

REVIEW ARTICLE

Applications of Nanoparticles in Treatment of Respiratory Disorders

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ABSTRACT

Respiratory disorders are very prevalent and high-incidence group of diseases having severe impacts on human health in the world. Some of the respiratory disorders are difficult to diagnose and treat, such as chronic obstructive pulmonary disease, asthma, lung cancer, and pulmonary tuberculosis. Lung cancer is the second most common cancer globally. Nano-delivery technologies have a great potential to improve the drug targeting in a specific area of infections in respiratory disease treatment. Not only nanoparticles concentrate the drug at specific-disease sites but also reduce the drug degradation and drug loss simultaneously. Sedimentation, nebulizers, carbon nanodots, and stimulus-responsive nanoparticles are currently being explored to use as a source for delivering nanodrugs to treat lung cancer. Various nanoparticles such as steroids, salbutamol, liposome-mediated, and polystyrene are used in the treatment of asthma and preterm birth diseases. This study focused on different kinds of nanoparticles like gold, solid lipid nanoparticles (NPs), steroidal and liposome-mediated nanoparticles which are used to treat different pulmonary or respiratory disorders and also examine the current therapeutic techniques for the diagnosis of lung diseases and therapy using nanoscale-based inhalers.

Key Words: *Asthma, Lung Cancer, Nanoparticles, Preterm Birth Disease, Respiratory Disorders, Nano Drug Delivery.*

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Introduction

Nanoparticles (NPs) are very small particles with a diameter of 1 to 100 nm that can be employed in the medical field to diagnose and cure several ailments.¹ Since nanoparticles act as a single unit, they can be used as an effective vehicle for drug delivery.² Besides this, nanoparticles can increase the solubility, stability, and bioavailability of the drug with less toxic effects because of targeted delivery.³ Nanoparticles can be delivered by different routes such as orally, subcutaneously, and by pulmonary inhalation.⁴

Transdermal medication-nanodrug delivery is also under consideration.⁵ Liposomes mediated, polymer and dendrimers nanoparticles are some of the most commonly employed nanocarriers in the

pharmaceutical industry for dermal or transdermal drug administration.⁶ When compared to intravenous treatment, subcutaneous delivery of nanodrugs boosts the efficacy of nanoparticles since the drug remains in the body for a longer period.⁷ The blood-brain barrier and the blood-cerebrospinal fluid barrier control the entry of nano-molecules into the brain.⁸ Nanoparticles can break the blood-brain barrier and work at the cellular level due to their small size, therefore their size has an impact on drug delivery.^{9,10} For example, liposomes, and solid lipid nanoparticles have been found to successfully transport drugs across the blood-brain barrier. The first medicine delivered to the brain coated with polysorbate 80 nanoparticles was hexapeptide dalargin.¹¹

Oral administration is the most common route of medication delivery due to its high level of body acceptance of the patient. The oral route is also the preferred route because of its convenience, efficacy, high patient compliance, and reduced risk of cross-infection.¹² One approach for overcoming the gastrointestinal barrier, protecting the drug from enzymatic breakdown, and releasing it in a

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controlled or systemic manner by nanoparticle encapsulation.¹³ The use of biodegradable polymeric NPs is another potential strategy for the pre-oral delivery of protein and peptide medications with improved efficacy.¹⁴

Compared to alternative delivery methods such as oral or injection, pulmonary delivery has some unique benefits. It avoids hepatic metabolism's initial pass, resulting in lower dosages and fewer side effects. Thus, therapeutics for respiratory illnesses such as chronic obstructive pulmonary disease, asthma, and cystic fibrosis can also be delivered locally via pulmonary track. Other advantages of the pulmonary route include a large surface area with quick absorption due to strong vascularization and avoidance of the first-pass metabolic effect.¹⁵ Nanoparticles may have a longer-lasting release in lung tissue and systemic circulation, resulting in reduced dosage frequency and greater patient compliance.¹⁶ Deposition of nanoparticles in the respiratory tract is determined by diffusional changes generated by the thermal motion of air molecules that interact with particles in the exhaled and inhaled air streams.¹⁷

Nanoparticle biodistribution and clearance are influenced by their size.¹⁸ Sub-micron sized nanoparticles have advantages over microparticles due to their small size and high mobility. Nanoparticles have a higher cell uptake than microparticles and are available to a broader range of cellular and intracellular targets. Due to their bigger surface area, they have a better loading efficiency than microparticles, which have a far lower loading efficiency.^{19,20} For application in the medical field, one must have a thorough understanding of nanoparticle features like form, biological response, size, and metabolism are necessary to make it beneficial in the treatment of disease.²¹ Pharmaceutical companies are reformulating conventional drugs by using different types of nanoparticles.²² Nanoparticles evolved or emerged as a rapidly growing field of research. In this article, we reviewed the nanoparticles applications in respiratory disorders like nanodrug is used as a carrier because it increases concentration and circulation time for the drug delivery at the site of the target area.²³

Types of Nanoparticles

There are different types of nanoparticles like inorganic, organic and carbon-based. Organic nanoparticles or polymers are generally known as liposomes, dendrimers, ferritin, hydrogels and micelles. These nanoparticles are non-toxic and biodegradable with some having a hollow core, such as micelles and liposomes. Non-carbon nanoparticles are known as inorganic nanoparticles. Inorganic nanoparticles are made up of metal and metal oxide-based nanoparticles. Carbon-based nanoparticles are those that are entirely comprised of carbon. Fullerenes, carbon nanotubes, graphene, carbon black, carbon nanofibers, and activated carbon in nanosize are all examples of carbon nanoparticles.²⁴

Gold (Au) is an essential nanomaterial that is used in the electronics and medical field. Gold nanoparticles (Au-NPs) are excellent candidates for transporting biological molecules into cells due to their good carrier capabilities, making them an attractive platform for medication and drug delivery.²⁵ Nanoparticles enter the body via different routes, including inhalation, ingestion, and diffusion method by the skin. Gold has long been regarded as a noble, inert metal and noncytotoxic having therapeutic and medical properties. Because of its capacity to conjugate with peptides and proteins, gold nanoparticles can be targeted to specific interaction partners.²⁶ In a chronic obstructive pulmonary disease (COPD) animal model, gold NPs were successfully transported to alveolar epithelial cells.²⁷ Solid lipid nanoparticles (SLN) are widely used in pulmonary drug delivery systems and chemically synthesized from phospholipids and triglycerides.²⁸ Solid lipid nanoparticles have several advantages, including physical stability, preservation of the incorporated drug against degradation, regulated release, and low cytotoxicity. Nanoparticles can also be easily aerosolized into droplets or encapsulated in aerodynamically compatible particulates, allowing for adequate deep lung deposition of an active chemical.²⁹

Synthetic polymer-based nanoparticles have a wide range of benefits in various fields. They're easy to create and less likely to harm the environment biologically. Depending on the chemical makeup of its building blocks, each form of the polymer has

distinct features.³⁰ For example polyethylene glycol coated nanoparticles, (PEG)- can also permeate respiratory mucus due to their muco-inert characteristics.³¹

Nanoparticles in the Treatment of Respiratory Diseases

The respiratory system is an important organ system of the human body that involves the inhalation of oxygen, exhalation of carbon dioxide, and maintenance of the body pH. Respiratory diseases are increasing, with an anticipated 1.8 million deaths. Lung cancer is one of the leading causes of cancer death (18 %).³² The advanced drug delivery system can offer a new system for the treatment of pulmonary diseases.³³

1. Lungs Cancer

The lungs consist of the bronchi, blood vessels, lymph tissues, and alveoli. Lungs consist of 500 million alveoli.³⁴ The alveoli are covered by the layer of phospholipids.³⁵ The surface tension in the alveoli is reduced by these phospholipids and surface proteins. This reduction in surface tension is necessary for gaseous exchange like carbon dioxide and oxygen.³⁶ Lungs cancer is the world's second most prevalent cancer. Non-small cell lung cancer (NSCLC) accounts for more than 80% of lung cancer cases, while small cell lung cancer (SCLC) accounts for 15% to 20% of all lung cancer cases.³⁷

Treatment of Lungs Cancer

Radiotherapy is not advised for the treatment of lungs cancer due to its severe side effects on normal tissues.³⁸ As an alternative, nano and microparticles can be used to treat lung.³⁹ Nanoparticles function as a target-sensitive biomarker in the case of lungs cancer.⁴⁰ Drugs-based inhalable nanoparticles have also been used to treat lungs cancer.⁴¹ The nanoparticles provide various benefits as a delivery channel for non-invasive medications, particularly for localized treatments, such as lung cancer and the treatment of airway illnesses like asthma, chronic obstructive pulmonary disease, and cystic fibrosis. Anti-cancer medications are regularly administered systemically to treat lung cancer, although this strategy frequently results in sub-optimal therapeutic concentrations of pharmaceuticals at tumor sites and harms the healthy cells and organs. As a result, local inhalation delivery is a viable option for delivering increased local medication

concentrations to the specific site. Dry powder inhaler (DPI), a pressurized metered-dose inhaler (pMDI), nebulizer, and soft-mist inhalers are four clinically successful aerosol pulmonary delivery methods.⁴² In the case of lungs cancer treatment, nebulizers offer more appealing options for chemotherapeutic drug administration, particularly for drug formulations created as particles of nano-sized in suspensions. Nebulizers are chosen because they can deliver a greater volume of aerosolized medicine in small droplets over a longer length of time.⁴³

Nanoparticles in the form of anticancerous drugs proved highly effective in different types of cancers. Nanoparticles decrease the toxic effect of anticancerous drugs in the targeted area.⁴⁴ Nanosystems, have been reported to target and administer the medicine in situ to selectively destroy cancer cells, reducing toxicity and adverse effects on healthy organs and tissues. It has been observed that some nanoparticles can overcome tumor resistance. Many types of nanosystems for diagnosis and therapy have been described with promising results, including dendrimer, gold NPs, polymeric micelles, liposomes, and other lipid nanoparticles. Nanoparticles can reach the target region without being identified by the immune system and undergo cellular absorption or deliver the medicine in the tumor proximity due to their biocompatibility and small size.⁴⁵

Anticancerous drugs in the form of nanocrystals are capable of delivering a large number of drugs to the target site. In short, nanoparticle-based drug administration via pulmonary ways can reduce the toxic effects of anticancerous drugs in lungs cancer.⁴⁶ Anti-cancer medications' therapeutic index can be improved by enhancing their bioavailability, stability, and residence at specific lung regions using nano-based systems such as liposomes, polymeric nanoparticles, or micelles.⁴⁷

Methods of Nanodrugs Delivery for the treatment of Lungs Cancer

Sedimentation: This method is widely used for the deposition of the particles in the case of nanodrug delivery system.⁴⁸ For the treatment of lung disorders such as cystic fibrosis, asthma, respiratory infection, lung cancer, different types of nanoparticles like carbon nanodots and stimulus-response

nanoparticles by medical aerosols are used.⁴⁹ These aerosols are magnetically targeted.⁵⁰

Nebulizers: This procedure is used for the inhalation of nanodroplets. A nebulizer converts the suspension of nanoparticles into droplet form that can be inhaled easily, therefore, this method is very effective in the treatment of lungs cancer. In routine, nanodroplets are delivered by aerosolization which is another example of nebulization.⁵¹

Pressurized metered-dose inhalers (pMDI): This procedure is also used to produce droplet suspension of nanodrugs. The aerosols from pMDI cannot be quickly removed from the lungs, therefore, pMDI application in lungs cancer treatment is limited.⁵²

Carbon Nanodots: Carbon nanodots are nanoparticles of carbon compounds with specific optical properties due to quantum conformations. Reduction in the size of carbon nanodots results in high compatibility, dispersion, and biochemical reactions. The drugs having amino groups can be attached to C-Nanodots that have carboxylic groups coated on the surface area by an amide linkage. C-Nanodots have replaced toxic quantum dots.⁵³

Stimulus-responsive nanoparticles: Stimulus-responsive nano-carrier system shows fast conversion of reversible phase in response to external stimulus and secretes specific contents at the specific site of interest. Pertaining to these advantages, stimulus-responsive core-shell nanocarrier conjugated to folic acid has been developed for lungs cancer treatment (Figure 1).⁵⁴

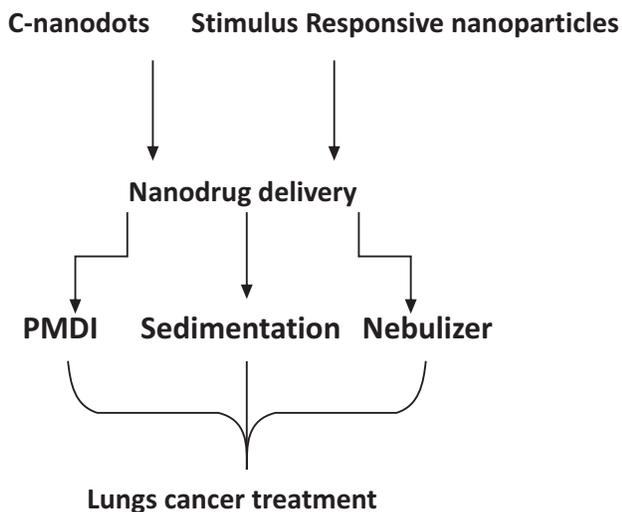


Fig 1: Flow chart representation of nanodrug delivery in lungs cancer treatment

2. Asthma

Asthma is a chronic condition, characterized by inflammation of the airways of the lungs, a persistent cough, wheezing, and shortness of breath.⁵⁵ Corticosteroids or bronchodilators are the typical therapies for asthma that can reduce the disease symptoms however their side effects are very prominent. Thus, nanoparticles can be used to reduce side effects with beneficial impacts in asthma treatment. Gold nanoparticles administered by nasal openings prevent allergen-induced asthma in several murine and reduce the disease symptoms with fewer side effects.⁵⁶ These studies show that gold nanoparticles can reduce the asthma symptoms such as airway hyperreactivity, lung remodeling, and inflammation. The protective effects are assumed to be due to a reduction in the production of pro-inflammatory cytokines and chemokines in lung tissue, which is linked to oxidative stress reduction.⁵⁷

Treatment of Asthma

Different types of nanoparticles are used in the treatment of asthma (Figure 2).

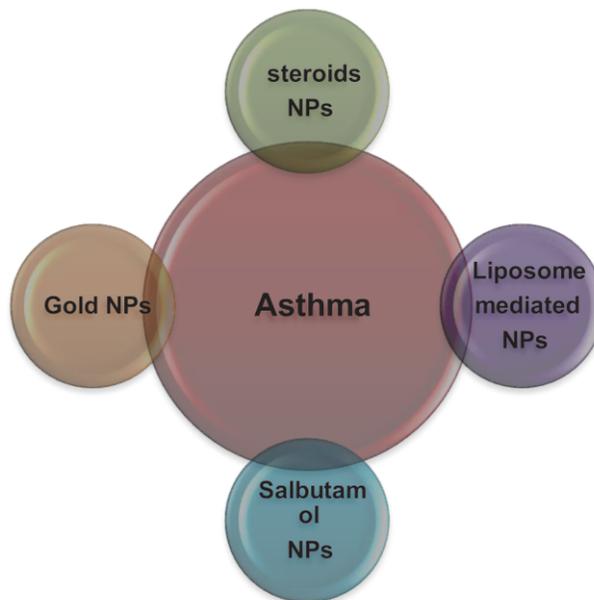


Fig 2: Treatment of Asthma by using different types of nanoparticles (NPs)

Steroidal nanoparticles: Steroidal-nanoparticles are more effective in the treatment of airway inflammation as compared to free steroids.⁵⁸

Salbutamol nanoparticles (SBML): Salbutamol encapsulated in nanoparticles is also used to deliver the drugs to the lungs membrane in case of asthma.⁵⁹

Liposome-mediated nanoparticles: Liposome-

mediated nanoparticles of salbutamol sulfate enhance the therapeutic effects by elevating the concentration and retention time of the drug inside the lungs.⁶⁰

3. Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death which is an important chronic inflammatory lung disease.⁶¹ It is due to inhalation of certain particles and gases which leads to inflammation in pulmonary airways that cause dyspnea and obstruction in airflow.⁶²

Gold nanoparticles: Au-Nps are used to treat COPD because of their less toxicity. It can be easily coated with any pharmacological compounds.⁶³

The gold nanoparticles are administrated to the epithelial surface which is taken up by the alveolar epithelium and gives therapeutic effects to lung parenchymal cells.⁶⁴

Poly (glycerol adipate –co-pentadecalactone) or PGA-co-PDL encapsulated nanoparticles: PGA-co-PDL encapsulated nanoparticles are used for targeted delivery of vaccines and proteins which increase the adsorptive properties of drugs in case of COPD.^{65,66} Different types of nanoparticles are used for the treatment of different kinds of respiratory disorders (Figure 3).

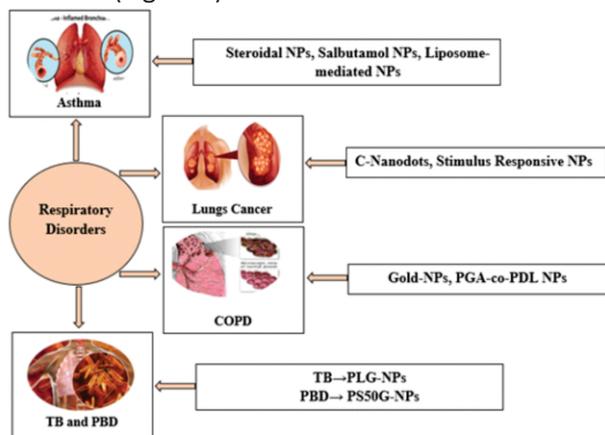


Fig 3: Respiratory disorders- Lungs Cancer, Asthma, Chronic Obstructed Pulmonary Disease (COPD), Tuberculosis (TB) and PBD (Preterm Birth Disease) can be treated by using different types of nanoparticle

4. Tuberculosis (TB)

TB is one of the leading causes of death among infectious diseases. TB has two major categories, pulmonary and extrapulmonary, and is caused by *Mycobacterium tuberculosis* which disturbs the lungs functions.^{67,68} TB can be treated by using

nanoparticle-encapsulated compounds. Poly DL-lactide-co-glycolide (PLG) nanoparticles associated with anti-tubercular drugs such as rifampicin, isoniazid are used to treat TB.⁶⁹

5. Preterm Birth Disease

Preterm birth is one of the causes of neonatal mortality. Mechanical ventilation leads to preterm birth disease in 20% of infants. Lungs inflammation can be reduced by using nanoparticles subsequently preventing preterm birth.⁷⁰

Polystyrene (PS50G) nanoparticles: Polystyrene nanoparticles are coated with glycine is administered intratracheally to reduce parenchymal lungs inflammation in an adult mouse, PS50g also give same effects in human.⁷¹

S. No	Disease	Nanoparticles	Study model	Improvements	References
1	Lungs cancer	C-nanodots Stimulus responsive Nps	Mouse	Effective	53,54
2	Asthma	Steriods, salbutamol Liposome mediated Nps	Mouse	-	58
3	COPD	Gold PDL-co- PGA Nps	Mouse	-	66
4	TB	PGL Nps	Murine mice	-	69
5	PBD	PS50G NPs	Mice	-	71

Conclusion

Nanoparticles offer a wide range of uses in the medical sector due to their small size and vast surface area. We reviewed the use of gold, solid lipid nanoparticles (SLN), steroidal, liposome-mediated, and polystyrene nanoparticles in the treatment of respiratory and pulmonary disorders such as lung cancer, tuberculosis, and chronic obstructed pulmonary disease (COPD), and preterm birth disease. Subcutaneous, oral, and inhalation are administration routes for nanoparticles. In this study, we concluded that nanotechnology is an emerging field to cure different types of respiratory diseases.

Future Perspectives

The beneficial effects of nanoparticles, in the treatment of respiratory disorders, require further research. One aspect could be the evaluation of other biochemical associated-nanoparticles with

high impacts and lesser side effects. The drug delivery technologies have the potential to revolutionize the drug therapy and catapult it to new heights, but the toxicity of nanosize formulations, on the other hand, should not be underestimated. It is imperative to develop methodologies that can assess both the short-term and long-term toxicity of nanoscale drug delivery devices.

REFERENCES

- Majdalawieh A, Kanan MC, El-Kadri O, Kanan SM. Recent advances in gold and silver nanoparticles: synthesis and applications. *Journal of nanoscience and nanotechnology*. 2014; 14: 4757-80.
- Dames P, Gleich B, Flemmer A, Hajek K, Seidl N, Wiekhorst F, et al. Targeted delivery of magnetic aerosol droplets to the lung. *Nature nanotechnology*. 2007; 2: 495-9.
- Brigger I, Dubernet C, Couvreur P. Nanoparticles in cancer therapy and diagnosis. *Journal of Advanced Drug Delivery Reviews*. 2012; 64: 24-36.
- Schneider CS, Xu Q, Boylan NJ, Chisholm J, Tang BC, Schuster BS, et al. Nanoparticles that do not adhere to mucus provide uniform and long-lasting drug delivery to airways following inhalation. *Science advances*. 2017; 3: e1601556.
- Prow TW, Grice JE, Lin LL, Faye R, Butler M, Becker W, et al. Nanoparticles and microparticles for skin drug delivery. *Advanced drug delivery reviews*. 2011; 63: 470-91.
- Baroli B. Penetration of nanoparticles and nanomaterials in the skin: fiction or reality?. *Journal of pharmaceutical sciences*. 2010; 99: 21-50.
- Kang H, Han M, Xue J, Baek Y, Chang J, Hu S, et al. Renal clearable nanochelators for iron overload therapy. *Nature communications*. 2019; 10: 1-1.
- Bicker J, Alves G, Fortuna A, Falcão A. Blood–brain barrier models and their relevance for a successful development of CNS drug delivery systems: a review. *European Journal of Pharmaceutics and Biopharmaceutics*. 2014; 87: 409-32.
- Senapati S, Mahanta AK, Kumar S, Maiti P. Controlled drug delivery vehicles for cancer treatment and their performance. *Signal transduction and targeted therapy*. 2018; 3: 1-9.
- Wilczewska AZ, Niemirowicz K, Markiewicz KH, Car H. Nanoparticles as drug delivery systems. *Pharmacological reports*. 2012; 64: 1020-37.
- Alyautdin R, Gothier D, Petrov V, Kharkevich D, Kreuter J. Analgesic activity of the hexapeptide dalargin adsorbed on the surface of polysorbate 80-coated poly (butyl cyanoacrylate) nanoparticles. *European journal of pharmaceutics and biopharmaceutics*. 1995; 41: 44-8.
- Das S, Chaudhury A. Recent advances in lipid nanoparticle formulations with solid matrix for oral drug delivery. *Aaps Pharmscitech*. 2011; 12: 62-76.
- Ensign LM, Cone R, Hanes J. Oral drug delivery with polymeric nanoparticles: the gastrointestinal mucus barriers. *Advanced drug delivery reviews*. 2012; 64: 557-70.
- Makhlof A, Tozuka Y, Takeuchi H. Design and evaluation of novel pH-sensitive chitosan nanoparticles for oral insulin delivery. *European journal of pharmaceutical sciences*. 2011; 42: 445-51.
- Paranjpe M, Müller-Goymann CC. Nanoparticle-mediated pulmonary drug delivery: a review. *International journal of molecular sciences*. 2014; 15: 5852-73.
- Schürch S, Gehr P, Im Hof V, Geiser M, Green F. Surfactant displaces particles toward the epithelium in airways and alveoli. *Respiration physiology*. 1990; 80: 17-32.
- Geiser M, Rothen-Rutishauser B, Kapp N, Schürch S, Kreyling W, Schulz H, et al. Ultrafine particles cross cellular membranes by nonphagocytic mechanisms in lungs and in cultured cells. *Environmental health perspectives*. 2005; 113: 1555-60.
- Gaumet M, Vargas A, Gurny R, Delie F. Nanoparticles for drug delivery: the need for precision in reporting particle size parameters. *European journal of pharmaceutics and biopharmaceutics*. 2008; 69: 1-9.
- Mohanraj VJ, Chen Y. Nanoparticles – A Review. *Tropical Journal of Pharmaceutical Research*. 2006; 5: 561-73.
- Singh R, Lillard Jr JW. Nanoparticle-based targeted drug delivery. *Experimental and molecular pathology*. 2009; 86: 215-23.
- van Rijjt SH, Bein T, Meiners S. Medical nanoparticles for next generation drug delivery to the lungs.
- Majdalawieh A, Kanan MC, El-Kadri O, Kanan SM. Recent advances in gold and silver nanoparticles: synthesis and applications. *Journal of nanoscience and nanotechnology*. 2014; 14: 4757-80.
- Schütz CA, Juillerat-Jeanneret L, Mueller H, Lynch I, Riediker M. Therapeutic nanoparticles in clinics and under clinical evaluation. *Nanomedicine*. 2013; 8: 449-67.
- Ealia SA, Saravanakumar MP. A review on the classification, characterisation, synthesis of nanoparticles and their application. *In IOP Conference Series: Materials Science and Engineering*. 2017; 263: 032019.
- Hussain S, Vanoirbeek JA, Haenen S, Haufroid V, Boland S, Marano F, et al. Prior lung inflammation impacts on body distribution of gold nanoparticles. *BioMed research international*. 2013.
- Elbakary RH, Okasha EF, Ragab AM, Ragab MH. Histological effects of gold nanoparticles on the lung tissue of adult male albino rats. *Journal of microscopy and ultrastructure*. 2018; 6: 116.
- Geiser M, Quaile O, Wenk A, Wigge C, Eigeldinger-Berthou S, Hirn S, et al. Cellular uptake and localization of inhaled gold nanoparticles in lungs of mice with chronic obstructive pulmonary disease. *Particle and fibre toxicology*. 2013; 10: 1-0.
- Beck-Broichsitter M, Ruppert C, Schmehl T, Guenther A, Betz T, Bakowsky U, et al. Biophysical investigation of pulmonary surfactant surface properties upon contact with polymeric nanoparticles in vitro. *Nanomedicine: Nanotechnology, Biology and Medicine*. 2011; 7: 341-50.
- Weber S, Zimmer A, Pardeike J. Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) for pulmonary application: a review of the state of the art. *European Journal of Pharmaceutics and Biopharmaceutics*. 2014; 86: 7-22.
- Jokerst JV, Lobovkina T, Zare RN, Gambhir SS. Nanoparticle

- PEGylation for imaging and therapy. *Nanomedicine*. 2011; 6: 715-28.
31. Schuster BS, Suk JS, Woodworth GF, Hanes J. Nanoparticle diffusion in respiratory mucus from humans without lung disease. *Biomaterials*. 2013; 34: 3439-46.
 32. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: a cancer journal for clinicians*. 2021; 71: 209-49.
 33. Azarmi S, Roa WH, Löbenberg R. Targeted delivery of nanoparticles for the treatment of lung diseases. *Advanced drug delivery reviews*. 2008; 60: 863-75.
 34. Strunz M, Simon LM, Ansari M, Kathiriya JJ, Angelidis I, Mayr CH, et al. Alveolar regeneration through a Krt8+ transitional stem cell state that persists in human lung fibrosis. *Nature communications*. 2020; 11: 1-20.
 35. Krahl VE. Microscopic anatomy of the lungs. 1959; 80: 24-44.
 36. Tena AF, Clarà PC. Deposition of inhaled particles in the lungs. *Archivos de Bronconeumología (English Edition)*. 2012; 48: 240-6.
 37. Mangal S, Gao W, Li T, Zhou QT. Pulmonary delivery of nanoparticle chemotherapy for the treatment of lung cancers: challenges and opportunities. *Acta pharmacologica sinica*. 2017; 38: 782-97.
 38. Gobbo OL, Sjaastad K, Radomski MW, Volkov Y, Prina-Mello A. Magnetic nanoparticles in cancer theranostics. *Theranostics*. 2015; 5: 1249.
 39. Hitzman CJ, Wattenberg LW, Wiedmann TS. Pharmacokinetics of 5-fluorouracil in the hamster following inhalation delivery of lipid-coated nanoparticles. *Journal of pharmaceutical sciences*. 2006; 95: 1196-211.
 40. Hirsch FR, Varella-Garcia M, Cappuzzo F. Predictive value of EGFR and HER2 overexpression in advanced non-small-cell lung cancer. *Oncogene*. 2009; 28: S32-7.
 41. Lee WH, Loo CY, Young PM, Traini D, Mason RS, Rohanizadeh R. Recent advances in curcumin nanoformulation for cancer therapy. *Expert opinion on drug delivery*. 2014; 11: 1183-201.
 42. Dolovich MB, Dhand R. Aerosol drug delivery: developments in device design and clinical use. *The Lancet Journal*. 2011; 377: 1032-45.
 43. Respaud R, Vecellio L, Diot P, Heuzé-Vourc'h N. Nebulization as a delivery method for mAbs in respiratory diseases. *Expert opinion on drug delivery*. 2015; 12: 1027-39.
 44. Müller RH, Mäder K, Gohla S. Solid lipid nanoparticles (SLN) for controlled drug delivery—a review of the state of the art. *European journal of pharmaceuticals and biopharmaceutics*. 2000; 50: 161-77.
 45. Bahadori M, Mohammadi F. Nanomedicine for respiratory diseases. *Tanaffos*. 2012; 11: 18-22.
 46. Farokhzad OC, Langer R. Impact of nanotechnology on drug delivery. *ACS nano*. 2009; 3: 16-20.
 47. Lee WH, Loo CY, Traini D, Young PM. Inhalation of nanoparticle-based drug for lung cancer treatment: advantages and challenges. *Asian journal of pharmaceutical sciences*. 2015; 10: 481-9.
 48. Yang W, Peters JI, Williams III RO. Inhaled nanoparticles—a current review. *International journal of pharmaceuticals*. 2008; 356: 239-47.
 49. Rao RD, Markovic SN, Anderson PM. Aerosol therapy for malignancy involving the lungs. *Current cancer drug targets*. 2003; 3: 239-50.
 50. Ally J, Martin B, Khamesee MB, Roa W, Amirfazli A. Magnetic targeting of aerosol particles for cancer therapy. *Journal of magnetism and magnetic materials*. 2005; 293: 442-9.
 51. Zhou QT, Tang P, Leung SS, Chan JG, Chan HK. Emerging inhalation aerosol devices and strategies: where are we headed?. *Advanced drug delivery reviews*. 2014; 75: 3-17.
 52. Conti DS, Brewer D, Grashik J, Avasarala S, da Rocha SR. Poly (amidoamine) dendrimer nanocarriers and their aerosol formulations for siRNA delivery to the lung epithelium. *Molecular pharmaceuticals*. 2014; 11: 1808-22.
 53. Wu YF, Wu HC, Kuan CH, Lin CJ, Wang LW, Chang CW, et al. Multi-functionalized carbon dots as theranostic nanoagent for gene delivery in lung cancer therapy. *Scientific reports*. 2016; 6: 1-2.
 54. Menon JU, Kuriakose A, Iyer R, Hernandez E, Gandee L, Zhang S, et al. Dual-drug containing core-shell nanoparticles for lung cancer therapy. *Scientific reports*. 2017; 7: 1-3.
 55. National Heart, Lung, Blood Institute. National Asthma Education Program. Expert Panel on the Management of Asthma. Guidelines for the Diagnosis and Management of Asthma. National Asthma Education Program, Office of Prevention, Education, and Control, National Heart, Lung, and Blood Institute, National Institutes of Health; 1991.
 56. Cooper V, Metcalf L, Versnel J, Upton J, Walker S, Horne R. Patient-reported side effects, concerns and adherence to corticosteroid treatment for asthma, and comparison with physician estimates of side-effect prevalence: a UK-wide, cross-sectional study. *NPJ primary care respiratory medicine*. 2015; 25: 1-6.
 57. Barreto E, Serra MF, Dos Santos RV, Dos Santos CE, Hickmann J, Cotias AC, et al. Local administration of gold nanoparticles prevents pivotal pathological changes in murine models of atopic asthma. *Journal of biomedical nanotechnology*. 2015; 11: 1038-50.
 58. Liu FK, Chang YC. Using thiol-capped gold nanoparticles in the background solution of MEKC to concentrate and separate neutral steroids. *Chromatographia*. 2010; 72: 1129-35.
 59. Ahmad FJ, Mittal G, Jain GK, Malhotra G, Khar RK, Bhatnagar A. Nano-salbutamol dry powder inhalation: a new approach for treating broncho-constrictive conditions. *European Journal of Pharmaceuticals and Biopharmaceutics*. 2009; 71: 282-91.
 60. Chen X, Huang W, Wong BC, Yin L, Wong YF, Xu M, et al. Liposomes prolong the therapeutic effect of anti-asthmatic medication via pulmonary delivery. *International journal of nanomedicine*. 2012; 7: 1139.
 61. Barnes PJ, Shapiro SD, Pauwels RA. Chronic obstructive pulmonary disease: molecular and cellular mechanisms. *European Respiratory Journal*. 2003; 22: 672-88.
 62. Moller W, Felten K, Sommerer K, Scheuch G, Meyer G, Meyer P, et al. Deposition, retention, and translocation of ultrafine particles from the central airways and lung

- periphery. *American journal of respiratory and critical care medicine*. 2008; 177: 426-32.
63. Brandenberger C, Rothen-Rutishauser B, Mühlfeld C, Schmid O, Ferron GA, Maier KL, et al. Effects and uptake of gold nanoparticles deposited at the air–liquid interface of a human epithelial airway model. *Toxicology and applied pharmacology*. 2010; 242: 56-65.
 64. Geiser M, Quaile O, Wenk A, Wigge C, Eigeldinger-Berthou S, Hirn S, et al. Cellular uptake and localization of inhaled gold nanoparticles in lungs of mice with chronic obstructive pulmonary disease. *Particle and fibre toxicology*. 2013; 10: 1-0.
 65. Kunda NK, Alfagih IM, Miyaji EN, Figueiredo DB, Gonçalves VM, Ferreira DM, et al. Pulmonary dry powder vaccine of pneumococcal antigen loaded nanoparticles. *International journal of pharmaceutics*. 2015; 495: 903-12.
 66. Kunda NK, Alfagih IM, Dennison SR, Tawfeek HM, Somavarapu S, Hutcheon GA, et al. Bovine serum albumin adsorbed PGA-co-PDL nanocarriers for vaccine delivery via dry powder inhalation. *Pharmaceutical research*. 2015; 32: 1341-53.
 67. Ai JW, Zhou X, Xu T, Yang M, Chen Y, He GQ, et al. CRISPR-based rapid and ultra-sensitive diagnostic test for *Mycobacterium tuberculosis*. *Emerging microbes & infections*. 2019; 8: 1361-9.
 68. Tuberculosis Drug Screening Program*. Search for new drugs for treatment of tuberculosis. *Antimicrobial agents and chemotherapy*. 2001; 45: 1943-6.
 69. John AE, Lukacs NW, Berlin AA, Palecanda A, Bargatze RF, Stoolman LM, et al. Discovery of a potent nanoparticle P-selectin antagonist with anti-inflammatory effects in allergic airway disease. *The FASEB journal*. 2003; 17: 2296-8.
 70. Inocencio IM, Bischof RJ, Xiang SD, Zahra VA, Nguyen V, Lim T, et al. Exacerbation of ventilation-induced lung injury and inflammation in preterm lambs by high-dose nanoparticles. *Scientific reports*. 2017; 7: 1-0.
 71. Hardy CL, LeMasurier JS, Mohamud R, Yao J, Xiang SD, Rolland JM, et al. Differential uptake of nanoparticles and microparticles by pulmonary APC subsets induces discrete immunological imprints. *The journal of immunology*. 2013; 191: 5278-90.
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