International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 16, Issue 6, 2024

Review Article

PHARMACEUTICAL NANOCRYSTALS: AN EXTENSIVE OVERVIEW

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Received: 05 Aug 2024, Revised and Accepted: 17 Sep 2024

ABSTRACT

In pharmaceutical development, pharmaceutical nanocrystals sized between 10 and 1000 nanometers have been found to hold promise in improving drug solubility. Since they comprise only the active pharmaceutical ingredient, nanocrystals have dramatically increased surface area-to-volume ratios, ensuring improved in vitro dissolution and solubility profiles.

In view of their strengths and limitations, different production strategies have been reviewed: methods of size reduction such as wet milling and high-pressure homogenization; the bottom-up approaches of controlled precipitation and supercritical fluid technology; and efficient ways to stabilize nanocrystal formulations aided by excipients like surfactants and polymers.

Techniques used in this characterization of nanocrystals include size analysis, surface-charge measurement, and assessment of crystalline structure. The routes of administration, such as oral, injectable, inhaled, and topical application, are reviewed alongside commercially successful products and clinical trials.

This work reviews dynamic regulatory scenarios and current challenges of large-scale production, long-term stability, and nanotoxicity evaluation. In addition, it addresses the emerging trends in nanocrystal technology in the field of personalized medicine, targeted drug delivery, and theranostic approaches associated with how nanocrystals can help optimize the outcome of a patient in drug delivery systems.

Keywords: Pharmaceutical nanocrystals, Drug delivery, Bioavailability enhancement, Nanotoxicity, Regulatory considerations, Stabilization strategies

DOI: https://dx.doi.org/10.22159/ijap.2024v16i6.52257 Journal homepage: https://innovareacademics.in/journals/index.php/ijap

INTRODUCTION

Nanocrystals are a stupendous development in pharmaceutical drug delivery, especially for poorly water-soluble drugs. These are nanosized particles, normally between 10 and 1000 nm in size, with the most common size being 100-300 nm, made purely of drug substances [1]. The concept came into being in the 1990s to solve poor bioavailability, which had become a significant issue for promising drug candidates [2]. This was very important because it is known that about 40% of approved drugs and 90% of drugs under development suffer from low water solubility [3].

Nanocrystals' efficiency is based on the fundamental laws of physics. When the size of particles decreases, the surface area-to-volume ratio increases, and, therefore, according to the Noyes-Whitney equation [4], dissolution rates increase. Increased solubility of sub-micrometer particles was explained by the Ostwald-Freundlich equation [5].

While other nanoparticle formulations contain excipients, nanocrystals contain the active drug substance only. This is a benefit that gives them an advantage over all other drug delivery forms in terms of the highly concentrated amount of a drug to be administered in small volumes, offering one main advantage for high-dose medicinal products [6].

The methods in nanocrystal production mainly rely on two approaches: one is top-down techniques, in which drug particles of larger size are brought down to the nanosize, and the other is the bottom-up technique, where the formation is from dissolved drug molecules in the form of nanoparticles. Again, each method has its own advantages and limitations [7].

Three nanocrystal drugs have now reached the market and include the following: Rapamune (sirolimus), Emend (aprepitant), and Tricor (fenofibrate), clearly signifying the practical feasibility of the nanocrystal formulations in the clinical [8].

Besides dissolution and absorption, nanocrystals show huge potential for both targeted drug delivery and controlled release, new administration routes like transdermal and pulmonary delivery, with enhancing developments increasing their scope of technology in many treatments [9]. With improved research in the field, the role of nanocrystals in drug delivery is expected to be even more significant in the future, especially with poorly soluble drugs.

Such progress may enable more effective treatments and new indications of old drugs.

These unique properties, in conjunction with their versatility in drug delivery and administration routes, make nanocrystals the powerful tool needed to combat the challenges from poorly water-soluble drugs. Thus, bioavailability enhancement can go hand in hand with targeted delivery, enabling new approaches for the formulation of drugs and for treatment strategies.

In a developing field, attention is also focused on the optimization of the production methods, improvement in stability, and extension in the spectrum of applications. Commercial successes with nanocrystal-based products have prepared the ground for the development, implementation, and widespread use of this technology in pharmaceutical research and clinical application.

Most of the nanocrystal technological developments are definitely going to play a vital role in drug delivery systems in the near future and would definitely change the face of treatments for many diseases and prove beneficial for patients.

The selections of articles for the present review were searched from specialized databases (Range of years: 2014-2024) such as Elsevier, Pubmed, and Cambridge using the keywords Nanocrystals, Nanotoxicity, and Regulatory consideration. Other selections include articles from Springer Wiley, information from Internet sources, and online published articles from The Lancet Respiratory Medicine, Medscape, and Statpearls.

Key features and benefits of drug nanocrystals in medicine

Nanocrystals of drugs offer several advantages during pharmaceutical development, particularly for those drugs with poor water solubility. The biggest benefits are based on increased dissolution rates and

enhanced solubility. Since the surface area-to-volume ratio is dramatically increased by rendering drug particles to nanosized levels, this results in increased dissolution rates, explained by the Noyes-Whitney equation. Thus, this will improve the absorption rate and pharmacokinetics. For particles less than 1 μ, this is explained using the Ostwald-Freundlich equation: saturation solubility rises very drastically for nanoparticles below 100 nm [5].

Such properties thus contribute to much-improved bioavailability, which would be especially useful for drugs in the BCS Class II and Class IV. The bioavailability may be enhanced several-fold over conventional formulations, hence improving therapeutic efficacy while allowing a dose reduction [6, 7].

Nanocrystal technology decreases the variability in absorption due to food intake and lowers the fed/fasted effect, providing more consistent drug exposure [8]. Nanocrystals in the size range of 50-300 nm offer passive targeting potential in tumors, especially through the so-called enhanced permeability and retention effect, opening perspectives for more effective cancer chemotherapy.

Such versatility makes nanocrystals administrable by other parenteral, pulmonary, and dermal administration routes other than oral. They have high drug loading capacity with minimal content of stabilizing agents-advantageous for high-dose medications. The physical and chemical stability of nanocrystal preparation is usually good because of its crystalline nature.

Controlled-release formulations with modulated nanocrystal properties, combined with suitable excipients, may lead to reduced dosing frequency and improved patient compliance. Production costs are often lower, especially for top-down techniques like wet milling or high-pressure homogenization [7-13].

It has been revealed that nanocrystal preparations provide better content homogeneity, which is particularly useful for low-dose products [14]. Although certain benefits might differ with the drug, preparation method, and application, such characteristics have established nanocrystals as a very promising approach for the development of poorly soluble drugs to achieve enhanced efficacy and improvement in the outcomes of treated patients.

Production methods for pharmaceutical nanocrystals

Pharmaceutical techniques for nanocrystal manufacturing can be broadly classified into two classes, each with rather different methodologies, benefits, and shortcomings: top-down and bottom-up.

Top-down approaches mostly go for the reduction of larger drug particles in size and thus are more attractive to the pharmaceutical industry. The most widely used technique includes media milling (wet milling), which, in turn, includes dispersing the drug in a liquid medium with stabilizers and treating it with high-energy milling using particular beads [7]. This represents a large-scale manufacturing method that produces particles below 100 nm and can be used for a variety of drug substances. There is; however, some potential risk for contamination from milling materials, and some probable amorphization of the drug may occur. Alkermes' NanoCrystal ® technology uses this process [15].

High-pressure homogenization is a process that forces a suspension under high pressure through a narrow gap [11]. This technique allows for both aqueous and nonaqueous media, amenable for mass production, with less contamination risk than media milling. On the other hand, it could require cycles to be repeated and tends to heat up during processing. The DissoCubes ® technology utilizes this process [2].

Bottom-up approaches form nanocrystals from dissolved drug molecules. In such approaches, finer and more uniform particles can be produced, but there are scaling difficulties. Precipitation methods imply the precipitation of a drug from a supersaturated solution [16]; they present lower energy demands but are associated with challenging particle size control. Variants include sonoprecipitation and evaporative precipitation [17, 18].

Supercritical fluid methods are primarily based on CO2 as a solvent or antisolvent [19]. They are environment-friendly but require drug solubility in supercritical CO2; at the same time, they have high equipment costs. The microemulsion method is based on templates of nanocrystals made by microemulsions [20]; in this way, small and uniform particles are prepared with low energy input, while the drug loading capacity is limited.

Table 1: Characterization techniques for pharmaceutical nanocrystals

Technique	Principle	Benefits	Drawbacks	Reference
Particle size analysis: Dynamic Light Scattering (DLS)	Measures Brownian motion of particles	Fast, Non-destructive, and Suitable for suspensions	Assumes spherical particles and Sensitive to large particles	[21]
Laser Diffraction	Measures scattered light intensity at different angles	Wide particle size range	Assumes spherical particles	[22]
Nanoparticle Tracking Analysis (NTA)	Tracks the motion of individual particles in real-time	Provides concentration data, and can identify aggregates	Low concentration at the bottom end, and Sample dilution required	[23]
Zeta potential measurements: Electrophoretic Light Scattering	Measures particle velocity in an electric field	Reflects suspension stability/surface charge	Temperature sensitive, pH-dependent	[24]
Morphology studies: Scanning Electron Microscopy (SEM)	Scans surface with focused electron beam	High-resolution and 3D-like images	Sample preparation may affect morphology and requires a vacuum	[25]
Transmission Electron Microscopy (TEM)	The electron beam passes through the ultra-thin sample	Very high resolution and reveals internal structure	Complex sample preparation, 2D projections	[26]
Atomic Force Microscopy (AFM)	Mechanical probe scans surface	3D topography can be measured in liquid	Slow scanning, tip artifacts	[27]
Crystallinity analysis: X-ray diffraction (XRD)	Measures X-ray diffraction by crystal lattice	Confirms crystalline state and Identifies polymorphs	Challenging for very small crystals, difficult amorphous content quantification	[28]
Differential Scanning Calorimetry (DSC)	Measures heat flow differences during heating/cooling	Detects melting point, glass transition, crystallization, and quantify amorphous content	Low sensitivity for small samples, Risk of sample degradation during heating	[29]
Surface area analysis: Brunauer-Emmett-Teller (BET) Method	Measures gas adsorption on the particle surface	Quantifies specific surface area	Requires dry samples	[30]
Dissolution testing: *In vitro* Dissolution Studies	Quantifies drug release over time in simulated conditions	Predicts *in vivo* performance and quality control	Choice of dissolution medium, maintaining sink condition	[31]
Chemical composition and purity: High-Performance Liquid Chromatography (HPLC)	Separates and quantifies components	Quantifies drug content and detects impurities, High sensitivity and specificity	Lack of structural information, Limited size range, and Aggregation risk	[32]
Stability studies: Accelerated Stability Testing	Subject samples to stress conditions	Predicts long-term stability and Determines shelf life	Choice of conditions and Packaging considerations	[33]
Advanced techniques: Small-angle X-ray Scattering (SAXS)	Analyzes X-ray scattering at very low angles	Can measure in suspension and Provides size distribution	Complex data interpretation	[34]
Raman Spectroscopy	Measures inelastic scattering of monochromatic light	Non-destructive Can detect polymorphs and crystallinity	Weak signal, Fluorescence interference	[35]

The combination of top-down and bottom-up techniques shall optimize the production of nanocrystals. Techniques such as Smart Crystal [8] will give smaller particles, hence reducing processing time and energy consumption.

The choice of the production method will, therefore be based on the physicochemical properties of the drug, desired characteristics of the particles, scalability needs, and production economics.

Components of pharmaceutical nanocrystals

Nanocrystals in the pharmaceutical field are normally 10-1000 nm in dimension and include a new, promising delivery system of drugs. The major constituents of these formulations are surfactants and polymers acting as stabilizers.

Surfactants are either ionic, like sodium dodecyl sulphate, or non-ionic, like Tween 80 and Pluronic F68. Ionic surfactants provide electrostatic stabilization but are sensitive to changes in electrolyte and pH [36]. Non-ionic surfactants provide steric stabilization, which is much less affected by environmental factors; however, they may need to be used at higher concentrations [37].

These polymers contribute steric stabilization and additional functionalities. On their own, the cellulose derivatives Hydroxypropyl Methylcellulose (HPMC) and Hydroxypropylcellulose (HPC) demonstrated good nanoparticle stabilization, with HPMC actually improving dissolution rates [7]. Polyvinylpyrrolidone (PVP) showed some extent of stabilization and even a potential inhibition of crystal growth, but it might have an impact on the stability of the formulations due to its hygroscopic nature [14]. Polyethylene plastics (PEG) bring about biocompatibility and extended *in vivo* circulation; however, its efficacy is molecular weight-dependent [38].

These components will thus differently participate in the stability, functionality, and bioavailability of pharmaceutical nanocrystals, rendering it a very effective drug delivery system.

Stabilization strategies for pharmaceutical nanocrystals

Effective stabilization is one of the most important requisites of nanocrystal formulations for avoidance of aggregation, maintenance of the desired size, and long-term stability. Stabilization approaches basically can be divided into two major types: combination strategies and new-age techniques.

Combinations of stabilizers often result in increased stability. Polymer-surfactant combinations can provide both steric and electrostatic stability; careful balancing may be required [39]. Combinations like Sodium Dodecyl Sulphate (SDS) with poloxamer 188, and ionic-nonionic surfactant combinations, offer stability over a wide range but may have the disadvantage of competitive adsorption issues [40].

The newer age stabilization strategies include the technologies of layer-by-layer coating and lipid coating. However, in layer-by-layer coating, the oppositely charged polyelectrolytes are adsorbed successively, providing added functionality of sustained release, but at the cost of complicating the process and causing retardation in dissolution [41]. Although lipid coating may enhance oral absorption and improve targeting, it is believed that it reduces the dissolution rate [10].

Several factors should be considered to achieve proper stabilization. For electrostatic stabilization, zeta potential should be more than |30 mV| and should be checked periodically [42]. The surfactant concentration should generally be higher than the Critical micelle concentration (CMC), considering the effects of drug solubility [5]. Ostwald ripening can be inhibited by the slightly soluble stabilizers where the effect of those on drug solubility should be monitored properly [43].

Processing conditions are important since the high energy applied in some processes can degrade or destroy the stabilizers. Checks should be made on the thermal stability after high-pressure homogenization [2]. Long-time stability studies at different storage conditions should be performed in relation to the role of these stabilizers on the glass transition temperature for the dried formulations [12].

Finally, regulatory considerations are important, and innovative stabilizers likely will require more safety data. Regulatory status, like generally recognized as safe (GRAS) or inclusion in a pharmacopeia, should be a consideration for the selection of the stabilizer [15].

The right stabilization strategy would hence be selected based on the physicochemical properties of the drug, manufacturing process, route of administration, and target product profile. Optimization typically requires a combination of approaches to achieve both stability and performance.

This means that effective stabilization of nanocrystal formulations comes out as the result of a highly complex interplay of aspects and techniques. Different facets of such mastering form the ground for the development of stable, efficient, and regulatory-compliant nanocrystal-based drug delivery systems.

Applications of nanocrystals in drug delivery

Such pharmacological nanocrystals bear a high degree of versatility in terms of administration routes and a wide spectrum of therapeutic areas. Their applications in drug delivery are manifold and full of promise:

Oral delivery is the most frequent application and increases the bioavailability of poorly soluble drugs [6, 109]. Immediate-release formulations, for example, Rapamune ® and Emend ®, provide an increased dissolution rate and bioavailability for immunosuppressants and antiemetics respectively [9]. Modified release formulations are possible by a combination of nanocrystals with polymers or matrix systems and lead to controlled release in, for example, the treatment of chronic diseases [10]. Gastroretentive systems provided by mucoadhesive nanocrystal formulations prolong the residence time in the stomach and increase drug absorption [44].

Based on this, the parenteral administration can be broadly classified into intravenous and intramuscular [8]. The intravenous administration allows the infusion of smaller volumes and avoids toxic cosolvents present in PaxceedTM for metastatic breast cancer [45]. Intramuscular administration facilitates the formation and sustained release of drug depots, just like Invega SustennaR for antipsychotic treatment [46, 108].

Pulmonary delivery improves the efficacy of inhaled medications [47]. Dry powder inhalers with nanocrystals embedded in microparticles increase lung deposition and dissolution [48]. Nebulized formulations enhance the local concentration and provide for systemic delivery [49].

Dermal and transdermal applications enhance skin penetration and allow localized drug action [50]. Topical formulations for the treatment of psoriasis, such as Neoral, provide higher skin penetration [51], whereas transdermal delivery techniques allow increased permeation for systemic delivery [52].

Oculary delivery increases the bioavailability and residence time [53]. Topical ophthalmic formulations increase the corneal permeation as evidenced by the BromSite post-operative inflammation [54]. Intravitreal delivery maintains the level of drugs within the eye and reduces the frequency of injections [55].

Targeted drug delivery thus can be based upon surface-engineered nanocrystals [56]. Passive targeting is typically exploited for the Electron paramagnetic resonance (EPR) phenomenon for the management of solid tumors with the aid of Theralux™ by IDEXX [57]. By active targeting, we mean that the addition of targeted elements that are conjugated to nano-crystal surfaces produces enhancements in cellular intake [58].

Combination products have fixed-dose combinations for better compliance and synergistic effects [59, 60] and theranostics combine diagnosis and treatment [61].

Nanocrystal delivery of a vaccine can increase the immune response to antigens especially subunit vaccines by giving them enhanced stability and increasing cellular uptake [62, 63].

It is a fledgling area of development that continuously gives rise to new techniques and technologies for formulation, with flexibility across diversified routes of dosing and therapeutic areas.

Commercial products and clinical studies of pharmaceutical nanocrystals

Several drugs have been developed using this approach to the point where they are in commercial use demonstrating proof of concept [9] (table 2). There are several nanocrystal-based formulations currently under clinical evaluation (table 3). Since the field is developing and research is presently in the stage of overcoming traditional issues associated with pharmaceutical nanocrystals, newer applications are being looked upon. This drug delivery technology is likely to remain upbeat due to the success of marketed products and encouraging results of several molecules under clinical trials (table 4).

Table 2: Marketed nanocrystal-based products

Product name	Generic name	Manufacturer	Use	Technology	Benefits	Reference
Rapamune®	Sirolimus	Pfizer (originally Wyeth)	Prevents rejection of transplanted organs	Elan's NanoCrystal®	Improved uptake (tablet form rather than liquid).	[64]
Emend®	Aprepitant	Merck	Treats chemotherapy-induced nausea	Elan's NanoCrystal®	More food independent, better absorption.	[65]
Tricor®	Fenofibrate	AbbVie	Reduces blood lipids	Elan's NanoCrystal®	Less food effect, lower doses required.	[6]
Megace ES®	Megestrol acetate	Par Pharmaceutical	Appetite stimulation in AIDS patients	Elan's NanoCrystal®	Smaller volume per dose, increased absorption.	[66]
Invega Sustenna®	Paliperidone palmitate	Janssen Pharmaceuticals	Schizophrenia and related disorders	Elan's NanoCrystal®	Long-acting injectable form improved the drug's behavior in the organism.	[67]
Ryanodex®	Dantrolene sodium	Eagle Pharmaceuticals	Malignant hyperthermia	SkyePharma's IDD-P®	Short preparation time, smaller infusion.	[2]

Table 3: Clinical studies and pipeline products

Product name	Developer	Intended use	Progress	Benefits	Reference
SUBA™-Itraconazole	Hedgepath Pharmaceuticals	Basal cell carcinoma nevus syndrome	Complete Phase 2b trial	Improved bioavailability of itraconazole for cancer therapy.	[68]
Theralux™ (thymectacin)	Celmed BioSciences	Solid tumors	Phase 2 trial	Better tumor targeting and lesser general toxicity.	[57]
Paxceed™ (paclitaxel)	Angiotech Pharmaceuticals (now Argon Medical Devices)	Rheumatoid arthritis	Phase 3 trials (abandoned)	Reduced toxicity and ability to be administered orally.	[69]
NKTR-181	Nektar Therapeutics	Chronic axial (lower back) pain	Phase 3 completed (not FDA approved)	Novel opioids with minimal abuse liability.	[70]
Docetaxel-NC	Samyang Biopharmaceuticals	Various cancers	Phase 2 trials	Improved solubility potential for oral dosing.	[10]

Table 4: Ongoing research and future prospects

Research area	Focus	Potential uses	Benefits	Reference
Combination Products	Development of nanocrystals with several drugs	HIV therapy, cardiovascular diseases	Improved patient compliance, potential synergistic effects [71].	[71]
Targeted Nanocrystals	Surface engineering with nanocrystals for targeted delivery	Cancer treatment, inflammatory disorders	Enhanced efficacy and reduced side effects [72].	[72]
Nanocrystals for Non-Oral Routes	Nanocrystal development for lung, skin, and eye delivery	Respiratory, skin, and eye diseases	Local delivery minimized systemic exposure [8].	[8]
Theranostic Nanocrystals	Merging of treatment and diagnostic capabilities	Cancer therapy, personalized medicine	Simultaneous imaging and drug delivery [61].	[61]

Regulatory considerations for pharmaceutical nanocrystals

Along with the increasing technological capability comes the related regulatory landscape associated with nanocrystal-based pharmaceuticals. Global regulators develop guidelines to provide for safety and efficacy in the context of such rapid innovation.

The U. S. Food and Drug Administration has led in the development of a regulatory framework for products based on nanotechnology [73]. Their definition encompasses products from 1 nm to 100 nm, or up to 1000 nm for size-related properties, thus covering pharmaceutical nanocrystals [75]. Material analysis, production process, physical and chemical characteristics, and biological behavior have been pointed out as key issues for the regulation of such materials [76]. Nanocrystal formulations of existing drugs are processed as the 505(b) (2) pathway, while new chemical entities in nanocrystal form will be processed as a New Drug Application [11].

Several of the various regulatory problems on nanomedicines, including nanocrystals, have been addressed by the European Medicines Agency [74]. These reflection papers refer to the development of nanomedicines in relation to environmental risk assessment and data requirements for nanoparticle products administered intravenously [77]. The key areas of focus that are targeted are physical and chemical characterization, non-clinical studies, clinical development, and quality with manufacturing [78].

The International Council for Harmonisation (ICH) develops internationally applicable guidelines that are important for nanocrystal formulations and includes those on impurities,

specifications, pharmaceutical development, quality risk management, and pharmaceutical quality systems [12, 79].

Nanocrystals-specific regulatory considerations include characterization of particle size by using multiple analytic methods [80], adaptation of methods for dissolution testing [81], long-term stability studies [12], total description and validation of manufacturing processes [13], bioequivalence for generic products [82], safety aspects including the toxicological impact at nanoscale [83].

Global harmonization efforts in regulation are on their way, such as the International Pharmaceutical Regulators Programme Nanomedicines Working Group [84] or the development of International Organization of Standardization (ISO) standards for the characterization of nanoparticles [85].

Some of the regulatory challenges that lie ahead include pathways for nanocrystal-based combination products [86], new uses for nanocrystals in targeted delivery and theranostics [61], and frameworks to evaluate long-term safety and potential environmental impact [87].

In the final analysis, pharmaceutical nanocrystals are still subject to regulatory changes. Broadly speaking, manufacturers should initiate early and several reviews with the regulatory agencies regarding compliance, smoothness, and acceleration of approval procedures. With many nanocrystal-based products coming into the market, it is hoped that the regulatory frameworks will become more mature and focused.

Key focus areas involve dimension, distribution, morphology, and surface properties of the material. The manufacturing process, homogeneity, and scale-up are quite crucial in ensuring quality and consistency. Physical and chemical properties, including solubility and dissolution rate, have a great impact on the bioavailability of the product and its overall effectiveness. Lastly, the biological behavior of the material, such as pharmacokinetics and biodistribution, is helpful in forecasting therapeutic outcomes and profiles of safety.

This involves validation of manufacturing processes, identification of critical process parameters, and reproducibility in order to meet regulatory requirements. Extended *in vivo* bioequivalence studies under various conditions, such as food effect studies, are vital for the establishment of stability and performance of the product in case of various eventualities. Long-term stability studies would also be important, as over a period of time, altered distribution and potential nanotoxicity may be observed. Finally, other critical issues include safety concerns regarding cellular uptake and any possible environmental impacts, which need to be analyzed in detail to minimize risks resulting from the use of the product.

It is, therefore, expected that with new applications and combination products, and in establishing the long-term safety concerns associated with nanocrystal-based pharmaceuticals, the challenges to regulatory agencies will further increase as the field continues to evolve.

Challenges and Future Perspectives

Nanocrystal formulations raise a number of challenges in scale-up, long-term stability, nanotoxicity, and personalized medicine applications. Scale-up problems include a decrease in the uniformity of the particles' size [88], a rise in heat generation [89], and significant investment in equipment is needed [9]. Process parameters mostly vary significantly between the laboratory and industrial scales during translation, so substantial adjustment could be required [14]. New continuous manufacturing, innovative milling techniques [72], and quality-by-design approaches will be future perspectives to overcome these challenges.

Such issues of long-term stability include particle aggregation [12], Ostwald ripening [91], drug degradation [92], and efficiency of different classes of stabilizers [37]. To deal with these problems, improved methods of stabilization [10] are being developed, and surface engineering strategies [1] are already in use, along with predictive models of stability [93] and new developments in freeze-drying techniques [94].

It has a nanotoxicity potential due to modified drug distribution [95], unique cellular interactions [96], and unknown long-term effects [87]. Further complicating the assessment of toxicity is a lack of standardized testing protocols [97]. In this respect, future prospects include the development of advanced in vitro models [98], computational prediction methods [99], and genetic toxicity assessments, with the establishment of safety guidelines [101].

Specialized applications in personalized medicine bring about development challenges for individual-specific formulations [102], rapid small-batch production [15], multi-drug loading [59], and diagnostic/therapeutic function integration [103]. The prospects of this area include additive manufacturing [104], genetic personalization [105], responsive delivery systems [106], and point-of-care production [107].

Continuous production methods may guarantee more consistency in the overcoming of scale-up issues [90]. New milling technologies are under development for large-scale nanocrystal production, and quality-by-design approaches should guarantee consistent quality across the different scales [36].

Improvement in long-term stability will need the development of more active and efficient stabilizers, notably multi-component formulations [10]. Surface engineering strategies are currently being investigated to improve stability [1], and predictive models are under development for long-term stability from data of short-term experiments [93].

It will be very important to establish better testing models that will most closely approximate the *in vivo* situation to address nanotoxicity concerns [98]. Computational prediction methods [99] and genomic and proteomic techniques [100] are under study for their potential to give insight into the mechanisms of nanotoxicity.

In this respect, future prospects include 3D printing of bespoke nanocrystal formulations [104], incorporation of genetic information in formulation design [105], and responsive delivery systems that adapt to patient characteristics [106]. Point-of-care production systems are developed to manufacture personalized nanocrystal formulations [107].

These developments are targeted to overcome the present limitations, thereby opening a broader scope of application for nanocrystal formulations in drug delivery and personalized medicine.

DISCUSSION

Pharmaceutical nanocrystals are thus one of the most promising approaches in formulating low-solubility drugs: they enhance bioavailability and steep dose-response relationships, demonstrating reduced food effects on absorption. The successes among commercial products such as Rapamune®, Emend®, and Tricor® have proved the validity of nanocrystal formulations at the clinical level [7]. Nanocrystals have a variety of administration options: oral, parenteral, pulmonary, dermal, and ocular applications, which give totally new prospects for drug delivery [11].

Manufacturing processes can be segregated into top-down and bottom-up processes. Among them, top-down approaches like media milling and high-pressure homogenization are used industrially in continuous manufacturing because of their scalability issues and homogeneous properties seen in the product [11]. However, it suffers from a lack of control over the particle size when scaled up and heat generation problems [88, 89]. The bottom-up process produces smaller and more homogeneous particles but has dimension control problems in the particles and issues with scale-up.

Stabilization remains central in nanocrystal development. Several approaches using surfactants, polymers, and layer-by-layer coating have been previously studied [12, 36, 37, 41]. Future studies must, therefore, focus on finding better stabilizers and the use of multiple-component stabilizations for long-term stability.

The regulatory landscape for nanocrystal-based pharmaceuticals is shifting. Food and Drug Administration (FDA) and European Medicines Agency (EMA) guidelines deal with the development and evaluation of nanomedicine products [73, 74]. Critical concerns include the characterization of particle size, long-term stability

demonstration, and nanotoxicity assessment [75, 76, 83]. When this field continues to progress, so will regulatory frameworks with respect to newer applications in the areas of personalized medicine and theranostics.

Nanocrystal technology contributes to drug delivery and extends medical applications of established and new treatments in a wide range of administration routes.

CONCLUSION

Nanocrystal technology has achieved greater potential in addressing the solubility issues associated with poorly aqueous soluble drugs. This technology shall be utilized for various routes of administration to improve the bioavailability and enhanced efficacy of drugs. However, many issues are taken into consideration such as scaling up technology, long-term stability and assessment of toxicity. Apart from these, regulatory frameworks are essential to evaluate and approve nanocrystal-based formulation in the field of drug targeting, combination therapy, and personalized medicine which would be expected to improve patient outcomes for the management and treatment of diseases.

ACKNOWLEDGEMENT

The authors would like to thank the Department of Science and Technology-Fund for Improvement of Science and Technology Infrastructure (DST-FIST) and Promotion of University Research and ScientificExcellence (DST-PURSE) and Department of Biotechnology-Boost to University Interdisciplinary Life ScienceDepartments for Education andResearch program (DBT-BUILDER) for the facilities provided in our department.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

Gurubaran Sivanathan: Literature review, Data curation, Writing-original draft, and Evaluation; Sanjai Rajagopal: Literature review, Data curation, and Writing-original draft; Giridhara Mahadevaswamy: Writing-original draft, Conceptualization, Critical Evaluation; Gowtham Angamuthu: Writing-original draft, Conceptualization, Critical Evaluation; Nagasamy Venkatesh Dhandapani: Review and editing, Supervision, Evaluation, Visualization.

CONFLICTS OF INTERESTS

The authors declare no conflict of interest

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