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Place : **Sincerely,**

Date : **[Miss. Pratiksha A. Ghode]**

INDEX

Current Advances In Drug Delivery Of Nanoparticles For Respiratory Disease Treatment

ABSTRACT

Cases of respiratory diseases have been increasing around the world, affecting the health and quality of life of millions of people every year. Chronic respiratory diseases (CRDs) and acute respiratory infections (ARIs) are responsible for many hospital admissions and deaths, requiring sophisticated treatments that facilitate the delivery of therapeutics to specific target sites with controlled release. In this context, different nanoparticles (NPs) have been explored to match this demand, such as lipid, liposome, protein, carbon-based, polymeric, metallic, oxide, and magnetic NPs. The use of NPs as drug delivery systems can improve the efficacy of commercial drugs due to their advantages related to sustained drug release, targeting effects, and patient compliance. The current review presents an updated summary of recent advances regarding the use of NPs as drug delivery systems to treat diseases related to the respiratory tract, such as CRDs and ARIs. The latest applications presented in the literature were considered, and the opportunities and challenges of NPs in the drug delivery field are discussed

Keywords : *Lipids, liposomes proteins and extra cellulers vesicles Metallic, oxide, and phosphate nanoparticles.*

INTRODUCTION

Diseases involving the respiratory tract are among the leading causes of death and disability around the world. According to the World Health Organization (WHO), more than 9 million deaths were related to respiratory diseases in 2016, corresponding to about 15% of deaths worldwide. Chronic obstructive pulmonary disease (COPD), lower respiratory infections, lung cancer, and tuberculosis are respiratory injuries listed among the ten leading global causes of death.[1] The o extremely vulnerable to airborne infections and injuries, and must be listed among the priorities of the health sector.[2] The respiratory system is responsible for gas exchange in multicellular organisms, which is fundamental to survival.[3,4] The gas exchange occurs via the inhalation of oxygen from the atmosphere into the lungs, followed by the exhalation of carbon dioxide into the atmosphere. The respiratory system consists of two major divisions: upper airways and lower airways. The upper airway system includes the nose and the nasal cavity, frontal sinuses, maxillary sinus, larynx, and trachea. The lower airway system involves the lungs, bronchi, and alveoli.[5] Both upper and lower airways are vulnerable to respiratory diseases, causing a decrease in the quality of life and impairing the vital functions of the human body.

The main respiratory system conditions include -

- Chronic respiratory diseases (CRDs)
- Acute respiratory infection A9RIs)

- **Chronic respiratory diseases (CRDs)**

CRDs are responsible for reducing the quality of life in many patients, innumerous hospital admissions and expenses, and in the worst cases, deaths. The most well-known CRDs include asthma, allergic rhinitis, cystic fibrosis, lung cancer, and chronic obstructive pulmonary disease (COPD).[6] The major factor responsible for CRDs is the deterioration of air quality, especially due to road vehicles, fuel combustion, and particulate matter from chemical reactions and industrial processes. Another important risk factor is associated with the genetic characteristics of the patient. Asthma is the most common noncommunicable CRD, affecting more than 300 million people around the world.[7]

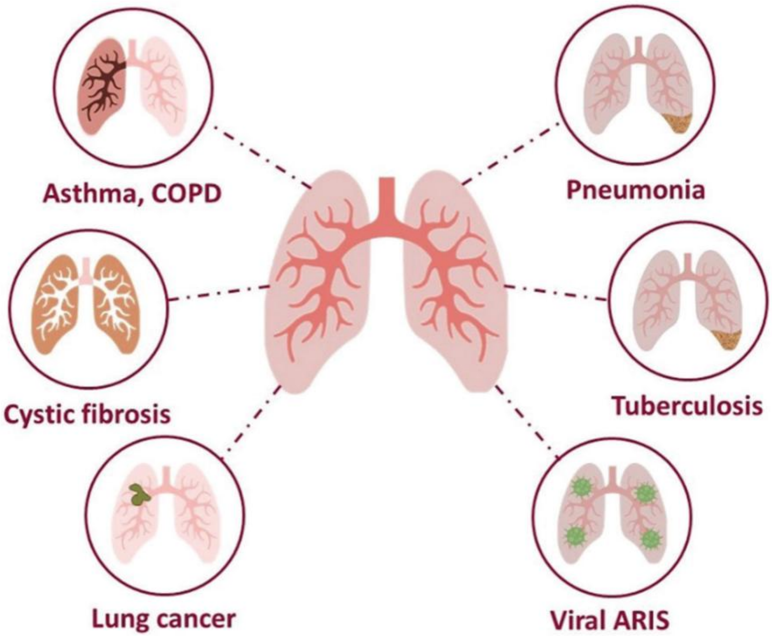

Fig. 1 Examples of CRDs (lung cancer, asthma, chronic obstructive pulmonary disease (COPD), and cystic fibrosis) and ARIs (pneumonia, viral ARIS, tuberculosis).[45]

- **Acute respiratory infections (ARIs)**

ARIs, also known as acute respiratory syndromes (ARSs), are among the leading causes of death around the world and are responsible for about 4 million deaths annually, and are the major cause of death among children under 5 years old.2 Viruses and bacteria are mainly responsible for lower respiratory-tract infections, causing conditions such as the common cold, pharyngitis, laryngitis, bronchitis, pneumonia, and tuberculosis.[8] The severity of ARIs increases year by year with the emergence of new virus-related diseases, such as the new coronavirus, known as COVID-19. Seven known human coronaviruses have been reported since the mid-1960s, being responsible for about 15% of common cold cases.[9] The coronaviruses with higher mortality rates in the human population are the severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV), and the most recent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 or COVID-19). MERS-CoV was first recognized in Saudi Arabia in 2012, being responsible for about 2494 cases and 858 deaths from 27 different countries. SARS-CoV and SARS-CoV-2 were both first isolated in China. In 2002 and 2003, SARS-CoV was responsible for 8422 cases with about 919 deaths in 32 different countries.[10] The most recent ARI caused by coronaviruses, COVID-19, was first recognized in December 2019 and has infected 54 075 995 people and caused 1 313 919 deaths in almost all countries in the world (as of November 16, 2020).10 COVID-19 majorly affects the lower respiratory system, and the initial symptoms in the affected patient is fever, fatigue, dry cough, and difficulty in breathing. In addition, vital organs, such as the liver, kidneys, heart, and gastrointestinal tract are also compromised by the disease, leading to multiple organ complications.[11]

Respiratory disease treatment limitations

The lack of innovative strategies to combat CRDs and ARIs cause a significant decline in the quality of life due to adverse effects, especially for elderly patients.[12] The main obstacles frequently experienced in respiratory disease treatments (e.g., multidrug-resistant strains, lack of innovative solutions, earlydetection difficulty, unsuccessful therapeutic trials, adverse effects, and high cost) may be somewhat overcome through the use of nanotechnology.[13] Nanotechnology removes the barriers between biological, physical, and materials science through the use of nanostructures. Nanomaterials are defined as materials with a particle size between 1 and 100 nm, which present unique properties due to their large surface area. In this way, nanomaterials have been largely studied in nanomedicine science to be used as biosensors, in microfluidics, as fillers for tissue engineering, and in drug-delivery systems.[14] Nanoparticles (NPs) are more effective when compared to some conventional systems due to the direct targeting effect, capacity of enhancing the treatment efficacy, and reducing the collateral effects. As a result, sensitive reduction in toxicity and adverse reactions can be achieved.[15]

Organic nanoparticles

Lipids, liposomes, proteins, and extracellular vesicles

There is a consensus that the potential success of NPs in the clinic relies mainly on considering parameters such as NP fabrication strategies, their physical properties, drug loading efficiencies, and drug release potential. In addition, NPs should have a minimum toxicity themselves.[16] Among the innumerous possibilities, only a limited number of drug-loaded NPs are successful in their clinical applications. Due to their low or lack of toxicity, NPs produced using an assembly of natural biomolecules such as lipids and proteins are a promising choice for clinical applications.[17,18] The choice of a nanocarrier system largely depends on the intended therapeutic effect. For example, albumin is one of the proteins most used as a nanocarrier due to the possibility that it can be attached via either covalent or non-covalent linkages to different drugs.[19] Among the various lipid-based nanocarriers, some examples are solid lipid NPs (SLN), nanostructured lipid carriers (NLC), and lipoplexes. Lipid-based nanocarriers were developed to improve the performance of nanoemulsions, in which the liquid phase is substituted with a solid one (SLN) or a blend of solid and liquid lipids (NLC).0 Lipoplexes are complexes formed by a combination of cationic liposome and negatively charged DNA[20]

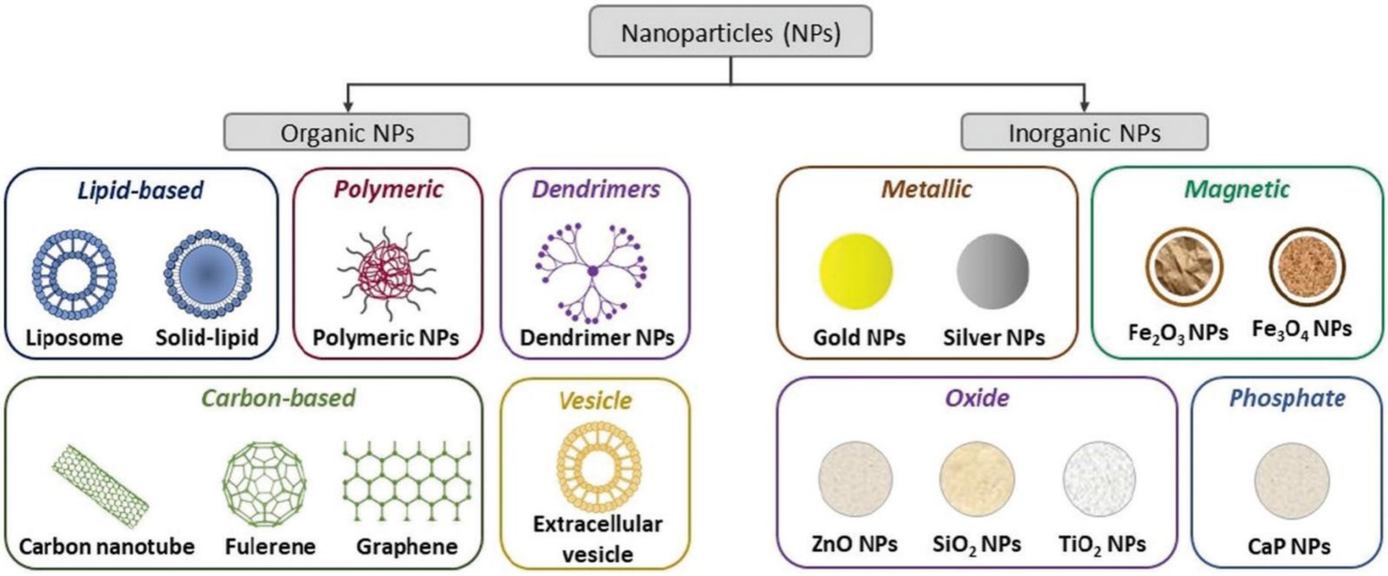

Fig. 2. Example of NPs used in drug delivery for respiratory disease treatment.[45]

Carbon-based nanoparticles

Structures exclusively formed by carbon atoms with nanometric dimensions, called carbon NPs, such as carbon nanotubes (CNT), graphene (GPH), and fullerene (FUL), have emerged as potential materials in several fields of research, due to their outstanding physical–chemical properties.[21] Usually, CNTs are obtained by arc discharge, laser ablation, and chemical vapor deposition. GPH can be synthesized via exfoliation, and FUL can be prepared by arc vaporization of graphite or laser ablation and hydrocarbon combustion.[22,23] CNTs, the most widely studied carbon NPs, are being used for biomedical applications,

such as sensors, composites for implants, and drug delivery systems.[24] CNTs are potential nanocarriers due to their excellent optical properties and are able to be functionalized, making them easy to attach to the desired chemical groups.[25]

Polymeric nanoparticles and dendrimers

Tested the co-encapsulation of theophylline (hydrophilic) and budesonide (lipophilic) into poly (lactic acid) (PLA) NPs for pulmonary drug delivery. Budesonide is a commonly prescribed inhaled corticosteroid used for the treatment of asthma and COPD, with predominant effects on the lungs. On the other hand, theophylline is a powerful bronchodilator and is generally prescribed, via the oral route, as an option for asthma treatment. The objective of the authors was to produce a compound that presented sustained release of both drugs, increasing the dosing interval and patient adherence. The co-encapsulation of PLA NPs with budesonide and theophylline occurred using a double emulsification solvent diffusion (DESD) method. Furthermore, mono-encapsulated drug-PLA NPs were also prepared for comparison with the co-encapsulated drug-PLA NPs. The delivery systems produced were tested according to drug loading efficiency and drug release. The results showed similar release profiles for budesonide and theophylline from both mono- and co-encapsulated PLA nanoparticles. In addition, the tests showedsatisfactory controlled release by 24 hours, meaning that it can reduce the occurrence of adverse effects. According to the authors, in a practical situation, this would avoid the need for multiple inhalers. [26]

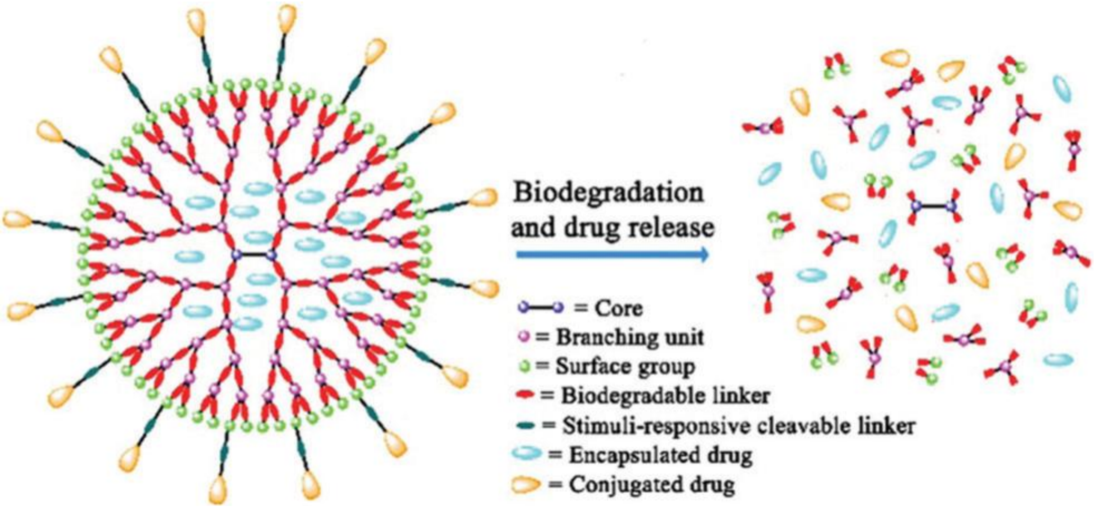

Fig.3. Schematic illustration of the biodegradation of dendrimers used as nanocarriers. Reprinted with permission.[27]

Table 1 Organic NPs used in drug delivery systems for respiratory disease treatment [26,36-40]

Nanoparticle	Drug	Disease	Effect
NLC	Lumacaftor and Ivacaftor	CF	Cellular penetration of the drugs and effect on intracellular processes.
SLN	EMB	Tuberculosis	High drug loading efficiency and slow release of drug.
Lipoplexes	PTX and Sur	Lung cancer	Effectively accumulate PTX in cancer cells, cytotoxicity against human lung cancer

PLA	Theophylline and Budesonide	COPD	Encapsulation of two drugs, avoiding the use of multiple inhalers.

Inorganic nanoparticles

Metallic, oxide, and phosphate nanoparticles

Inorganic NPs can be used in the biomedical field as drug delivery systems or as stand-alone therapeutic agents. They are characterized by easy modification and detection, high drug loading capacity, chemical stability and optical and magnetic properties.[28,29] For this reason, these NPs can be applied in simultaneous diagnosis and therapy of various diseases including cancer therapies.[29] Therefore, the most common inorganic NPs suitable for the biomedical field are silica NPs, gold NPs (AuNPs), silver NPs (AgNPs), titanium dioxide (TiO2), zinc oxide (ZnO), and calcium phosphate (CaP).[30,31]

Magnetic nanoparticles

Magnetic nanoparticles (MNPs) are increasingly used in several fields of science and industry. In the biomedical area, MNPs have been used due to properties such as biocompatibility and biodegradability, and especially because of their magnetic and heat-mediated characteristics.[32] As a consequence of these inherent properties, MNPs can be used in different applications including targeted drug delivery and hyperthermia-based therapy.[32–35] Various diseases can be treated utilizing MNPs, for instance, lung cancer and tuberculosis.[33,35-37] Besides, MNPs can be applied as contrast agents for magnetic resonance imaging, contributing to the identification of tumors and consequently helping in earlier diagnoses.[35]

The MNP technology could help in the identification of tumor cells, which facilitates suitable treatment. Besides, traditional therapies, such as chemotherapy and radiotherapy, frequently require high doses of drugs, and most of them do not reach the tumor target, while they can harm healthy tissue and cause side effects for patients. Recent studies have proven that MNPs, assisted by a magnetic field, can be used as drug carriers, making treatment faster, more efficient and causing less harm to normal cells. However, there are some drawbacks concerning MNPs. For example, hyperthermia requires a strong magnetic field to generate sufficient heat to kill cancer cells, which in some cases could damage both healthy and cancer cells.

One promising approach is combining hyperthermia with chemotherapy in the same multifunctional magnetic NP system. Another strategy widely investigated is combining two or more drugs in one MNP, using their synergic effect to improve the success of the treatment. Despite these potential data, more studies are still required to optimize targeted delivery of MNPs to diseased cells to guarantee that the treatment is safe for patients and fulfill the various regulatory requirements.

Table 2 : Inorganic NPs used in drug delivery for respiratory disease treatment[41-43]

Nanoparticle	Drug	Disease	Effect
Fe3O4	PEM	Lung cancer	Cytotoxicity against human lung cancer cells.
Fe3O4	Dox and MTX	Lung cancer	Cytotoxicity against human lung cancer cells.
Fe3O4	HSPI	Lung cancer	Lung cancer Cytotoxicity against human lung cancer cells with apoptotic effects.

Conclusions

This review gives an overview of different NPs used in drug delivery for respiratory disease treatment. CRDs and ARIs have increased over time, creating an enormous challenge to health and life quality. Curing these diseases must therefore be among the priorities of the global health sector. In this way, organic and inorganic NPs have been an excellent alternative to improve the drug distribution, due to their direct targeting effect and controlled release of therapeutics. New systems with enhanced treatment efficacy and reduced collateral effects can be produced by combining the medicines used nowadays with the new technological NPs. Among the organic NPs presented, innovative studies showed a great potential to treat ALI, ARDS, asthma, CF, COPD, lung cancer, and tuberculosis. In addition, inorganic NPs proved to be effective in the treatment of influenza, tuberculosis, and lung cancer. Although sustained drug release was achieved using NPs as drug carriers, some conflicts must be resolved to facilitate their transition from laboratories to clinics. Current biological barriers include the toxicity of these materials towards the human body and the drug side effects. Another challenge is related to the limited studies published about the topic, especially concerning in vivo analysis. A better evaluation of these new technological systems will be possible with the complete study of their behavior in long-term treatment and indepth research related to the real effects in human organisms. More studies are still required to optimize the targeting effect, controlled release and medicine efficacy, to guarantee that the treatment is safe for the patients and able to meet the expectations of a healthy life. In conclusion, the studies cited in this review showed that organic and inorganic NPs are fundamental to the production of multi-functional drug delivery systems with superior medical effects compared to the conventional ones.

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