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Review article

Curcumin Nanoformulation for Pulmonary Drug Delivery

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Abstract

Curcumin has various beneficial effects on human health, but its efficacy is yet to be proven in clinical trials. Curcumin has poor bioavailability, low solubility, and rapid metabolism which become the principal reasons behind the lack of curcumin efficiency in clinical trials. This review aimed to focus on nanotechnologies to improve the bioavailability of curcumin inhalation formulations. Many studies were done to improve curcumin's bioavailability by administering through nanoparticle drug carriers. Pulmonary drug delivery has some advantages such as giving a rapid onset of action and bypassing the first hepatic metabolism. Lungs also have a large area for absorption. So far, there are various methods to produce curcumin nanoformulations that are proper, stable, and effective, and are suitable to enhance curcumin pulmonary delivery in the form of liposomes, polymeric and solid lipid nanoparticles, nano suspensions, and cyclodextrin formulations. Therefore, analysis of the various methods, to conclude the best method for curcumin pulmonary delivery is needed. In conclusion, the best method to make nanocurcumin formulation is the one that gives the most advantage and lowest toxicity. Therefore the best choices for curcumin nanoformulations are curcumin nanosuspension and cyclodextrin formulated nanocurcumin/proliposomes.

Keywords: bioavailability; inhalation; toxicity

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Introduction

Curcumin is a phenolic substance derived from the spice herb *Curcuma longa* L., which is widely used as a part of cooking ingredients. *Curcuma longa* L. belongs to the ginger family Zingiberaceae. Curcumin has been studied in many experimental and clinical trial studies. It shows various effects on human health, such as anti-cancer, anti-inflammatory, antioxidant, wound-healing, antiemetic, and antiviral. It also helps to reduce anxiety and is effective on arthritis, hyperlipidemia, and many more [1-4]. In addition, it shows benefits to the lungs by reducing pulmonary fibrosis, cystic fibrosis, asthma, acute lung injury, lung cancer, and chronic obstructive pulmonary disease (COPD) [5-7]. Hemmnati et al. showed that nebulization of curcumin nanoformulation reduced the overall hydroxyproline content of lungs and significantly decreased the levels of inflammatory cytokines in bleomycin-induced pulmonary fibrosis rats.

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Hydroxyproline is a major component of collagen and plays a key role in the stability of the collagen triple helix. It can be used as an indicator to determine the amount of collagen [8]. Despite the advantages of curcumin, the limitation of curcumin is its low oral bioavailability. Studies showed that large amounts of curcumin were needed to produce measurable physiological level in humans. The oral bioavailability of curcumin in rats that was measured by LC-MS/MS was about 1% [9,10]. Several technologies have been applied to improve curcumin bioavailability, such as using natural and synthetic analogs and nanoparticles. However, these technologies have not solved the problem in curcumin bioavailability. Lungs have a large surface for absorption of drugs such as curcumin and may help in increasing curcumin availability for systemic delivery. The pulmonary route is a promising method of delivering drugs for both systemic and local treatment.

Administration of nanoparticles through the lungs shows several advantages compared with larger particle formulations, as nanoparticles provide larger absorption profile to alveolar epithelial cells, and are unlikely to be removed by pulmonary macrophage, particularly particles with a size smaller than 250 nm [11]. In the case of systemic drug delivery via the lungs, the advantage of nanoparticles is their rapid absorption into blood vessels and thus gives a rapid onset of action [12]. The aim of this review was to discuss the efforts to overcome curcumin bioavailability problems by pulmonary drug delivery.

Methods

The literature search was performed on March 4^{th,} 2021 on Pubmed and Google Scholar data base from Jan 2007 to March 2021 using keywords: curcumin, nanoformulation, inhalation, and pulmonary drug delivery. Data were analyzed and presented descriptively in the form of text and Tables. We addressed pulmonary drug delivery, the advantages and disadvantages, and various curcumin nanoformulations for pulmonary delivery systems.

Results and Discussion

We found 36 references and used them to prepare this review; from these references, ten were original articles on various curcumin nano formulations for inhalation, and their major outcomes. The other articles contained relevant information on curcumin and pulmonary drug delivery.

Pulmonary drug delivery

Inhalation therapy has been used for thousands of years and has been known as the optimal route to deliver pharmacologically active agents to treat respiratory tract local diseases. Inhalation therapy also offers a great potential for systemic treatment because the lungs have a large surface area that is available for absorption and have abundant vasculature and thin air-blood barrier. Besides, pulmonary drug delivery can avoid the first pass metabolism [13]. However, pulmonary drug delivery is a challenging route of administration because the effectiveness of the inhalation therapy depends on the site of deposition of the drug in the lung. The deposition of an inhaled drug depends on the anatomy and physiology of the lung, physicochemical properties of the drug, characteristic of the formulation, and the type of delivery system used for administration [14].

Pulmonary drug delivery is usually beneficial in treating various lung diseases. In local drug delivery by inhalation, it is expected to transport drugs to the place of its action and retain it for a required time. The inhalation efficiency for local drug delivery mainly depends on breathing conditions, lung aerodynamics, particle size, devices, and inhalation methods that are used. The best aerodynamic size of the drug for pulmonary deposition is in the range of 1-5 µm. For delivery to alveolar epithelium, it is required that the particles have an aerodynamic diameter of less than 3 µm [15]. Particles that are larger than 5 µm are primarily deposited in the upper airways, where the breathed air moves with a high velocity, and in the throat, where the airflow changes. Particles with aerodynamic diameter below 0.5 µm are trapped by Brownian motion and suspended for a long time in the breathed air. These particles are likely to be exhaled and leave the respiratory tract before being deposited (Table 1). Up to 80% of small aerosol particles (<1 µm) can be exhaled during breathing. However, nanoparticles up to 100 nm are able to deposit in the alveolar region in an acceptable amount. Drugs in the form of nanoparticles usually deposit by sedimentation after being released from the aerosol device due to an agglomeration process in the lung.

Table 1. Mechanism of particles deposition in the respiratory tract [12,16]

Size	Site of deposition	Mechanism of deposition
>5 µm	Upper airways (e.g., throat)	Impaction
1-5 µm	Lower respiratory tract (e.g., bronchial tree and alveoli)	Inertial impaction/ gravitational sedimentation
1-3 µm	Alveoli	Inertial impaction/ gravitational sedimentation
<0.5 µm	Mostly exhaled by the expiratory airflow	Diffusion

These agglomerated nanoparticles are able to sediment for more extended periods in the tracheobronchial section, thereby improving the biological activity of the delivered therapeutic agent [16].Nanoparticle systems need to form micron-size particles in the suitable range of size. Several methods to manufacture nanoparticle aerosols are available such as spray freeze drying, and spray drying, which can improve inhalable drug particles in the appropriate size range [12]. The potential of using the lungs as a portal of entry for drugs to the systemic circulation has long been recognized. Drugs given by inhalation to achieve systemic effects are of three main types: fast-acting small molecules with a molecular weight below 1000 Da, peptides and proteins, such as insulin, Exubera®, Afrezza®, and vaccines, such as measles vaccine [11,15].

The advantages of pulmonary drug delivery

The pulmonary route has some important advantages that make this route an interesting approach for drug delivery. For local respiratory diseases, the pulmonary route gives direct delivery that offers some benefits such as lowering systemic side effects and enhanced patient compliance. It also gives rapid onset of action and bypasses the first hepatic metabolism. Lungs also have a large surface area, allowing for efficient absorption, and have a very thin epithelial layer of alveolar sacs, providing an appropriate area for absorption of drug particles. The respiratory tract has low enzymatic activity, which avoids degradation or disruption of drug particles before absorption. Besides, pulmonary drug delivery can reduce adverse drug reactions as compared to conventional drug therapy. The delivery of aerosolized drug formulation provides an immediate contact and a noninvasive technique for successful targeting of different regions of the lungs [12, 17].

Limitation of pulmonary drug delivery

Delivering drugs by inhalation is relatively complex. A problem that needs to be solved is lung toxicity of the drugs. When a drug or other active substance is delivered via inhalation, the lungs are inherently exposed to its toxicity that might cause side effects. This is especially important in the case of highly toxic anti-cancer drugs. Healthcare workers who are involved in giving inhalation therapy can be potentially exposed to the nebulized drug. Besides that, the ability of the patient to use an inhaler device correctly is crucial [18].

Other factors that can limit the use of pulmonary drug delivery are the lung defense mechanisms. The respiratory tract has developed defense mechanisms that are intended to keep inhaled materials out of the lungs, as well as removing or inactivating them once they have been deposited. Major lung defense mechanisms include beating cilia, mucus blanket, macrophages, transporters, and enzymes. Inhalation devices, regimens, and delivery systems should be designed to evade these obstacles [15,18].

Various curcumin nanoformulations for pulmonary delivery system

Curcumin has been mentioned to have numerous biological effects including anti-inflammatory, antimicrobial, antitumoral activity, antioxidant, hypolipidemic properties, antiviral, antibacterial, antiasthma, antifungal, anti-depression and anxiety, antifibrosis, and many more [2,4,5,19, 20]. The chemical structure of curcumin (Figure 1) is 1,7-bis (4-hydroxy-3-methoxyphenol)-1,6-heptadiene-3,5-dione that has two hydrophobic phenyl domains. This structure makes curcumin to be hydrophobic. Low water solubility, rapid metabolism, and poor oral bioavailability of curcumin limit its use.

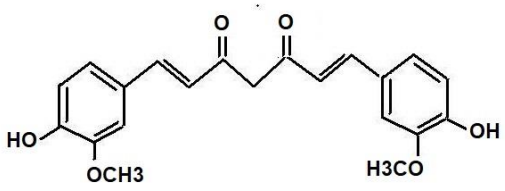

Figure 1. Curcumin chemical structure

Many researchers have tried to increase the pharmacological and biological activity of curcumin and overcome its drawbacks by efficient delivery systems, particularly by nanoencapsulation. Several studies have shown a satisfactory result of nano curcumin formulations [2,4,10]. As the pulmonary route is a promising way for drug delivery purposes, the use of nano curcumin formulation via pulmonary delivery system might give better results, especially for lung diseases. Many studies showed that curcumin has potential effects on lung diseases, such as COPD, asthma, pulmonary fibrosis, cystic fibrosis, acute lung injury, and lung cancer [7]. Therefore, studies that are related to the use of inhaled nano curcumin are growing, and many methods have been developed to produce a nano curcumin formulation that is proper, stable, and effective, i.e. liposomes [21,22], proliposomes [23,24] polymeric and solid lipid nanoparticles [6,25-28], nano suspensions [29,30], and cyclodextrin formulation [8,31-36]. Some of these formulations have been tested in vitro or in vivo (Table 2).

Curcumin liposome pulmonary drug delivery

Liposomes are aqueous units surrounding spherical vesicles, which are covered by single or multiple phospholipid bilayers that very closely resemble cell membrane structure and are usually in the form of micrometer-sized particles. They are attractive drug delivery agents as they can encapsulate both hydrophobic and hydrophilic molecules. Curcumin is a hydrophobic substance that will be dissolved in the lipid bilayer (gel phase) of liposomes, which can load more curcumin compared to conventional DMSO vehicles [21].

Zhang et al. [22] developed liposomal curcumin dry powder inhaler for inhalation therapy of primary lung cancer. This inhaler and curcumin powders were sprayed into the lungs of lung cancer rat models; liposomal curcumin dry powder showed higher anti-cancer, antioxidant and anti-inflammatory effects than ordinary curcumin powders. However, large-scale production of liposomes is not feasible due to the high cost of upscaling process. Besides that, liposome is a relatively unstable colloidal system.

Table 2. Various curcumin nano formula inhalations and their major outcomes

No	Curcumin nano formula	Test	Models used/ technology used	Major outcomes	References
1	Liposomal curcumin dry powder	In vivo (rat)	MCA and DEN induced lung cancer models	Higher anti-cancer effects compared to ordinary curcumin powders	[22]
2	Curcumin loaded proliposomes using HP-β-cyclodextrin	In vitro	Nanospray drying	Superiority over curcumin powder in rate and extent of absorption, and mean residence time in lung tissues	[24]
3	Curcumin loaded PLGA -LPMPs	In vivo (rat)	Idiopathic pulmonary fibrosis models	Superiority over curcumin powder in attenuating lung injuries, decreasing hydroxyproline contents, reducing collagen-1 synthesis, and antifibrotic activity	[6]
4	Curcumin loaded PLGA nanoparticles - PEG-Chitosan	In vitro	Spray drying	A new potential carrier system for sustained pulmonary delivery of curcumin using DPIs	[26]
5	Curcumin SLNs	In vivo (mice)	Asthma models	Suppressed airway hyperresponsiveness and inflammatory cell infiltration	[28]
6	Curcumin nanocrystals (curcumin DPIs)	In vivo (rabbit)	Wet milling combined with spray-dried powder	Drug dissolution was significantly enhanced, plasma curcumin concentration was enhanced, and most drug were deposited in the lung	[30]
7	Curcumin with HP-β- cyclodextrin	In vitro	Supercritical antisolvent micronization (ARISE system)	Fine particle fraction of curcumin with HP-β-cyclodextrin was 61%, while fine particle fraction of ordinary curcumin was 10%.	[34]
8	NDS27	In vivo (horse)	Neutrophilic airway inflammation models	NDS27 abolished LPS-induced neutrophil degranulation	[35]
9	Cyclodextrin formulated curcumin	In vivo (mice)	Acute respiratory distress syndrome models	Administration directly to the lung led to a reduction in mortality, inflammation, and oxidative stress	[36]
10	Curcumin with β-cyclodextrins	In vivo (rat)	Bleomycin induced pulmonary fibrosis models	Reduced hydroxyproline content in lungs of bleomicyn treated rats	[8]

Therefore, researchers have started to think about the concept of proliposomes.
Proliposomes are completely dry, free-flowing granular products that upon hydration or contact with biological fluids in the body, form liposomal dispersion. They are composed of water-soluble porous powder and phospholipid. Proliposomes have higher stability profiles than other lipid solutions [23]. Adel et al. employed nanospray drying to prepare proliposomes using hydroxypropyl β-cyclodextrin as a carrier [24]. Their study showed the superiority of proliposomal curcumin compared to ordinary curcumin powder in both the extent and rate of absorption, as well as the mean residence time in lung tissues.

Curcumin polymeric nanoparticle pulmonary delivery

Nanoparticles are particles of around 1-100 nm in diameter, 1000 times smaller than the average human body cells. Encapsulating drugs in nanoparticles can increase the drug solubility and pharmacokinetics, as well as can provide drug controlled release and targeted delivery. Polymeric carriers have the ability to produce a controllable pattern of drug release. They also protect therapeutic agents against degradation and enzymatic metabolism. Some of the most common polymers, which are used to prepare nanostructured carriers, are poly lactic-co-glycolic acid (PLGA), poly lactic acid (PLA), poly alkyl-cyano-acrylate, chitosan, and alginate. There are some limitations with polymeric carriers in the pulmonary delivery, such as irritancy and immunogenic specificity of the polymers. To avoid these, any biodegradable polymer or copolymer should be completely studied before application. In vivo and in vitro tests should be done to confirm the safety of the polymer itself and its degradation products [2,12]. PLGA has been investigated as a nanocarrier for pulmonary delivery, and is found to be safe. Biodegradable PLGA nanocarriers have produced a less inflammatory response in vivo than nonbiodegradable polystyrene particles. However, PLGA may not be recommended for therapies that require frequent dosing due to the slow rate of biodegradation and the high potential for lung accumulation [25]. Accumulation of curcumin and its nanocarrier may cause toxicity; thus, further investigation on frequent dosing is warranted.

Hu et al. developed inhalable curcumin loaded PLGA in the form of large porous microparticles (LPMPs) to treat bleomycin-induced pulmonary fibrosis in rats models [6]. They showed that curcumin LPMPs attenuated lung injuries, decreased hydroxyproline contents, reduced synthesis of collagen-1, and showed higher antifibrotic activity than ordinary curcumin powders. El-Sherbiny et al. developed a sustained pulmonary delivery of curcumin using dried powders for inhalation (DPIs) using PLGA nanoparticles that are encapsulated in amphiphilic poly ethylene glycol (PEG)-chitosan copolymer-based hydrogel microspheres [26]. However, they did not test the efficacy of the polymeric nanoparticles.

Curcumin solid lipid nanoparticles for pulmonary drug delivery

Solid lipid nanoparticles (SLNs) are colloidal particles that combine the nanopolymers (polymeric nanoparticles) and liposomes. The SLNs have exhibited high stability, but reduced toxicity that was the limitation of both nanopolymers and liposomes [21]. Solid lipid nanoparticles have some advantages such as: low toxicity, green synthesis, low to moderate costs of starting materials, and improved efficacy and pharmacokinetic profile. However, there are also some limitations as large scale and reproducible synthesis need to be developed, and physicochemical and microbiological stability need to be addressed to develop commercially available products [27].
Wang et al. used curcumin solid lipid nanoparticles (curcumin-SLNs) to treat asthma animal models and showed that in curcumin-SLNs treated group, curcumin SLNs effectively decreased airway hyper-responsiveness and inflammatory cell infiltrations, and suppressed the expression of T-helper-2-type cytokines, such as interleukin-4 and interleukin-13 in bronchoalveolar lavage compared to non-treated asthma group [28].

Curcumin nanosuspensions for pulmonary drug delivery

Nanosuspension is also known as nanocrystals. Pharmaceutical nanosuspensions of drugs are nanosized, heterogenous aqueous dispersion of insoluble drug particles that are stabilized by surfactants. Nanosuspension technique is the only

option when a drug molecule has many disadvantages, such as inability to form a salt, has a large molecular weight, and needs a high dose, so that it is hard to develop a suitable formulation. Nanosuspension can increase stability, may facilitate sustained release of the drug, increase efficacy through tissue targeting, experience minimum first-pass metabolism, and deep lung deposition. For pulmonary drug delivery, nanosuspensions are preferable due to their high drug loading efficiency. Curcumin is a poorly soluble drug, and nanosuspension formulation can overcome this obstacle [12,29].

Hu et al. used curcumin nanocrystals DPIs that were produced using wet milling in combination with spray drying method and showed that the drug dissolution was significantly enhanced, the plasma curcumin concentration was improved by inhalation, and most of the curcumin DPIs were deposited in the lungs [30].

Curcumin cyclodextrins for pulmonary drug delivery

Cyclodextrins, which are in the form of α, β, and γ-cyclodextrin, are multi-component hybrid soluble carrier systems that carry covalent bound drugs. β- and γ-cyclodextrin, and their derivatives have been widely used to deliver drugs due to their relatively easy synthesis, low price, and adaptability. They are often used to increase drug bioavailability and solubility of poorly water-soluble drugs by complex formation. For poorly water soluble drugs, which belong to class 2 (low solubility, high permeability) or class 4 (low solubility, low permeability) of the biopharmaceutics classification system (BCS), their solubility and permeability can be improved by the application of either of both cyclodextrins [31].

Curcumin is classified as a BCS class 4 molecules based on its poor aqueous solubility (11 ng/mL in aqueous buffer pH 5) and permeability through intestinal epithelial cells [32,33]. Recently, the significance of cyclodextrin in the curcumin inhalation delivery system was demonstrated by many studies. Kurniawansyah et al. processed curcumin with hydroxypropyl-beta-cyclodextrin (HP-β-cyclodextrin) and polyvinylpyrrolidone (PV) to form binary and ternary composites with enhanced flowability for pulmonary delivery [34]. The micronization process used the atomized rapid injection solvent extraction (ARISE) system. They found a synergistic effect of the excipients on the aerodynamic properties of micronized curcumin formulation. The fine particle fraction of curcumin in ARISE processed powders was higher than untreated curcumin.

Sandersen et al. used NDS27 inhalation, which is a lysin salt of curcumin incorporated in β-cyclodextrin, to treat lipopolysaccharides (LPS) induced airway neutrophilia in horses. They showed that NDS27 abolishes LPS induced neutrophil degranulation [35]. Zhang et al. delivered directly hydroxypropyl-γ-cyclodextrin formulated curcumin into the lungs of C57BL/6 mice that were inoculated with a lethal dose of *Klebsiella pneumoniae* [36]. This administration of hydroxypropyl-γ-cyclodextrin curcumin led to a reduction in mortality, inflammation, and oxidative stress. Hemmati et al. used nebulized cyclodextrin formulated nano curcumin and compared it with nebulized curcumin and oral curcumin. They showed that cyclodextrin formulated nano curcumin at the dose of 200 µg/Kg could effectively treat idiopathic pulmonary fibrosis [8].

Analysis to conclude the best curcumin nanoformulation

Although curcumin has a lot of benefits, poor bioavailability, low solubility, and rapid metabolism of curcumin have limited its use. Curcumin inhalation therapy might help to overcome this problem. In addition, the use of nanoformulations can increase the bioavailability and solubility of curcumin. The use of inhaled nano curcumin has given new hopes in treating various diseases, especially diseases related to the lungs.

The selection of the best nanocurcumin formulation method depends on the cost, purpose, and place of action, the advantages and the toxicity. Curcumin has low water solubility, and therefore nanosuspension might be a suitable formulation. Nanosuspensions have a stronger adhesiveness to mucosal surfaces, which will result in prolonged residence time at the target site, thus improving absorbance and maximally reducing drug loss. Cyclodextrin is relatively easy to synthesize and also can improve drug solubility. Lipid-based colloidal systems namely, solid lipid nanoparticles and liposomes, both have an added advantage owing to their physiological components in the formulation. For polymeric particles, degradation rate needs to be

analyzed, as they might be biodegradable. In addition, toxicity profiles of polymeric particles and other formulations need to be elaborately analyzed in various models, i.e. in vitro, ex vivo and in vivo models. Therefore, comparison of the various methods is needed to reach to the best method for making nanocurcumin formulations that gives the most advantages and lowest toxicity.

In addition to increasing the bioavailability and solubility, as well as producing the lowest toxicity, the ease of large scale production needs to be considered. As large scale production of curcumin liposome is not feasible [23], and solid lipid nanoparticle large scale production still needs to be developed [27]. Recently, available best choices for curcumin nanoformulations are curcumin nanosuspension and cyclodextrin formulated nanocurcumin/proliposomes.

Conclusion

The best method of nanocurcumin formulation is the one that gives the most advantage, i.e. stability, effectiveness and has the lowest toxicity. Therefore the best choices are curcumin nanosuspension and cyclodextrin formulated nanocurcumin/ proliposomes.

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Author contributions

Sandy Vitria Kurniawan was involved in developing the idea, literature searching, writing the manuscript draft and final approval. Jeanne Adiwinata Pawitan contributed in providing additional data, revising, editing, and final approval.

Declaration of interest

The authors declare that there is no conflict of interest. The authors alone are responsible for the content of the paper.

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Abbreviations

COPD: chronic obstructive pulmonary disease; PLGA: poly lactic-co-glycolic acid; PLA: poly lactic acid; LPMPs: large porous microparticles; SLNs: solid lipid nanoparticles; DPI: dried powders for inhalation; BCS: biopharmaceutics classification system; HP-β-cyclodextrin: hydroxypropyl- beta-cyclodextrin; PVP: polyvinylpyrrolidone; ARISE: atomized rapid injection solvent extraction; LPS: lipopolysaccharides; IPF: idiopathic pulmonary fibrosis