively stable in the stomach and small intestine and then released its payload predominantly after reaching the colon. Animal experiments showed that the system downregulated proinflammatory factors such as interleukin 1β (IL-1β) and interleukin 17A (IL-17A), upregulated transforming growth factor β1 (TGF-β1), and alleviated inflammation and repaired the intestinal mucosal barrier by suppressing classically activated (M1) macrophage polarization and promoting alternatively activated (M2) macrophage polarization. This study not only improved the efficiency of oral delivery of the two natural constituents but also demonstrated the value of composite nanocrystals for multicomponent synergistic therapy and colon-targeted drug delivery [8].

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3.2. Flavonoids

Quercetin is an antioxidant that is not highly water-soluble and thus poorly absorbed. Wang and others prepared quercetin nanocrystals with particle sizes of 50, 140 and 360 nm, and increased the aqueous solubility of quercetin by about 26-, 21- and 13-fold, respectively [9]. In a hydrogen peroxide-induced oxidative stress model of zebrafish, nanocrystals reduced reactive oxygen species and lipid peroxidation levels and increased zebrafish survival. The smaller-particle-size formulation had a stronger effect. High concentrations of small-particle-size nanocrystals may alter the heart rate and development of zebrafish. Thus, particle-size optimization needs to balance efficacy with safety [9].

Table 1. Designs and application outcomes of representative natural-product nanocrystal formulations

Active constituent	Nanocrystal design	Key performance	Application/limitation	Ref.
Paclitaxel (diterpenoid)	Fucoidan-stabilized; phospholipid-coated; inhalable lyophilized powder	Better flow and aerosolization; sustained release; higher lung retention; lower systemic exposure	Deep-lung delivery; local lung-cancer therapy; reduced solubilizer use	[7]
Piperine-glycyrrhizic acid (combined natural products)	Composite nanocrystals; Eudragit S100 coating; colon-targeted oral delivery	gastrointestinal (GI) stability; colon-triggered release; improved local co-delivery	Lower IL-1β/IL-17A; higher TGF-β1; M1 suppression/M2 promotion; mucosal repair	[8]
Quercetin (flavonoid)	Nanosuspensions: ~50, 140, and 360 nm	Solubility increased ~26-, 21-, and 13-fold; smaller size, stronger antioxidant effect	Lower reactive oxygen species (ROS)/lipid peroxidation; higher survival; small-size/high-dose safety concern	[9]
Silibinin (flavonolignan)	Albumin-coated; ~60 nm; 49.4% drug loading	Higher hepatic stellate cells (HSC) uptake; fibrotic-liver accumulation; improved bioavailability	SPARC-mediated active targeting; enhanced antifibrotic effect	[10]
Baicalin-berberine (flavonoid-alkaloid)	Composite nanocrystals; high-pressure homogenization; oral co-delivery	Higher dissolution and intestinal absorption; area under the drug concentration-time curve (AUC) increased ~7.49- and 2.64-fold	Co-absorption; synergistic delivery for compound traditional Chinese medicine (TCM) formulations	[11]
Resveratrol (polyphenol)	Nanocrystals in hyaluronic-acid dissolving microneedles; transdermal delivery	Bypass of GI barriers; improvement in transdermal delivery	Better rheumatoid-arthritis efficacy than that of oral dosing; nanocrystal-microneedle integration	[12]

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Note: AUC is the area under the drug concentration-time curve; SPARC stands for secreted protein acidic and rich in cysteine; IL is interleukin; and TGF-β1 is transforming growth factor β1. Cellulose nanocrystals are not listed in the table because they are natural nanomaterials and do not fall under the category of drug nanocrystals for improving the dissolution and absorption of poorly soluble active ingredients.

Silibinin is a flavonolignan that can inhibit fibrosis, but it has poor water solubility, low oral bioavailability, and limited hepatic distribution after oral administration, so it is not suitable for the treatment of liver fibrosis. Therefore, researchers have attempted to prepare silibinin nanocrystals to address these problems. Luo and others prepared albumin-coated silibinin nanocrystals with a particle size of about 60 nm and a drug-loading rate of 49.4%. Albumin on the surface of nanocrystals can bind to secreted protein acidic and rich in cysteine (SPARC), which is highly expressed by activated hepatic stellate cells. Thus, the albumin-coated nanocrystals are taken up and accumulate in fibrotic liver tissue, thereby increasing the bioavailability and antifibrotic effect of silibinin [10]. This study shows that protein surface modification can be used to achieve active targeting of natural-product nanocrystals

3.3. Other categories

Li and others prepared baicalin-berberine composite nanocrystals via high-pressure homogenization for an alkaloid-containing combination formulation. The nanocrystal formulation showed improved dissolution and intestinal absorption compared with the conventional complex, and the areas under the curve for the two components after oral administration were about 7.49-fold and 2.64-fold higher, respectively. Thus, nanocrystals help overcome the barrier to co-absorption of constituents in compound traditional Chinese medicine formulations [11]. Diao and others loaded resveratrol nanocrystals into hyaluronic acid-degradable microneedles to bypass the barrier to gastrointestinal absorption via transdermal delivery. The therapeutic effect in a model of rheumatoid arthritis was better than that of orally administered resveratrol [12].

Natural polysaccharides can also serve as nanocrystal materials. Zhu and others prepared rod-shaped cellulose nanocrystals from purple sweet potato peel residue by ultrasound-assisted maleic acid hydrolysis to provide a way for high-value use of agricultural waste [13]. However, such cellulose nanocrystals are natural nanomaterials and conceptually different from drug nanocrystals aimed at enhancing the dissolution of poorly soluble drugs. Therefore, they should be discussed separately in reviews. In short, nanocrystals have gone from being a way to enhance solubility to a platform for the co-delivery of multiple components, tissue targeting, and the construction of new drug delivery systems. However, their long-term stability, biosafety and large-scale production still need to be addressed (Table 1).

In short, the above cases show that nanocrystal technology can enhance the dissolution and oral absorption of various natural products, such as terpenoids, flavonoids, and alkaloids. However, due to differences in crystallinity, polarity and chemical stability, the above categories are affected differently by milling parameters, stabilizer types, and precipitation conditions and thus require targeted adjustments in process design. In recent years, research has moved beyond the scope of particle-size reduction and accelerated dissolution to explore various routes of administration, such as pulmonary inhalation, transdermal delivery, colon targeting and active hepatic targeting, and has also begun to investigate the potential of composite nanocrystals for synergistic multicomponent therapy. The above developments indicate that nanocrystals can be used as flexible platforms for natural product formulations. However, long-term storage stability and quality control during large-scale production still need to be systematically investigated.

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4. Limitations and challenges of nanocrystal formulation technology

Nanocrystal technology can be used to convert poorly soluble natural active ingredients into nanoscale crystalline particles. Thus, the specific surface area of the drug is significantly increased, and both saturation solubility and dissolution rate are improved to enhance drug absorption and bioavailability. Compared with carrier-based formulations such as liposomes and polymeric nanoparticles, drug nanocrystals are mainly composed of the active ingredient and a small amount of stabilizer, and have the advantages of high drug loading, low excipient requirements, relatively low preparation costs, and flexible routes of administration. Therefore, this technology is particularly suitable for poorly water-soluble terpenoids, flavonoids, alkaloids, and polyphenols that are not readily absorbed in vivo, and it provides a new technological route to improve their formulation performance and clinical utility.

Nanocrystal technology has many advantages, but it has not yet been widely applied to the production of natural-product-based formulations. First, natural extracts generally contain multiple structurally similar active components and impurities such as pigments, lipids and sugars. If the extract is used directly as the starting material, all the components may compete for nucleation and crystal growth through adsorption or co-precipitation, and it will be difficult to obtain high-purity nanocrystals with a uniform crystal structure. Different origins and collection areas, as well as different times of collection and processing for the natural raw materials, can also lead to batch-to-batch composition differences. Changes in the components of the solvent, temperature, shear force and drug concentration can also cause polymorphic transformation or amorphization of the drug, which affects its solubility, stability and bioavailability.

Secondly, nanocrystals have a high surface free energy and are thus more likely to be subject to sedimentation, aggregation and crystal growth over time. Small crystals may gradually dissolve and recrystallize on the surface of larger particles to form large crystals. Thus, the nanocrystals have a wider particle-size distribution, reduced redispersibility, and diminished dissolution advantages. Nanocrystals in the body are also subject to changes caused by plasma proteins, ionic strength, local pH and biological enzymes. Stabilizers may desorb from the crystal surface or be displaced by plasma proteins, which may lead to particle aggregation, premature dissolution, or altered tissue distribution. Therefore, the stability of nanocrystals should not be judged solely by short-term in vitro tests. Changes in particle size and crystal form after extended storage, freeze-thaw cycling, dilution and exposure to a physiological environment must also be comprehensively evaluated.

Process scale-up is another reason why natural-product nanocrystals have not been widely commercialized. At present, most studies remain at the laboratory scale. In the scale-up of methods such as wet media milling, high-pressure homogenization and antisolvent precipitation, it is difficult to replicate the energy density, mixing efficiency, residence time and temperature in the laboratory exactly. Thus, batch-to-batch variations in particle size, crystal form and stability are prone to occur. In addition, pharmacokinetic, tissue distribution and pharmacodynamic data for natural-product nanocrystals in animals are also lacking, and a clear connection between in vitro dissolution and in vivo absorption or efficacy has not been established. It is difficult to predict human outcomes and long-term safety.

To solve the above problems, future research could introduce smart stabilizers that are sensitive to pH, temperature, enzymes or redox conditions, thus keeping nanocrystals stable during storage and in the body, and releasing drugs at lesion sites. The production process can also be developed by using microfluidics, continuous crystallization and continuous milling, and online monitoring of particle size and crystal shape can be carried out to increase production efficiency and batch-to-

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batch consistency. Fluorescent probes or other imaging signals can be embedded in the crystal lattice so that researchers can observe the in vivo migration, dissolution and tissue distribution of intact nanocrystals. In addition, physiologically based pharmacokinetic (PBPK) predictive models can be developed that incorporate parameters such as nanocrystal dissolution, plasma-protein binding and tissue uptake and clearance to enhance the link among in vitro characteristics, animal pharmacokinetics and clinical efficacy.

In the future, the development of natural-product nanocrystals should move away from the narrow focus on reducing particle size and improving pharmacological effects in the short term. A multi-dimensional, systematic evaluation system that considers factors such as raw material variability, control over crystal shape, long-term stability, consistency during process scale-up, and biosafety should also be established. Only when the required formulation attributes are closely linked to in vivo absorption, distribution and excretion and multi-disciplinary approaches from materials science, pharmaceutical engineering and pharmacology are employed simultaneously can the current translational bottleneck be overcome and nanocrystal formulations gradually transition from laboratory research to clinical application [14].

5. Conclusion

Dissolution and absorption barriers affecting poorly soluble natural active constituents are common problems that limit the efficacy of their oral formulations. Nanocrystal technology uses the drug itself as the carrier, reduces its size to the nanoscale, and increases saturation solubility and dissolution rate, thus improving oral absorption, reducing the need for excipients, and increasing drug loading. Top-down processes, such as wet media milling and high-pressure homogenization, have a wide range of applications and a strong foundation for industrialization, but they are associated with high energy consumption, equipment wear, and potential contamination. Bottom-up processes, such as antisolvent precipitation, electrohydrodynamic atomization and spray drying, have good control over the particle size, crystal form and morphology, but they are subject to stricter requirements for solvent systems, mixing processes and drying conditions. In previous studies, nanocrystal technology has been applied to improve the formulation performance of various natural products, and its applications are now being extended in other ways, such as enhancing dissolution and bioavailability, co-delivering multiple components, targeting specific tissues, and enabling multi-route administration, for example pulmonary, colonic, and transdermal delivery.

Nevertheless, the complex composition and marked raw-material variability of natural products mean that their nanocrystal formulations face more pronounced challenges in constituent purity, uniformity of crystal form, and batch-to-batch consistency than formulations of single chemical drugs do. At the same time, particle aggregation, crystal growth, stabilizer desorption, and changes in the physiological environment may all affect long-term stability and in vivo behavior. Most existing studies remain at the laboratory or animal testing stage, and clear relationships among in vitro dissolution, in vivo absorption, and actual therapeutic effects have yet to be established. Future research should strengthen the standardization of natural raw materials and the control of critical quality attributes, develop combination processes, continuous manufacturing, and online monitoring technologies, and establish an evaluation system covering long-term storage, stability under physiological conditions, tissue distribution, and long-term safety. Only by integrating approaches from materials science, pharmaceutical engineering, pharmacokinetics, and pharmacology to further elucidate the relationships among nanocrystal material attributes, manufacturing processes, in vivo fate, and therapeutic effects can researchers improve the reproducibility and clinical predictive value

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of research findings and promote the steady translation of natural-product nanocrystal formulations from laboratory research to large-scale manufacturing and clinical application.

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