REVIEW ARTICLE

Potency of Natural Compounds in Inhaled Micro/Nanoparticle for Lung Infection Therapy

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ABSTRACT

Pulmonary infection is a disease-causing death worldwide that attacks the lower airway organs by various kinds of microorganisms. Antibacterial or antiviral has been used for the therapy of lung infections, but up to this point the case of resistance to drugs is still high. Therefore, to overcome this problem, it is necessary to develop new drugs, namely natural drugs. However, natural drugs have limitations (physicochemical properties and low bioavailability), so the development of inhalation natural drug delivery systems is needed. Various studies have been conducted to develop inhalation natural drug delivery systems such as microparticles, microsponges, nanoparticles, nanomicelles, etc. The use of these delivery systems has been shown to have a positive impact on the physico-chemical properties, bioavailability and antibiotic/antiviral activity of natural drugs through targeted delivery of lungs both *in-vitro* and *in-vivo*.

Keywords: Lung infection, Drug delivery system, Inhalation, natural materials, Microparticles, Nanoparticles.

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INTRODUCTION

Pulmonary infection is a type of disease that attacks the lower airway organs to the alveoli by various kinds of microorganisms, including bacteria, viruses, and fungi[1]. A wide variety of bacterial species can cause lung infections, such as *Haemophilus influenzae, Pseudomonas aeruginosa, Staphylococcus aureus, Burkholderia cepacia complex, Stenotrophomonas maltophilia*, and *Achromobacter*[2]. In addition, there are types of viruses that can cause lung infections such as *H. influenza* as well as various species of fungi, such as *Aspergillus fumigatus, Pneumocystis jiroveci, Cryptoccocua spp,*etc[3,4]. There are two types of pulmonary infection, also known as pneumonia, namely community-acquired pneumonia (CAP) obtained from the community and hospital-acquired pneumonia (HAP) obtained in a hospital environment. Pneumonia can be transmitted by aspiration or by inhalation of pathogenic microorganisms[5].

According to the WHO, infections of the lower respiratory are the world's fourth biggest killer, with 2.6 million deaths in 2019.[6] In overcoming lung infections, the use of various classes of antibiotics is used based on the cause[7]. However, the phenomenon of antimicrobial resistance is leading to an increase in the number of infections and deaths. Based on WHO data, in 2019 there were 1.27 million deaths related to antibiotic-resistant bacteria.[8] This is triggered by overuse and improper use of antibiotics, resulting in the development of bacteria that are resistant to various kinds of antibiotic drugs.[9] Antimicrobial resistance in bacteria is caused by frequent exposure to various antibiotics so that microbes are able to adapt to antibiotics with mutations in genes. This is frequently happening, especially in *Pseudomonas aeroginosa* and viruses.[10] This will require the development of new strategies to increase antibiotic activity and prevent the development of drug resistance.[11]

Currently, drug development studies from plants have been widely used. The effectiveness of natural drug ingredients has been studied in various diseases such as cardiovascular, infection, cancer, etc.[12] Some studies also prove that some

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phytochemical compounds extracted from plants are able to provide effective antibacterial and antiviral potential even against drug-resistant pathogens.[9,13] Therefore, the use of natural ingredients, especially phytochemicals, can be one of the new strategies to overcome lung infections.[14] Nevertheless, along with the development of evidence of the effectiveness of natural ingredients, there are some limitations in the preparation formulation. Phytochemicals tend to have large size and polarity properties that make it difficult to penetrate the gastrointestinal mucosa and circulatory endothelial lining, causing low amounts of drugs that can be absorbed[15]. Phytochemicals also have low hydrofunctionality properties thus decreasing their intrinsic dissolution speed[16]. In addition, exposure to enzymes in the gastrointestinal tract can cause degradation.[17] This results in phytochemicals having low bioavailability, thus decreasing the effectiveness of phytochemical drugs and requiring larger drug doses. Therefore, there is a need for the development of a delivery system formulation that can increase bioavailability, stability, and effectiveness.[16]

Natural Drugs in Lung Infection Therapy

Natural drugs are medicinal ingredients obtained through extraction from plants. Currently, the use of natural medicine is increasing due to the ineffective activity of conventional medicine due to the increasing incidence of drug resistance.[18] In pulmonary infection therapy, there are several natural drugs that are proven to have potential antimicrobial, antiviral, or even antifungal activities, as shown in Table 1.

Inhalation Delivery System

Along with the development of research related to the effectiveness of natural drugs as anti-infection of the lungs, it should be noted that there are several problems related to bioavailability, stability to the effectiveness of the medicinal properties of natural drugs [16]. The development of inhalation formulations can overcome these problems. Inhalation drugs have been the main strategy in pulmonary disease therapy for the last seventy years[19]. When compared to traditional dosage forms, inhalation drugs have many advantages, such as better targeting alveolar macrophages, avoiding first-pass metabolism, and greater surface area due to high vascularization, rapid onset of action, and non-invasive therapeutic properties for patients. On the other hand, this preparation also has the potential to increase the therapeutic effect because it is able to deliver the drug directly to the lung organs so that the concentration of the drug becomes higher in the targeted place with lower systemic toxicity[20]. In the development of the inhalation formula, there is a pulmonary drug delivery system where the drug will be delivered until it reaches the airway so that it can increase the effectiveness of lung drugs.[21]

Drug delivery system development is performed using particle design with optimized properties to overcome non-cellular and cellular barriers in infected lungs. The physical and chemical properties of the drug delivery system particles (such as size, shape, surface charge, and surface hydrophobicity) are modified to achieve targeted drug delivery at specific sites. Nanoparticles less than 100 nm in size have a superior ability to overcome the lender barrier to penetrate mucus. Furthermore, the adhesive interaction between mucus and drug particles can be effectively minimized by designing particles with a sufficiently hydrophilic surface and a net neutral charge.[22] The mechanism of microparticles/nanoparticles in antibiotic therapy was shown in Figure 1.

In the design of the inhalation drug delivery system, several factors influence the bioavailability profile of the developed drug delivery device, including morphology, aerodynamics, deposition and mucoadhesive properties. These factors are important parameters for predicting dry powder inhaler performance in delivering drugs to the lung organs.[23,24]

Morphology

Particle morphology can affect the ability of particles to move in the air. In this case, there are many studies that discuss the influence of particle morphology on particle flow ability. Conversely, spherical shapes have the advantage that they tend to roll or flow so that they are easily applied to inhalation products. On the one side, irregularly shaped particles with gaps and voids have a relatively high surface area. This results in a high drug-loading capacity[25]. Porous particles can change aerodynamic characteristics to reach deeper parts of the lungs than those that are not porous. Moreover, this approach is also a strategy for the particles to remain in the lungs for a longer period because it is less likely to be phagocytosed by alveolar macrophages[26].

Aerodynamic Properties

The main parameter that has an effect on the deposition capacity of particles is the aerodynamic diameter symbolized by D_{ae}. D_{ae} particles are geometric diameters related to flying speed[26]. D_{ae}, which is appropriate for use in the delivery of pulmonary drugs so that it is able to be well deposited in the lungs, is in the range of 1 to 5 µm. This is because particles that have D_{ae} smaller than 1-µm are easily exhaled, while particles that have D_{ae} larger than 5 µm can only be deposited in the upper airways[23,24]. Other aerodynamic parameters related to D_{ae} are median mass aerodynamic diameter (MMAD), geometric standard deviation (GSD) and fine particle fraction (FPF). MMAD is divided into two categories according to particle size, with 50% of the particles having a diameter below MMAD and the other 50% having a diameter above MMAD. The GSD

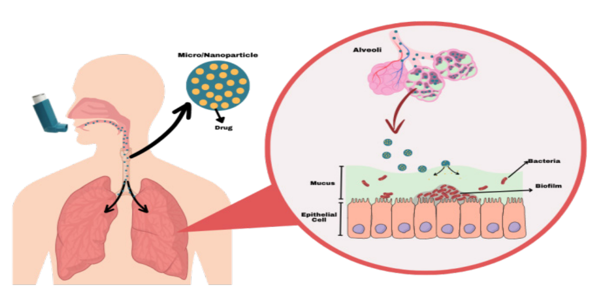

Figure 1: Mechanism of nanotechnology delivery system in amtibiotic therapy

Table 1: Medicinal activity of natural drugs as well as limitations in formulations

No.	*Active ingredients*	*Anti-infective activity*	*Bacteria/Fungi/Viruses*	*Limitations*
1	Curcumin	Curcumin is able to inhibit the growth of both gram-positive and negative bacteria by destroying biofilm structures, inhibiting DNA damage response, and inhibiting cell division by binding microtubulins[39] Curcumin may attenuate lipopolysaccharide toxicity by acting on PI3K/Akt, NFκB, TNF-α and TGF-β1 pathways in the cell wall of gram bacteria and confer a protective role in the lung[40]	*Pseudomonas aeruginosa, Escherichia coli, Helicobacter pylori, Staphylococcus aureus, Streptococcuspneumo-niae, Staphylococcus epidermidis, Salmonella*[39,40]	Hydrophobic (LogP = 3.2) with a solubility of 30 nM. Low intestinal *curcumin* absorption, fast metabolism leads to low bioavailability [41] low light stability [42]
		Curcumin is able to inhibit viral infection through molecular binding[40]	*SARS* and *COVID-19*[40]	
2	Quercetin	Quercetin has a broad spectrum of antibacterial activity through the destruction of bacterial cell walls, alteration of cell permeability, influence on the synthesis and expression of pro-proteins, reduction of enzyme activity, inhibition of nucleic acid synthesis[43] inhibiting biofilm formation [44]	*Salmonella enteritidis, Pseudomonas aerugi-nosa, Staphylococcus aureus, Escherichia coli, Proteus, Klebsiella pneumonia, Aspergillus flavus* [43]	Low water solubility, low bioavailability, low gastrointestinal tract absorbs, *first pass metabolism*, low solubility [45]
		Quercetin has antifungal activity whose mechanism is unknown to date[44].	*Aspergillus fumigatus, Aspergillus niger, Candida spp., C. albicans, Saccharomyces cerevisiae* [44].	
		Quercetin has anti-coronavirus activity through binding to the SARS-CoV 3CLpro catalytic pouch thereby inhibiting replication[46]	Coronaviridae [46]	
3	Resveratrol	Antibacterial activity through binding ATP synthase so that it inhibits bacterial metabolism, induction of DNA fragmentation so that it inhibits growth, destroys cell membranes by leaking potassium[47]	*Bacillus, Helicobacter pylori, M. smegmatis, Vibrio cholerae, Neisseria gonorrhoeae, Arcobactercryaerophilus, Mycobacterium tuberculosis, Campylobacter coli, S. auerus*[47]*Haemophilus influenza*[48]	Oral bioavailability of 70%, experienced *first pass metabolism,* unstable inhaled by oxidation, light, enzymes, and high temperature. Low water solubility (0.03 mg/ml)[49], and stable at acidic pH[48]
		Antifungal activity is proven through the apoptopic induction mechanism[50]	Candida albicans, B. cinereaconidia [47]	
		Antiviral activity by inhibiting viral replication with activation of IL-6, TRIF/TBK1[48].	H1N1 and H3N2 influenza A viruses, human influenza B virus[48]	
4	Silmaryn	Antituberculosis activity with macrophage activation resulting in the production of NO and O_2 free radicals for mycobacterial elimination[51] Antibiotic activity through phenolic groups capable of influencing bacterial DNA topoisomerase[52]	Mycobacterium tuberculosis, Pesudomonas aeruginosa, Bacillus substilus, Staphylococcus aureus [52]	Low water solubility (< 50µg/ml), lipophilic (LogP = 1.41). Absorption in the gastrointestinal tract is low. Low bioavailability[53]
		Antiviral activity through the induction of interferon-stimulated gene expression 15 as well as suppressing TMPRSS2 expression in cell membranes so as to avoid attachment of viruses to cells [54]	COVID-19[54]	
5	Epigallocatechin gallate (EGCG)	Antibacterial through inhibition of extracellular matrix formation [55]	*Staphylococcus aureus, Acinetobacter baumannii, Escherichia coli, Klebsiella pneumonia, Pesudomonas aeruginosa*[55].	Low stability at neutral and alkaline pH. Low bioavailability due to high polarity, formation of inactive metabolites by enzymes, and interaction with microorganism in the colon[56]
		Antiviral activity by targeting viral membrane proteins or host cellular proteins, or both, to inhibit the early stages of viral infection (attachment, entry and membrane fusion)[57] Anti-SARS-CoV-2 virus through inhibition of ACE2 domain binding receptors thus inhibiting virus entry into cells[58]	SARS-CoV-2 virus[58]	

is a representation of the particle size distribution parameters. If the GSD value =1, it can be considered monodispersed. Conversely, if GSD>1.2, then the particles can be said to be hetero-dispersed. FPF is a particle fraction that has a size of D_{ae}<5µm from all powders delivered from the inhaler.[26]

Deposition

The location and effectiveness of particle deposition are mainly influenced by three factors during breathing: (a) physical characteristic of a particle (diameter particle, density, surface properties, or shape); (b) airway anatomy and alveoli structure;

(c) ventilation parameters affecting particulate deposition are breathing patterns (breath holding and expiratory flow limitations), tidal volume, and flow rate, which determine airflow velocity and residence time in the respiratory tract.[27] Particles with a size of D_{ae} 1 to 5 µm are stored in the lower airways, where 50% of the number of particles measuring 3 µm are deposited in the alveolar. On the other side, particles with a diameter less than 3 µm can be deposited in alveoli as much as 50 to 60%[28]. This is shown in Figure 2.

Mucoadhesive

There are a number of issues to consider when delivering drugs to the lungs. These include rapid clearance from the workplace, poor accumulation in the terminal airways and inefficient penetration through the mucosal and epithelial barriers. Therefore, in developing a drug delivery system, mucoadhesive properties are used to overcome these problems. Mucoadhesive polymers are usually used for interaction with negatively charged mucus to extend its stay in the respiratory tract.[29]

Development of An Inhalation Drug Delivery System

Microparticulate

- *Microparticles*

Inhalation microparticles are one of the developments of delivery systems that are widely used for the therapy of respiratory tract disorders because they are able to increase the effectiveness of drugs. Microparticles are micron-sized spherical particles in which drugs are dispersed in synthetic or natural polymers. Microparticles have a thickness and level of permeability that can be modified so as to control the drug release rate from the system.[23] The application of the use of an inhalation microparticle drug delivery system containing natural drugs can be seen in Table 2.

- *Microcapsule*

Microcapsules are drug delivery systems that form thin membranes to enclose the active ingredients therein. Thin membranes are usually formed using polymers. Microcapsules are produced with sizes in the range of 1 to 100 µm. This drug delivery system has been developed to increase dosing efficiency by minimizing side effects. Through microcapsules, drugs can be released through various forms of release such as rapid release, extended-release, targeted release, delayed release, etc. With these advantages, the formation of microcapsules is expected to increase the service life of the drug so as to increase patient compliance[30].

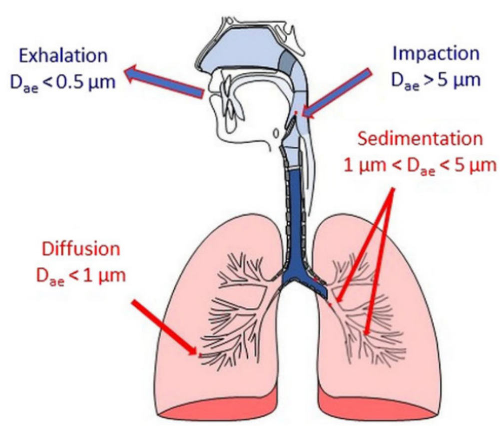

Figure 2: Relationship between aerodynamic diameter and the ability of particles to be deposited in the lungs[26]

- *Solid lipid microparticle*

Solid lipid microparticles (SLM) are a drug delivery system based on lipids. SLM consists of a solid lipid core. This is then stabilized by surfactants on its surface.. SLM exhibits several beneficial properties, such as organic solvent-free production, high drug loading rate and long-term stability. In addition, SLM can be considered an appropriate technology to provide suitable aerodynamic diameter values. This is important for the deposition of particles in the deep lungs because it can induce the process of inducing the endocytosis of alveolar macrophages. This is caused by many antimicrobials that are difficult to transport through cell membranes.[31]

- *Microsponge*

Microsponge is a polymer system consisting of porous microspheres. A microsponge is a small sponge-like spherical particle consisting of many interconnected cavities in a structure with a large porous surface that is utilized for controlled drug release. The size of the micro sponge ranges from 5 to 300 µm with a typical spherical shape and has up to 250000 pores.[32]

Nanoparticulate

Nanoparticles

Nanoparticles are a drug delivery system that is designed in the nanoscale size range. Using nanoparticulate lung delivery systems has several advantages such as homogeneous size distribution, increasing solubility and dissolution rate, regulating release, being able to deliver various macromolecules and internalization by cells. Various forms of nanoparticles are used in lung delivery, such as liposomes, polymeric nanoparticles, solid lipid nanoparticles, etc[33]. Physicochemical properties of nanoparticles that may influence nanoparticle clearance and translocation in the lung, such as particle size, surface charge and surface hydrophilicity[34]. The application of the use of an inhalation nanoparticle drug delivery system containing natural ingredients can be seen in Table 2.

Nanomicelles

The micelle is a nanotechnology-based drug delivery system. The micelle consists of small particles 10 to 400 nm in diameter formed by utilizing amphiphilic materials, which have hydrophilic and lipophilic groups. The micelles have three types of shapes based on their structure, namely (a) normal micelles (hydrophobic core inside and hydrophilic surface outside); (b) inverted micelles (hydrophilic core inside and hydrophobic surface outside); and (c) lamella bilayer. The loss of hydrophobic clusters from the aqueous environment results in the formation of micellar structures of

Table 2: Development of an inhalation pulmonary drug delivery system with natural drugs as anti-infection

No.	*Career Builder*	*Active Ingredients*	*Drug Delivery System*	*Method*	*Results*	*Ref.*
MICROPARTICLES						
1	Na Alginate	Quercetin	microspheres	Aerosolization ionic gelation technique, freeze drying	• Spherical particle morphology that assists *microsphere uptake* by alveolar macrophages • Increased concentration of alginate polymers can increase viscosity and droplet size so that microsphere size increases • Particle size <2µm making it optimal for inhalation delivery (<6µm) • The stability of quercetin-alginate microspheres at 25°C and 40°C for 28 days showed an increase in particle size but The particle size remained within the optimum size for inhaled administration.	59
2	PLGA/PEG-Chitosan	Curcumin	Nanosphere in microspheres	Single emulsion-solvent evaporation, Spray drying	• d_a are smaller than geometric diameters of 1.09±0.02 to 1.80±0.01 µm resulting in high respirability (R value $_f$) • Spherical particles with a smooth surface • The low humidity of particles in the range (1.21±0.10) % to (1.76±0.14) % causes a decrease in particle density, thereby increasing the aerodynamic ability of particles in the inhalation process • %FPF with d_a limit <4.46 µm of 30.2±6.5%	60
3	PLGA	Curcumin, Antibiotics (ciprofloxacin, tobramycin, Azithromycin), N-acetylcystein,	Nanoparticles in microspheres	Nanoprecipitation, spray drying	• Particle size was 105±1.5 nm with a zeta potential of -9.1 mV • NP-CUR-PLGA yields 68% encapsulation efficiency • %FPF of Ciprofloxacin microspheres is 64.48%, Tobramycin microspheres is 87.21%, Azithromycin microspheres is 68.83%,	61
4	Leucine, mannitol/ lactose	Shuang-Huang-Lian *(honeysuckle flower, radix Scutellariae and fructus Forsythiae)*	Microparticle	Spray drying	• Spherical particles with a median volume diameter between 1.93-2.12 µm • Particle has low Hauner ratio values resulting in low inter-particle cohesiveness. This improves particle flow properties • %FPF on fine surface particles by 52.2-56.5% • Coarse particles have a lower adhesive style than smooth surface parikel thus increasing aerosolization efficiency	62
5	PLGA	Resveratrol	Microsponge	Quasi-emulsion solvent diffusion method	• Formation of microsponges results in the creation of spherical particles with a porous surface, which is attributed to the increased viscosity of the internal phase • The surface of the particles is rough because there are resveratrol crystals due to the high encapsulation of resveratrol in the system resulting in precipitation in the microsponge • Particle size is in the range of 2.499 ± 0.56 to 6.424 ± 0.19 µm • Drug content was 44.72 ± 0.22% while entrapment efficiency was 89.45 ± 0.23% • Tapped density was 0.089 ± 0.14 g/ cm^3 (low) which makes particles have better aerosolization properties. • %FPF of 48.54% with MMAD of 2.13 µm • Resveratrol microspheres exhibit a substantial burst release of around 50% in the beginning due to a specific quantity of resveratrol present on the particle's surface. This was then followed by a controlled release because of where the resveratrol was layered on the particle. • Based on pulmonary pharmacokinetics, Cmax resveratrol microsponges is twice as large as resveratrol DPI with longer retention time and lower elimination due to the role of polymer matrix in microsponge particles.	63

6	Trehalose	Epigallocatechin Gallate (EGCG)	Microparticle	Spray freeze drying	• Fine spherical particles with a meso-porous structure so that they have a low particle density • Particle size was 5.4±1.92 µm • Encapsulation efficiency up to 91.24±14.37% • FPF of 72.8±6.7% • MMAD of 3.1±1.83 µm • Studies of antituberculosis activity in mouse macrophages infected with Mtb showed slightly higher bacterial reduction in microparticle compared to pure but insignificant. This occurs because the formula quickly breaks down to release the medication in a cell culture setting, where it is then internalized by macrophages. • Microparticles can be deposited in the lungs by >30% after 1 hour of inhalation of microparticles in mice • *In-vivo* activity studies in mice show that the use of inhaled microparticles in low doses is better than oral administration of EGCG	64
			NANOPARTICLES			
6	Soluplus® (Polyvinyl caprolactam-polyvinylacetate-PEG6000), Mannosylated Gelatin	Rifampicin, Curcumin	Nanomicelles	Solvent diffusion method, lyophilization	• Particle size in the range 101.8-366.7 nm • PDI is 0.218 – 0.424 • Spherical particles that facilitate the up-take process by macrophages • %FPF of 56% with d_a of 2.1- ±1.66 • Release with silf media at pH 7.4 (37°C) in 24 hours, nanomicelles are able to release 84.2% rifampicin and 56.2% curcumin. Lower curcumin release due to high affinity between curcumin and soluplus® polymers. • *In-vitro* testing using *M. tuberculosis* H37Rv bacteria was carried out by observing the viability of bacterial cells after treatment. The formation of rifampicin-curcumin nanomicells provides better antimicrobial activity compared to rifampicin nanomicels.	65
7	Mannosylated gelatin	*Glycyrrhiza glabra* extract	Nanoparticle	Double desolvation technique	• Particle size was 199.6 nm with a PDI of 0.231 • Spherical particles • Drug trapping by 23.87% • The release of Glycyrrhiza glabra Extract from gelatinous mannosylated (MnG) nanopaticles with gultaraldehyde as a crosslinker leads to a delayed drug release, leading to a steady release pattern • *In-vitro cell uptake* testing was carried out with raw 264.7 macrophage cells with the result that the cell uptake on MnG nanoparticles was 18.3 larger than the unmodified extract. This is supported by the targeting formulation with the use of mannose in the formulation. • *In-vivo* testing was performed using mice with *M. tuberculosis* H37Rv infection. After inhalation treatment of nanoparticle, high and low dose nanoparticles showed a reduction in bacterial load in the lungs of 1.6 and 0.97 log10, respectively..	66
8	Cellulose	Curcumin	Nanocellulose	Sulfuric acid hydrolysis	• Particle size was 50-100 nm • *Drug loading* amounted to 8.90±0.2 mg/g • All formulas show *intial bursts* where the highest concentration is 17.11±0.22 mg/L	67
9	PLGA/ cell membrane coated	Quercetin	Nanoparticle	Emulsification	• Size <250 nm and has a negative Zeta Potential value so it can be indicated that it will not be phagocytosed by macrophages • PDI <0.31 so that the particle size is homogeneous • *in-vitro* assay on H1299 cells related to inhibition of SARS-CoV-2 infection of AXL media. Quercetin nanoparticles effectively inhibit pseudo-viruses and infections.	68

10	Eudagrit ®	Tobramycin, Resveratrol	Nanoparticle	Nano-precipitation	• Produces spherical particles with sizes in the range 110-190 nm • Encapsulation efficiency more than 93% • PDI < 0.04 (high particle size homogeneity) • Drug release follows a non-fickian model where through diffusion and swelling mechanisms • Nanoparticle produce activity delays inhibiting the bacterial swarming process due to slow drug release	69
11	Albumin coated by chitosan	Silmaryn, curcumin	Nanoparticles	Lyophilization	• Spherical nanoparticles with nano-sized pores • Nanoparticles managed to trap silymarin by 96±0.3 µg/ml • Anti-COVID19 activity was tested using *plaque reduction assay* by measuring plaque formation by the virus. Nanoparticles with a concentration of 25µg/mL produced viral inhibition of 44.4%	70
12	Compritol 8888 ATO, poluvinyl alcohol	Yuxingcao essential oil	Solid lipid nanoparticles	High shear homogenization	• Particle size in the range of 171.2-811.9 nm with a PDI value of0.263-0.287 • Encapsulation efficiency of 76.61-90.20% • SLN experienced initial burst release for 5 hours then followed by sustained release for 48 hours • The volumetric median diameter (VMD) was in the rangeof 3.26-3.53 µm. The ability of particles to be inhaled is expressed in FPF < 5.4µm at >67.4% • An *in-vivo* lung retention study in rats proved that SLN was able to increase the AUC in the lung by a factor of 257 to 438 compared to the administration of an intravenous solution.	71

the associated monomers to reduce the free energy of the entire system. Micellar formation occurs when the concentration of amphiphilic molecules exceeds critical micelle concentration (CMC)[35].

Nanocellulose

Cellulocellulose (NC) is a cellulose fiber that is dispersed in nanomaterials of 100 nm or less. Nanocellulose has some advantages, including morphology, high crystallinity, biocompatibility, biodegradability, unique mechanical and rheological properties, high surface area, and geometric dimensions. Therefore, nanocellulose has been widely developed as a drug delivery system. In addition, this drug delivery system has the potential as a drug delivery system because it can be chemically modified so that it can bind and provide release to various drugs.[36,37]

Solid lipid nanoparticle

Solid lipid nanoparticle (SLN) is a nanotechnology-based drug delivery system that uses fat.SLN is a ball-shaped of physiologically compatible lipids that makes it classified as a non-toxic drug delivery system. SLNs consist of active ingredients encapsulated in a lipid layer, which typically consists of phospholipids, cholesterol, polyethylene glycol (PEG)-linked lipids and ionizable cationic lipids. SLN is formed in a size range between 50 to 1000 nm. SLN has various advantages, such as protection from drug degradation, increasing stability, increasing drug retention in target organs, and reducing systemic toxicity.[38] The application of the SLN drug delivery system containing natural drugs can be seen in Table 2.

CONCLUSION

The development of new strategies to increase antibiotic activity for lung infections and prevent the occurrence of drug resistance has been widely explored. Strategies for developing natural drug candidates such as curcumin, quercetin, resveratrol, and others in the pulmonary drug delivery system can be an alternative choice in the development of lung infection therapy by identifying the physicochemical and bioavailability properties that have been a limitation in the development of formulas. Inhaled drug delivery systems can deliver directly to the lungs, thus increasing the effectiveness of pulmonary drugs. The use of microparticles and nanoparticle technology as a natural material of drug delivery systems in the development of antituberculosis therapy has shown significant potential in various studies. Developing this system has been shown to increase the efficacy of natural medicines used as inhaled anti-infective therapies. Further research is still needed to overcome technical and clinical challenges, including efficient production methods on an industrial scale and clinical trials in humans.

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