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Review Article

Optimizing pulmonary treatments with nanocrystals: Current status and future prospects

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Abstract

Pulmonary diseases, including chronic obstructive pulmonary disease (COPD), pulmonary arterial hypertension (PAH), asthma, lung cancer, and cystic fibrosis, remain a global health concern due to the limitations of conventional therapeutic approaches, such as poor bioavailability, systemic side effects, and inefficient drug targeting. Nanocrystals have emerged as a transformative approach to optimize pulmonary drug delivery due to their ability to enhance solubility, increase drug absorption, and facilitate targeted delivery. This review provides a comprehensive analysis of the current advancements and future directions in the use of nanocrystals for pulmonary treatments. Key formulation methods, including high-pressure homogenization, antisolvent precipitation, and spray drying, are discussed, along with their application in developing inhalable drug delivery systems such as dry powder inhalers (DPIs) and nebulizers. The advantages of nanocrystals in overcoming challenges associated with conventional therapies, including their potential for controlled drug release, enhanced stability, and improved patient compliance, are highlighted. By synthesizing recent developments, this review aims to provide insights into the potential of nanocrystals to revolutionize pulmonary treatments and guide future research directions.

Keywords: Pulmonary diseases, Nanocrystals, COPD, Lung cancer, Bioavailability, Inhalable formulations, Dry powder inhalers (DPIs).

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1. Introduction

Pulmonary diseases are a major global health problem because the lungs are highly vulnerable to infections and damage from environmental factors. Issues like rising air pollution, tobacco use, occupational hazards, aging populations, and lifestyle changes have led to an increase in the number of people affected by lung diseases each year.[1,2] These diseases can be caused by air pollution, genetic factors, or infections from viruses and bacteria. Airborne pathogens can easily infect the lower respiratory system, leading to serious conditions such as acute respiratory infections.[3-5] Examples include recent and past outbreaks caused by viruses like COVID-19, SARS, MERS, and avian influenza. Chronic respiratory diseases, such as asthma, COPD, cystic fibrosis, hay fever, and lung cancer, are also worsened by environmental factors. With the growing impact of these diseases, there is an urgent need to find new treatments that are tailored to the structure and function of the lungs to better prevent and manage these conditions.[6] Pulmonary drug delivery system (PDDS) research and development has received a lot of attention lately in an effort to alleviate the rising burden of lung diseases. The capacity to maintain high drug concentrations in the lungs to promote therapeutic efficacy, controlled drug release, less systemic side effects, tailored delivery for localized treatment, and enhanced patient compliance are just a few advantages of PDDS.[7,8] Despite these advantages, drug delivery to the lungs efficiently comes with a number of difficulties. The mechanical, chemical, and immunological defenses of the respiratory tract, which either block inhaled medication particles from entering the lungs or aid in their removal after deposition, are the main challenges.[9,10]

Many approaches have been developed and patented to address these issues. One interesting option among these is

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the use of nanostructured carriers, like nanocrystals.[8,11-13] Because of their small size and high surface-to-volume ratio, nanocrystals assist prevent quick lung clearance and allow for effective drug absorption via the lung epithelium. A novel and successful strategy for maximizing pulmonary drug delivery, nanocrystals can also improve cellular absorption, increase drug stability and solubility, and reduce any potential toxic effects.[14] Nanocrystals are nanoscale solid particles of a drug that typically range in size from 1 to 1000 nanometers. These particles are composed of the pure drug substance and are characterized by their simple structure and composition. Due to their small size and large surface area, nanocrystals offer enhanced solubility, stability, and bioavailability compared to conventional drug forms. They are used in various therapeutic applications, including oral,[15] dermal,[16] pulmonary,[17] and systemic drug delivery,[18] as well as for targeted therapies[19] and intraperitoneal chemotherapy.[20] The simplicity and versatility of nanocrystals make them a promising tool in the pharmaceutical industry for improving the effectiveness and safety of drug treatments.

2. Fundamentals of Nanocrystals

The size reduction of drug particles leads to an increased surface area, resulting in a faster dissolution rate. Therefore, micronization is an effective method to enhance the bioavailability of drugs where dissolution is the rate-limiting step. Further reducing particle size to the nanoscale (nanonization) significantly increases the surface area and further improves dissolution velocity.[21,22] Nanocrystals, with sizes below 1000 nm, exhibit enhanced saturation solubility, which increases as particle size decreases. Drug nanocrystals typically have sizes below 1 µm, optimizing their dissolution and absorption properties. Nanocrystals are composed of 100% drug substance without the need for a carrier matrix, maximizing drug loading. Stabilizers are generally required to maintain the stability of nanocrystals and prevent aggregation during processing and storage.[23,24] Nanocrystals can exist in either a crystalline or an amorphous structure, depending on the drug and preparation method. The use of nanocrystals significantly improves the dissolution velocity of poorly water-soluble drugs. Nanocrystals enhance saturation solubility, enabling better therapeutic performance for drugs with low water solubility.[16]

The **Figure 1** illustrates polymeric nanoparticles, nano emulsions, solid lipid nanoparticles (SLN), and nanostructured lipid carriers (NLC) are all matrix-based particles, while drug nanocrystals are distinct in their composition. SLNs are made entirely of solid lipids, while NLCs are a mix of solid and liquid lipids, but both remain solid at body temperature. In matrix particles, the drug is either distributed throughout the matrix or adsorbed onto the surface. In contrast, drug nanocrystals are composed entirely of the drug, with no additional matrix material.[25]

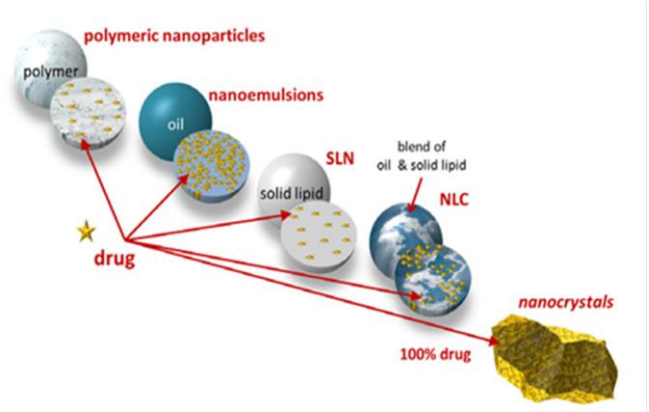

Figure 1: Composition of different nanocarriers

3. Nanocrystal Preparation Methods

Today, the implemented preparation methods **(Figure 2)** of nanocrystal formulations can be classified as “bottom-up,” “top-down,” “top-down and bottom-up,” and “spray drying.” “Bottom-up” technology begins with the molecule; the active drug substance is dissolved by adding an organic solvent, and the solvent is then removed through precipitation. “Top-down” technology applies dispersing methods using different types of milling and homogenization techniques. “Top-down” technology is more popular than “bottom-up” technology and is commonly referred to as “nanosizing.” In other words, it is a process that breaks down large crystalline particles into smaller pieces. In “top-down and bottom-up” technology, both methods are utilized together. Spray drying is also a method for preparing drug nanocrystals, offering a faster and more practical approach compared to other methods.[26]

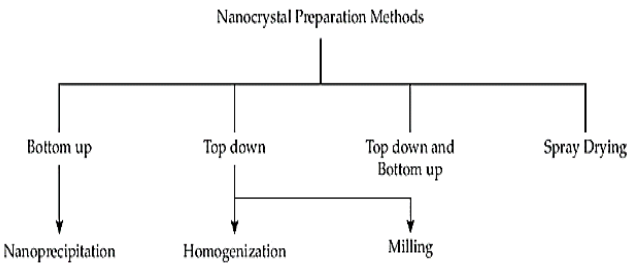

Figure 2: Preparation methods of drug nanocrystals

3.1. Top-down technology

"Top-down" technology utilizes various grinding and homogenization techniques for dispersion methods. This approach, more commonly used than the "bottom-up" technology, involves breaking large crystal particles into smaller fragments. Top-down technology can be implemented through homogenization or milling processes.[27]

3.2. Homogenization

High-pressure homogenization has been widely used for many years in various industries to produce emulsions and suspensions. A key advantage of this technology is its scalability, making it suitable for processing even very large

volumes. In the food industry, for example, it is used for milk homogenization, while in the pharmaceutical industry, it is employed for the production of parenteral emulsions. For drug nanosuspensions, typical pressures range from 1000 to 1500 bar (100–150 MPa, 14,504–21,756 psi), with the number of homogenization cycles varying between 10 and 20, depending on the drug's properties. Most homogenizers operate on the piston-gap principle, although jet-stream technology is also an alternative.[28]

The Microfluidizer (Microfluidics TM Inc., USA) uses the jet-stream principle, where two liquid streams collide to reduce droplet or crystal size, mainly through particle collision, with some cavitation occurring. It has been used for producing drug nanosuspensions, but the process typically requires 10 to 50 cycles, which is not ideal for large-scale production. The Microfluidizer is suitable for soft drugs; however, for harder drugs, some particles remain too large (in the micrometer range) to achieve the desired increase in saturation solubility.[29]

A piston-gap homogenizer forces liquid through a narrow gap, typically 5-20 mm wide, depending on the pressure and the dispersion medium's viscosity. The process involves a piston pushing the liquid at pressures between 100 and 1500 bar. As the liquid moves through the gap, its velocity increases while the static pressure drops, causing water to boil and form gas bubbles. When the liquid exits the gap and pressure returns to normal, the bubbles collapse, creating shock waves. These shock waves help break droplets or disintegrate crystals, effectively reducing particle size.[30]

3.3. Milling machine process

Classic Nanocrystal® technology uses ball or bead mills to reduce drug particle size. This method has been used since the early 20th century to produce fine suspensions. In this process, the grinding chamber is filled with grinding media (such as beads), a dispersion medium (usually water), stabilizers, and the drug. The movement of the grinding beads creates impact and shear forces that reduce particle size. This is a low-energy method compared to high-pressure homogenization. The grinding beads can be made from materials like ceramic, stainless steel, glass, or coated polystyrene to minimize contamination caused by bead erosion. However, some challenges include contamination from bead wear and the product sticking inside the mill. The grinding process can involve either stirring the grinding material with an agitator or moving the entire container in complex patterns. Usually, 76% of the grinding chamber is filled with beads, which makes it hard to process large batches. To scale up, multiple mills are often used. Grinding time can vary from 30 minutes to several hours or days, depending on factors like the drug's hardness, viscosity, stabilizer content, temperature, and bead size.[31]

3.4. Bottom-up technology

This method works by dissolving the active drug substance in an organic solvent, which is then added to a nonsolvent that is miscible with the organic solvent. In the presence of stabilizers, nanocrystals are formed through precipitation. The main advantages of this technique are its simplicity, low cost, and ease of scaling up. However, several parameters must be carefully controlled to produce uniform nanocrystals. These include the stirring rate, temperature, solvent-to-nonsolvent ratio, drug concentration, viscosity, type of solvent, and stabilizer.[32]

3.5. Top down and bottom-up technology

In "top-down and bottom-up" technology, both methods are integrated to achieve desired results. An example of a product developed using this combination is NanoEdge. In this approach, precipitation is typically followed by high-pressure homogenization, combining the strengths of both techniques for enhanced nanocrystal production.[27]

3.6. Nanoedge technology

Baxter's NANOEDGE® process combines microprecipitation with an annealing step using high shear or thermal energy. The process begins by adding an organic solution of a water-insoluble drug to an antisolvent, such as an aqueous surfactant solution, to form a fine suspension.[33] Depending on the precipitation conditions, the particles formed can be small amorphous or crystalline drug particles in the nanometer range or larger, friable needle-like crystals in the micrometer range. The subsequent energy input has two effects: small particles are stabilized in size by annealing, preventing growth, while larger needle-like crystals are broken down into smaller particles using high-pressure homogenization. This method produces drug particles ranging from 400 to 2000 nm in size. However, care must be taken to completely remove the organic solvent from the nanosuspension to prevent particle growth (Ostwald ripening) and toxic solvent residues. The NANOEDGE® process is particularly effective for drugs soluble in non-toxic, nonaqueous solvents like N-methyl-2-pyrrolidinone.

3.7. Spray drying

For tablet production, an aqueous nanosuspension can be used as a granulation fluid, or a dry form of the nanosuspension, such as powder or granulate, can be employed. The process begins with an aqueous macrosuspension containing the original coarse drug powder, surfactant, and water-soluble excipient. Homogenization can then be performed in a single step to yield a fine aqueous nanosuspension. To obtain a dry powder, the water needs to be removed from the suspension. Freeze drying is one method, but it is complex, costly, and results in a highly sensitive product.[34] A simpler and more suitable method for industrial production is spray drying. The drug nanosuspension can be directly produced by high-pressure

homogenization in aqueous solutions of water-soluble matrix materials, such as polymers (PVP, polyvinyl alcohol, or long-chained PEG), sugars (sucrose, lactose), or sugar alcohols (mannitol, sorbitol). The resulting aqueous drug nanosuspension can then be spray-dried under appropriate conditions, producing a dry powder with drug nanocrystals embedded in a water-soluble matrix. The **Table 1** illustrates the different evaluation parametrs for nanocrystals formulations.

Table 1: Various methods of characterization of nanocrystals formulations

S. No.	Category	Characterization method	Principle	Information	References
1.	Size and morphology	Dynamic light scattering (photon correlation spectroscopy)	Fluctuation of Rayleigh scattering of light associated with Brownian motion of nanoparticles	Particle size, particle size distribution	35
		Scanning electron microscopy (SEM)	Backscattering of electrons	Topographical information about particles	36
		Transmission Electron microscopy	Transmission of electrons	Density information	37
2.	Solid state forms	X-ray powder diffraction (XRPD)	Diffraction of x-rays from lattice planes	Polymorphic form (unique diffraction peaks), amorphous form (no peaks)	38
		Differential scan -ning calorimetry (DSC	Change in heat flow due to sample changes during heat/cooling	Polymorphic form (melting temperature, Crystallization temperature) Amorphous form (glass transition temperature), crystallinity (enthalpy of fusion, enthalpy of crystallisation)	39
		Infrared (IR) spectroscopy (mid IR spectroscopy)	Change in dipole moment during molecular vibrations	Polymorphic form (peak shifts and relative intensities), crystallinity (broadening of bands, peak shifts and rela3.tive intensities)	40
		Raman spectroscopy	Change in polarizability during molecular vibrations	Polymorphic form, crystallinity	41
3.	Surface properties	Zeta-potential	Dynamic electrophoretic mobility under electric field	Surface charge (zeta potential)	42
		Surface plasmon resonance (SPR)	Changes in refractive index in the vicinity of a planar sensor surface	Surface adsorption	43
4.	Drug delivery	Dissolution testing	Dissolved drug analysed over time, usually using UV spectroscopy or HPLC	Dissolution profile	40
		Fluorescence microscopy	Fluorescence by endogenous or added fluorophores	Localization of nanocrystals in relation to cells and tissues	38
		Nonlinear Raman microscopy	Change in polarizability during molecular vibrations.	Label free localisation of particles	44

4. Mechanisms of Nanocrystals in Drug Delivery

Nanocrystals improve drug solubility and bioavailability through their small size and large surface area. The increased surface area enhances the dissolution rate and water solubility of poorly water-soluble drugs, resulting in faster and more efficient absorption. Nanocrystals can also be designed for controlled drug release, ensuring a steady therapeutic effect while reducing the frequency of dosing. Additionally, their ability to deliver drugs directly to specific sites in the body enhances treatment effectiveness. Moreover, the targeted delivery and controlled release mechanisms contribute to a reduction in systemic side effects, improving patient safety and compliance. These attributes make nanocrystals a versatile and powerful platform in pharmaceutical development.[45]

5. Nanocrystals for Pulmonary Diseases

Pulmonary diseases represent a significant global health concern, often characterized by difficulty in drug delivery due to poor bioavailability, the need for localized treatment, and challenges in overcoming the pulmonary barriers. Nanocrystals, with their unique properties, have emerged as promising candidates to address these challenges. Here, we will explore how nanocrystals are being utilized for the treatment of specific pulmonary diseases.

5.1. Asthma

Asthma is an inflammatory disorder of the lungs characterized by reversible airway obstruction, bronchial hyper-responsiveness, and chronic airway inflammation.[46] Long-term exposure to irritants triggers an inflammatory response in the lungs, leading to the narrowing of small airways and lung tissue damage.[47] The anti-inflammatory effects of nanocrystals have been demonstrated in various inflammatory disorders. Nanocrystals enhance the therapeutic effect by facilitating the targeted delivery of drugs, improving drug deposition directly in the lungs.

Curcumin has demonstrated remarkable potential as an adjunctive compound in the therapeutic management of asthma, attributable to its immunomodulatory and anti-inflammatory mechanisms of action. Nevertheless, its limited solubility in aqueous environments and suboptimal bioavailability result in diminished therapeutic efficacy, a challenge that can be addressed through its formulation into nanocrystal structures. Casula et al.[48] developed a multicomponent formulation designed for the pulmonary delivery of curcumin (CUR) and beclomethasone dipropionate (BDP) in the form of aqueous nanosuspensions (NS) **(Figure 3).** Single component formulations, specifically CUR-NS and BDP-NS, alongside a multicomponent formulation designated as CUR+BDP-NS, were synthesized utilizing a wet ball media milling methodology, incorporating P188 as an innocuous stabilizing agent. The CUR-NS formulation was subjected to optimization procedures, resulting in enhanced long-term stability and a significant improvement in the apparent solubility of the nanocrystals. The three distinct formulations demonstrated a mean diameter of nanocrystals ranging from 200 to 240 nm, accompanied by a uniform particle size distribution. No observable phenomena of aggregation or sedimentation were detected within the multicomponent formulation after a storage period of 90 days at ambient temperature. Ultimately, the nebulization assessments of the three formulations revealed optimal aerodynamic characteristics, with a mass median aerodynamic diameter (MMAD) of less than 5 µm.

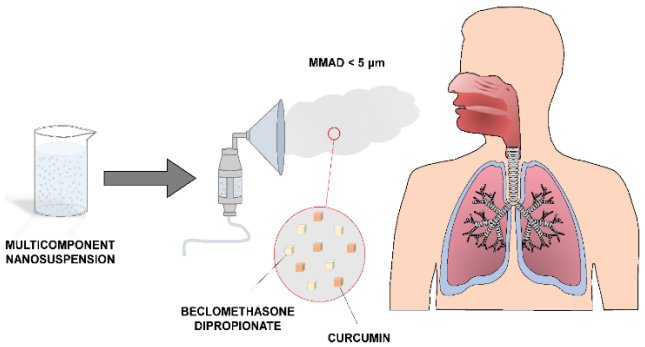

Figure 3: Pulmonary administration of curcumin and beclomethasone dipropionate within a multifaceted nanosuspension for the therapeutic intervention of bronchial asthma. Creative Commons Attribution (CC BY).[48]

5.2. Chronic obstructive pulmonary disease (COPD)

COPD is a chronic inflammatory lung disease that causes airway obstruction. Its symptoms include difficulty breathing, coughing, and increased mucus secretion. The disease is primarily caused by long-term exposure to irritating or airborne particles, often due to cigarette smoke.[49] In COPD, the airways become narrowed, and their flexibility is reduced, leading to air trapping in the lungs.[49] Nanocrystal-based drugs have shown therapeutic potential for various respiratory disorders, as they are effective in small quantities and can be precisely targeted to the diseased tissue microenvironment, thereby minimizing side effects.

5.3. Pulmonary fibrosis

Pulmonary fibrosis is a chronic lung disease that gradually affects the interstitium, causing difficulty breathing (dyspnea), reduced quality of life, and eventually leading to respiratory failure and death.[51] It results from an abnormal wound healing process that involves inflammation, fibroblast activation, excessive collagen buildup, and impaired resolution, causing scarring and stiffening of the lungs. The disease primarily affects individuals aged 50 to 70, with an estimated 13 to 20 cases per 100,000 people and 30,000 to 40,000 new cases worldwide each year. Current treatments for pulmonary fibrosis include pirfenidone and nintedanib.[52] Pirfenidone is a modified pyridine with antioxidant, anti-inflammatory, and antifibrotic properties, which suppresses TGF-β and reduces collagen formation, slowing the progression of the disease.[53] Nintedanib is a tyrosine kinase

inhibitor that targets various receptors involved in fibrosis, reducing fibroblast activity.[54] However, these treatments can be expensive and may not significantly affect the disease's course or its high mortality rate within 3 to 5 years of diagnosis.[55] Studies are being conducted to explore alternative therapies, including medicinal plants, which have chemical properties beneficial for treatment but may suffer from poor bioavailability and solubility issues.[56,57] Nanocrystals offer a potential solution to these challenges. By improving the solubility and bioavailability of poorly soluble drugs, nanocrystals can enhance the delivery and absorption of active ingredients in pulmonary fibrosis therapy. This approach could help overcome the limitations of medicinal plants and other drugs, improving treatment outcomes for patients with pulmonary fibrosis.

5.4. Pulmonary infections

Pulmonary fungal infections have been increasing over the past few decades, particularly due to the rising number of immunocompromised individuals, such as those with HIV, cancer, hematologic disorders, or organ transplants.[58] Common fungal infections include histoplasmosis, sporotrichosis, blastomycosis, coccidioidomycosis, paracoccidioidomycosis, and candidiasis. To treat these infections, several antifungal drugs are available, including caspofungin, itraconazole, voriconazole, and amphotericin B deoxycholate (AmB). Among these, AmB is the gold standard for treating life-threatening cases. However, a major clinical drawback of AmB is its nephrotoxicity and cardiotoxicity, which can require discontinuation of treatment.[59] To overcome these limitations, AmB has been incorporated into various nano drug delivery systems (nano-DDS),[60,61] including nanocrystals. Nanocrystals can improve the solubility and bioavailability of AmB, potentially reducing side effects and enhancing the delivery of the drug to the lungs for more effective treatment of pulmonary fungal infections.

6. Formulation and Administration

6.1. Inhalation therapy

Inhalation has long been the most common and traditional method for delivering drugs to the lungs and airways. The primary purposes of inhaled drugs are prophylaxis, treatment of topical or systemic diseases, and therapy management. Various inhaler devices, such as nebulizers, metered-dose inhalers, dry powder inhalers, and other aerosol-based technologies, are used for drug delivery. Inhalation provides targeted delivery, requiring lower drug doses compared to systemic delivery. This targeted approach minimizes systemic side effects typically associated with oral or injectable routes and enhances the therapeutic index by delivering the drug directly to the affected site. Additionally, inhalation is used for systemic administration through the alveoli, taking advantage of the large surface area of the lungs. Drugs are absorbed more rapidly through the lungs compared to other non-invasive delivery methods.[62] Oral inhalative delivery is also found to be more effective than intranasal administration, with a concentration loss as low as 20%.[63]

In order to proficiently facilitate the pulmonary administration of CUR, innovative inhalable mucus-penetrating nanocrystal-based microparticles (INMP) were synthesized. The D-Tocopherol acid polyethylene glycol 1000 succinate (TPGS) modified CUR nanocrystals (CUR-NS@TPGS) were fabricated through high-pressure homogenization and subsequently transformed into nanocrystal-based microparticles (CUR-INMP@TPGS) utilizing the spray-drying technique. It was elucidated that CUR -NS@TPGS demonstrated minimal interaction with the negatively charged mucin, attributable to a significant electrostatic repulsion phenomenon and the presence of PEG hydrophilic chains, and displayed a markedly enhanced ability to penetrate the mucus layer in comparison to poloxamer 407 modified CUR -NS (CN-NS@P407) and tween 80 modified CN-NS (CUR -NS@TW80). The aerodynamic findings revealed that the CUR -INMP formulation incorporating 10% TPGS as a stabilizing agent exhibited a significantly elevated Fine Particle Fraction, signifying superior deposition within the pulmonary system following inhalation delivery. Furthermore, pharmacokinetic assessments conducted in vivo illustrated that the Area Under the Curve (AUC(0-t)) for CUR -INMP@TPGS (2413.18 ± 432.41 µg/L h) was observed to be 1.497- and 3.32-fold greater in comparison to the AUC values of CUR-INMP@TW80 (1612.35 ± 261.35 µg/L h) and CUR -INMP@P407 (3.103 ± 196.81 µg/L h), respectively. These findings suggest that the CUR-INMP@TPGS formulation underwent rapid absorption subsequent to pulmonary administration, leading to an enhancement in systemic bioavailability **(Figure 4).**

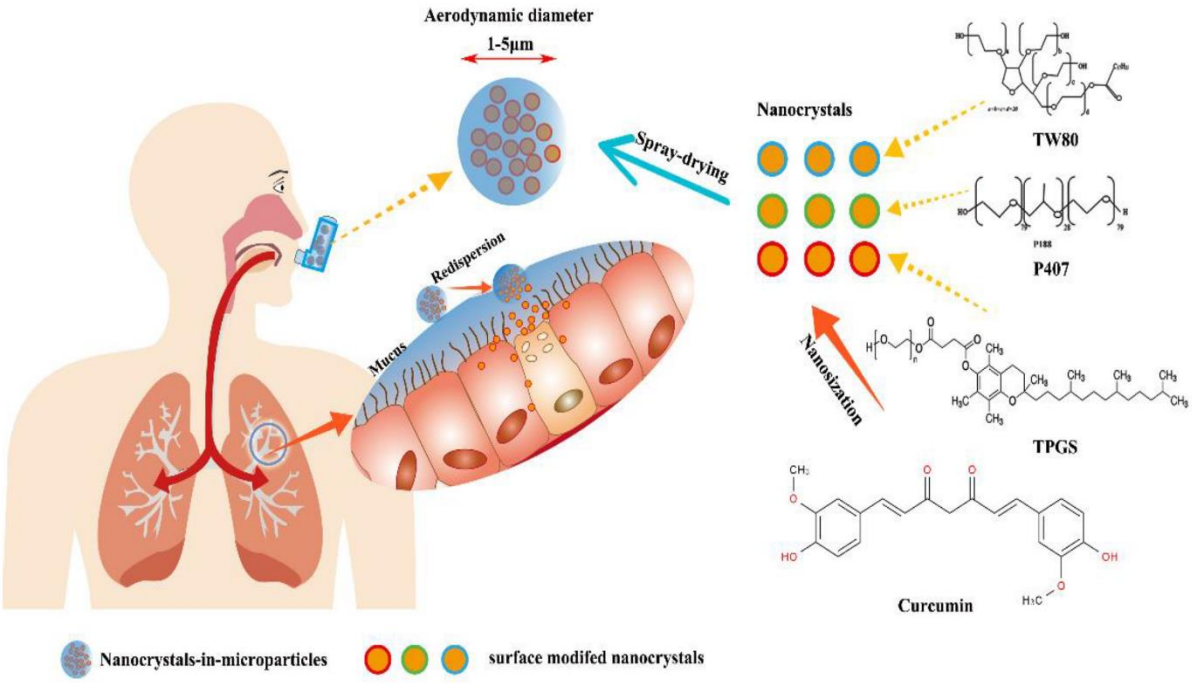

Figure 4: Augment mucus infiltration and pulmonary bioavailability of pharmaceuticals via inhalable nanocrystals-in-microparticles. Creative Commons Attribution (CC BY).[29]

6.2. Dry powder inhalers (DPIs)

Dry Powder Inhalers (DPIs) are devices that deliver drug formulations containing particles with an aerodynamic diameter of 1–5 μm, ideal for reaching deep lungs.[64] There are two types of DPI formulations: carrier-free (micronized drug particles) and carrier-based (drug particles mixed with coarse carrier particles like lactose). Carrier-free formulations can be cohesive and have poor flowability, while carrier-based formulations improve flow but may reduce lung deposition due to incomplete separation of drug particles during inhalation.[65] DPIs are categorized into single-unit dose inhalers (capsule-based), multi-unit dose inhalers (blister or disk-based),[66] and reservoir inhalers (metered dose from bulk).[67] These devices can be either passive (breath-activated) or active (powered by external energy like compressed air). Passive devices rely on patient inhalation, while active devices use external energy to enhance medication delivery, making them suitable for patients with limited lung function.[68]

6.3. Nebulizers

Nebulizers are devices used to generate aerosol droplets of 1 to 5 μm for pulmonary drug delivery. The two main types of nebulizers are jet and ultrasonic, which differ in the mechanisms they use to create aerosols. Jet nebulizers rely on pressure to generate small aerosol particles, while ultrasonic nebulizers use sound waves to break large droplets into smaller ones. Nebulizers do not require coordination between inspiration and actuation, making them suitable for patients who may have difficulty using pMDIs or DPIs. They can also administer large doses of medication. However, factors like drug solution volume, viscosity, air pressure, and mouthpiece design must be optimized for efficient delivery. Formulation for nebulizers is cost-effective and simple compared to pMDIs and DPIs. A significant drawback is that nebulizers must be assembled, loaded, cleaned, and disassembled after each use, which can be challenging for untrained patients.[69,70]

6.4. Metered Dose Inhalers (MDIs)

Pressurized metered-dose inhalers (pMDIs) are commonly used for treating respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD).[70] These devices deliver various drug formulations, either as single agents or combinations of multiple drugs. Despite their widespread use, patients often find it challenging to use pMDIs correctly. A typical pMDI consists of components like a metal canister, metered valve, actuator, and mouthpiece.[71] The metered valve ensures precise delivery of the aerosol with each actuation. The pMDI formulation usually includes a suspension or solution containing suspending agents, surfactants, cosolvents, excipients, and propellants. When the drug particles are released into the air, the difference in temperature between the formulation's boiling point and room temperature causes the formation of aerosolized droplets.[72] The particle size of the aerosol can vary depending on the specific product.

The **Table 2** depicts the summary of nanoformulations of different pulmonary disease

Table 2: Summary of nano-formulations for pulmonary diseases

Type of nanoparticle used	Drug	Treatment type	Particle size (nm)	Zeta Potential (mV)	Encapsulation efficiency (%)	In-vitro/in-vivo model	Outcomes	References
Solid lipid nanoparticles (SLNs)	Docetaxel	Lung cancer	141.8 ± 9.2	−17.8 ± 2.8	98.0 ± 0.1%	Colorectal (C-26) and malignant melanoma (A- 375) cell lines/C-26- implanted BALB/c mice	Prevent the proliferation and spread of cancer cells by destroying or preventing them from dividing.	74
Polymeric Micelles	Paclitaxel	Lung cancer	195.6 ± 18.6	-13.8 to -9.4	30% to 41%	Human lung cancer cell line(A549)-implanted BALB/c mice	The formulation effectively delivered paclitaxel to the lungs, preventing cancer cell proliferation and inducing cell death through apoptosis, while minimizing side effects.	75
PLGA nanoparticles	Tadalafil	Pulmonary arterial hypertension	35.07 and 301.7	-1.47 and -3.6	61.64 to 96.12 %	(A549) lung epithelial cell line	The formulation inhibited pulmonary smooth muscle cell proliferation, enhanced lung drug deposition, and provided sustained tadalafil release, reducing pulmonary pressure and improving lung function.	76
Solid lipid nanoparticles (SLNs)	Gefitinib	Lung cancer	105.20 – 363.73	-8.86 and -19.10	94.84 and 99.10%	Lung cancer cell line (A549) and tumour-bearing BALB/c nude mice	Prevented the proliferation and spread of lung cancer cells by inducing apoptosis, disrupting EGFR signaling pathways, and improving gefitinib delivery efficiency to the lungs.	77
Lipid NP	Itraconazole	Lung infections	108	−32.7 ± 0.7	98.78%	In-vitro drug release	Treat infections caused by fungus.	78
Solid lipid nanoparticles (SLNs)	Budesonide	Asthma	218.2 ± 6.6	-26.7 ± 1.9	92.5 ± 1.52	In-vitro drug release	Used to treat and prevent asthma and its symptoms (such as wheezing and trouble breathing).	79
Solid lipid nanoparticles (SLNs)	Amikacin	Lung infections	164 ± 7	-	89 ± 6%	-	Enhanced local drug concentration in the lungs improved antibacterial efficacy, reduced bacterial proliferation, and limited systemic side effects by targeting infected lung tissues.	80

6.5. Oral and intravenous administration

Oral delivery is the preferred method of drug therapy due to its safety, patient compliance, ease of production, and scalability. However, its main limitation is related to drug bioavailability. Nanocrystals can enhance bioavailability by improving solubility and dissolution rates, increasing the concentration gradient at membranes, and promoting adhesion to the gastrointestinal wall. For Class II drugs, where dissolution is the rate-limiting step, nanocrystals are a promising solution.[73] One of the earliest studies demonstrating this concept was conducted on danazol, a poorly soluble drug with low bioavailability. It was formulated in three ways: an aqueous nanosuspension (169 nm), a danazol-hydroxypropyl-β-cyclodextrin complex, and an aqueous microsuspension (10 µm). In beagle dogs, the area under the curve (AUC) after oral administration showed that the nanosuspension and cyclodextrin complex had similar bioavailability, while the microsuspension had lower bioavailability. The nanosuspension outperformed the microsuspension due to its ability to overcome the dissolution rate limitations typical of conventional suspensions. This study led to the proposal of nanoparticles as an ideal formulation for dissolution-rate-limited absorption. Since this pioneering work, numerous studies have confirmed the effectiveness of nanocrystals in improving oral bioavailability, resulting in several drug products currently in clinical trials or already on the market.

Nanocrystals can increase the effectiveness of drugs via various parenteral routes such as intravenous, subcutaneous, intramuscular, intraarticular, and intraperitoneal. In conventional drug delivery systems, an intravenous formulation of poorly soluble drugs requires various excipients like surfactants and cosolvents. However, these excipients lead to an increase in dose volume and may cause adverse reactions. Due to their small particle size, nanocrystals can be administered by intravenous injection with a reduced dose, fast onset of action, and maximum bioavailability. For the parenteral route of administration, the size of nanocrystals should be ≤ 100 nm. There are various suitable nanocrystals that have successfully delivered drugs through the intraperitoneal route. Paclitaxel nanosuspension has shown promising results compared to pure Taxol in reducing the median tumour burden.

7. Conclusion

Nanocrystals represent a promising technological advancement in overcoming the inherent challenges of pulmonary drug delivery, including poor aqueous solubility, limited bioavailability, and systemic side effects. Their ability to enhance drug solubility, enable targeted delivery, and provide controlled drug release has demonstrated significant potential for the management of pulmonary diseases, such as asthma, chronic obstructive pulmonary disease (COPD), pulmonary fibrosis, and pulmonary infections. Furthermore, their application in advanced inhalation systems, such as dry powder inhalers (DPIs) and nebulizers, has shown improved therapeutic efficacy and enhanced patient adherence.

8. Future Perspective

Future research is anticipated to focus on the refinement of particle engineering techniques to optimize drug deposition and improve bioavailability while mitigating adverse effects. Additionally, advancements in inhalation device technology, including the integration of digital monitoring systems and dose optimization features, are expected to contribute to improved treatment precision. The potential application of nanocrystals in the delivery of complex therapeutic agents, such as biologics and vaccines, also represents an intriguing area for future investigation. Continued exploration and optimization of nanocrystal-based pulmonary drug delivery systems are essential for harnessing their full therapeutic potential. Such efforts could pave the way for safer, more effective, and highly targeted treatments, thereby advancing the management of pulmonary diseases and improving patient outcomes.

9. Source of Funding

None.

10. Conflict of Interest

None.

11. List of Abbreviations

COPD: Chronic obstructive pulmonary disease; PAH: Pulmonary arterial hypertension; DPIs: Dry powder inhalers; PDDS: Pulmonary drug delivery system; SLN: Solid lipid nanoparticles; NLC: Nanostructured lipid carriers; CUR: Curcumin; BDP: Beclomethasone dipropionate; NS: Aqueous nanosuspensions; MMAD: Mass median aerodynamic diameter; Dyspnea: Difficulty breathing; AmB: Amphotericin B deoxycholate; INMP: Inhalable microparticles; TPGS: D-alpha-tocopheryl polyethylene glycol succinate; MDIs: Metered dose inhalers; pMDIs: Pressurized metered dose inhalers; AUC: Area under the curve; IPF: Idiopathic pulmonary fibrosis.

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