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LUNG CANCER: THERAPIES, IMPEDIMENTS, AND TOXICITY OF INHALED POLYMERIC NANOPARTICLES

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ABSTRACT

Cancer of the lung is the most prevalent kind since it is identified in a considerable number of individuals and has a low chance of survival. Lung cancer comes in a variety of forms, the most common being non-small cell carcinoma, which accounts for the majority of cases diagnosed globally. In order to treat the lung carcinoma there is a advent of many therapies such as chemotherapy, immunotherapy, gene therapy, photodynamic therapy and nanotechnology based therapy having numbers of advantages as well disadvantages. The inhalable polymeric nanoparticles for drug targeting is one of the most ideal approach for the drug delivery in the lung cancer as it is less toxic, having high biocompatibility with good biodegradability and also there is efficient transport of drug to the cancerous cells. However, because the lungs have so many clearance mechanisms, including enzymatic, respiratory, and fast systemic absorption, it is challenging to achieve stable localization in the respiratory tract upon drug inhalation. Polymeric nanoparticles although appears to be best candidate for targeted drug delivery but they do offers toxicity to the healthy cells which is affected by numerous types of characteristics like size, shape, charge, biodegradability and disease condition as well as interaction with the lungs environment. This review paper highlights the lung cancer with its types and the therapies which are being applied for its treatment and drug delivery. There is also discussion about the challenges faced by

the polymeric nanoparticles upon inhalation and the factors affecting the toxicity of inhaled nanoparticles.

Keywords: Lung cancer, non-small cell lung carcinoma, photodynamic therapy, nanotechnology, enzymatic clearance, shape, structure, toxicity

1. INTRODUCTION

Globally with a 15% chance of survival, lung cancer ranks among the leading causes of cancer-related deaths [1]. Lung cancer are usually categorized in to two categories as shown in figure 1, i.e, small cell lung carcinoma and non-small cell lung carcinomas in which the non-small cell lung carcinoma is mostly diagnosed in number of patients worldwide as compared to the small cell lung carcinoma[1]. The most distinct factor which is shown by the small lung cancer is that they have neuroendocrine properties due to which are easily diagnosed with the help of histology as well as immunohistochemistry. There are three subtypes of non-small cell lung carcinoma: adenocarcinomas, squamous cell carcinomas, and large cell carcinomas. Adenocarcinomas are the most prevalent classification of non-small cell lung cancer among all of these types of lung cancer patients. The existence of a pathological distinction between small cell lung carcinoma and non-small cell carcinoma is crucial since it determines the best course of treatment for lung tumours[2].

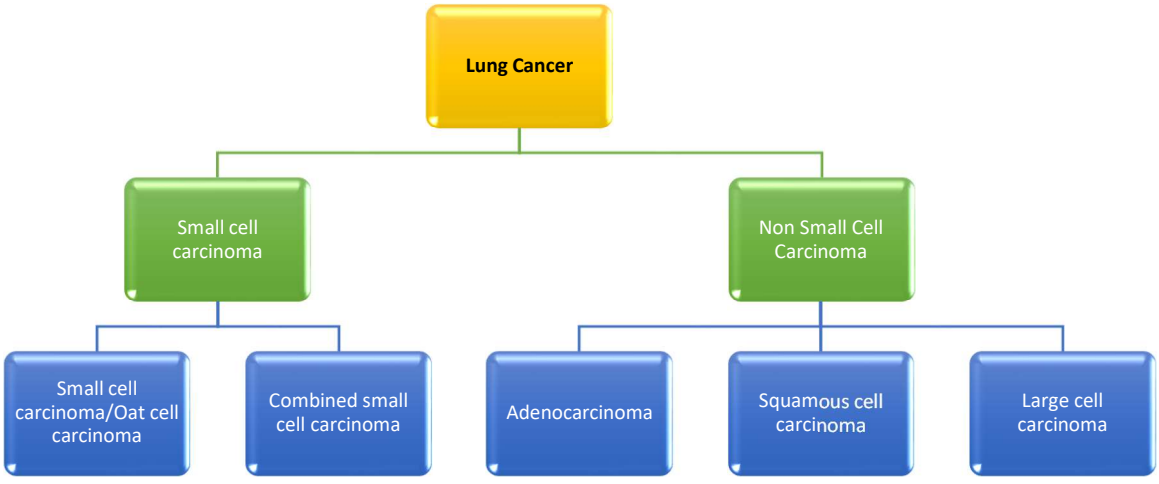


Figure 1: Classification of lung cancer[2]

There are an astounding 220,000 new cases of lung cancer diagnosed each year, with non-small cell lung cancer accounting for 85% of cases[2]. Comparatively speaking to non-small cell lung cancer, small cell lung cancer is more dangerous. It is also more difficult to treat because patients with small cell lung cancer frequently experience recurrence after receiving initial rounds of

chemotherapy. Small cell lung cancer is one of the least common types of lung cancer cases; only about 1 in 10 people are estimated to have this type of cancer[3]. Figure 2 illustrates the proportion of instances of lung cancer that have been diagnosed.

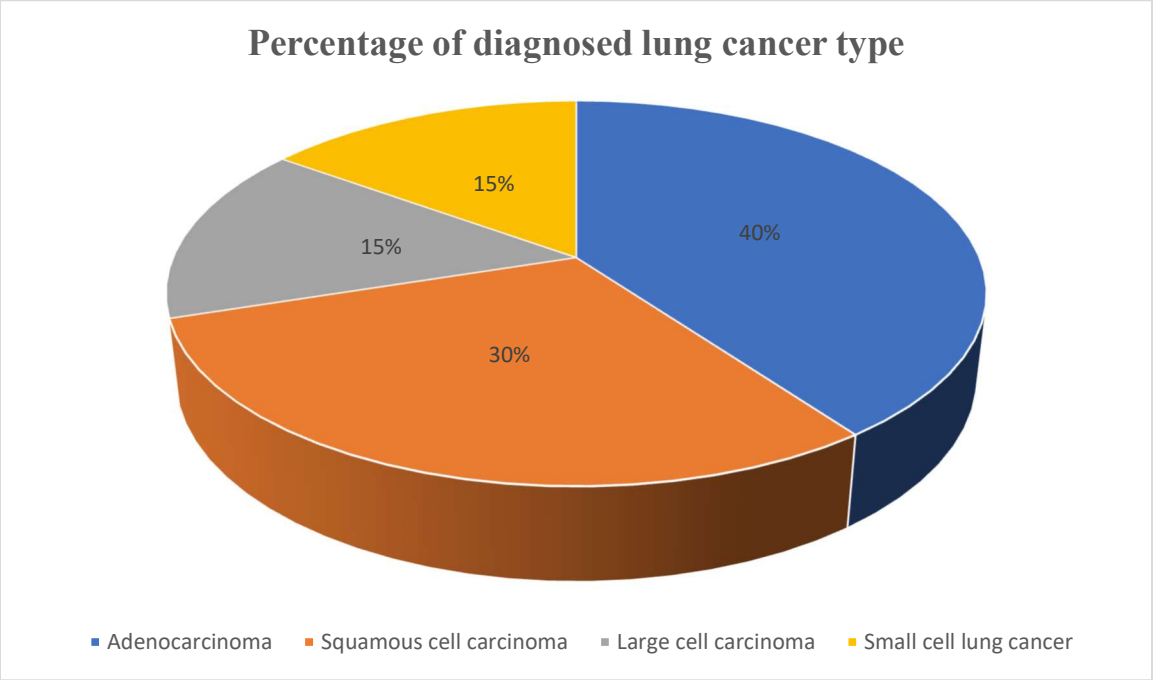


Figure 2: Percentage of diagnosed lung cancer cases[4]

At present lung cancer therapy mainly dependent upon types of malignancy along with the stage of cancer[5] and is usually of following types as depicted in the given figure 3.

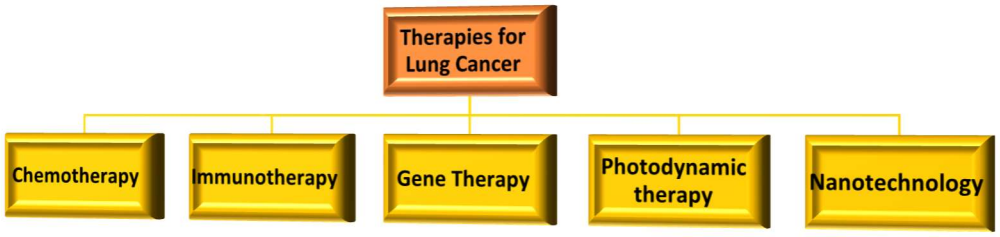


Figure 3: Different therapies for lung cancer[5]

Chemotherapy or the treatment with the help of the chemotherapeutic agents is one of the most widely selected type of treatment for lung cancer in which the anti-cancer drugs are often administered via IV route where it targets the tumor site and destroys the cancerous tissues or cells after reaching with the help of the systemic blood circulation. The most common used anti-

cancerous drugs which are used are carboplatin and cisplatin. Although chemotherapy is best line of treatment it possess some of the adverse effects for example chemotherapy which is platinum based is conjugated with various types of dose limited side effects for example: anemia, nephrotoxicity, cardiotoxicity, nausea and intestinal injury etc. In order to deal with this type of disadvantages platinum based chemotherapy is often administered along with the other types of anticancerous drugs i.e, as a combination therapy which not only improve the effectiveness but also decreases the amount of dosage administered to the patient. However despite of all of these advantages the dosage of chemotherapeutic agents at high amount is limited due to the water hating nature or hydrophobicity of majority of the anti-cancerous drugs due to which they are poorly water soluble and thus possess poor absorption by the cells[6,7]. To increase the effectiveness of chemotherapeutic agents many new types of therapies have been developed for example: immunotherapy, gene-based therapy, photodynamic therapy and nanotechnology.

Immunotherapy usually makes use of immune system to fight and destroys the cancerous cell/tissue. In this type of therapy as depicted in figure 4, immunoactive agents are usually administered which usually interferes with the various growth promoting activities of the tumors cells that leads to decrease in the immunosuppressive activity of the cancer cells[8]. By obstructing growth factors, hormones, and their receptors, immunologically active medications prevent the cascades that lead to tumour formation. In lung cancer there is overexpression of growth factor receptors like the epidermal growth factor receptor (EGFR/Her1). When the ligand epidermal growth factor (EGF) binds to the EGFR, the signalling pathways for cell survival and proliferation are activated, which leads to a fast and unchecked development of tumours[5]. Cetuximab, a monoclonal competitive anti-EGFR antibody, blocks endogenous EGF ligand-mediated cell proliferation signalling, weakening the signals that promote cell survival and inducing tumour cell death.

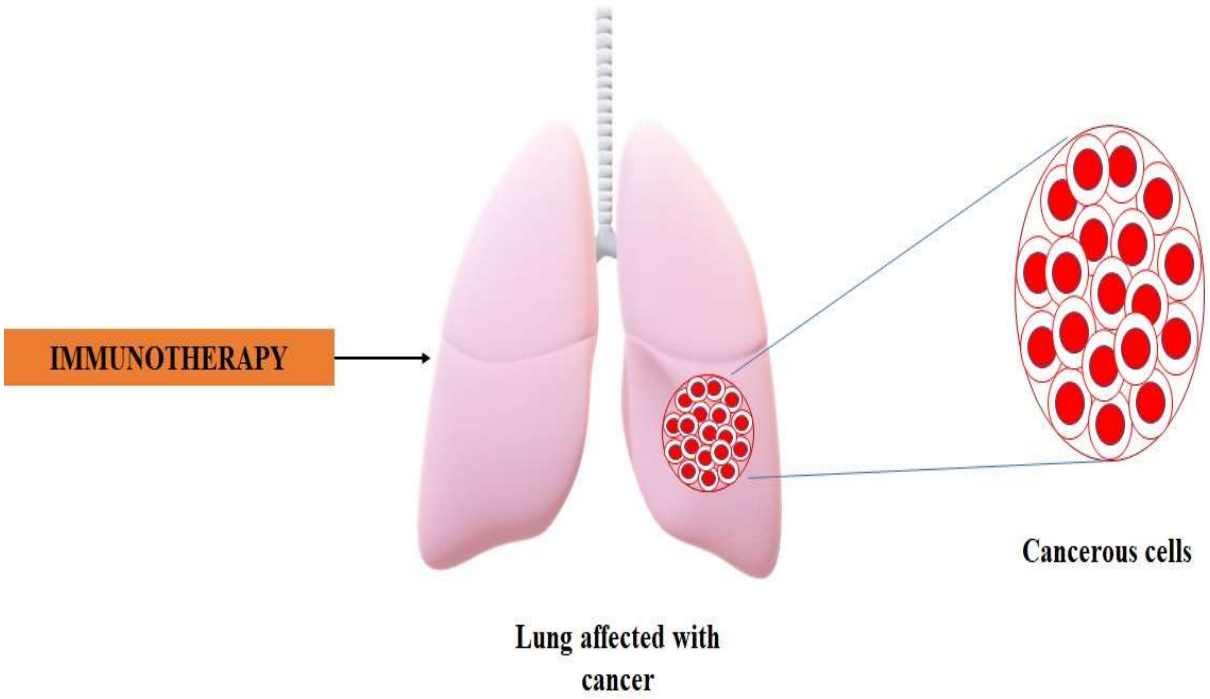


Figure 4: Immunotherapy for Lung cancer

Gene therapy is defined as the introduction of healthy genes into the affected cells for the purpose of treatment and prevention of the diseases. A novel approach to the management and treatment of cancer is gene therapy[9]. There are two approaches in gene therapy, first one is the in-vivo gene therapy in which there is direct delivery of the genes in the cells of the affected tissues whereas in the ex-vivo therapy there is a delivery of the genes to the cultured cells. Gene therapy mainly use the vectors for delivery of the therapeutic genes to the selected cancerous sites. In gene therapy vectors are defined as the vehicles which delivers the genes. There are two types of vectors which are viral vector and non-viral vector. Viral vectors are predominantly used as compared to non-viral vectors however they presents some type of immune reaction in the host.

A different approach to treating lung cancer is photodynamic therapy. In the photodynamic therapy as shown in figure 5, there is a use of the photosensitizer which gets activated upon incidence of the laser light and reacts with the oxygen which results in the development of highly active oxygen free radical that ultimately kills the cancerous cells. At current lung cancer is treated with a combination of the photodynamic therapy along with the chemotherapeutic agents however due to the low solubility of the photosensitizer the use of photodynamic therapy is limited[5].

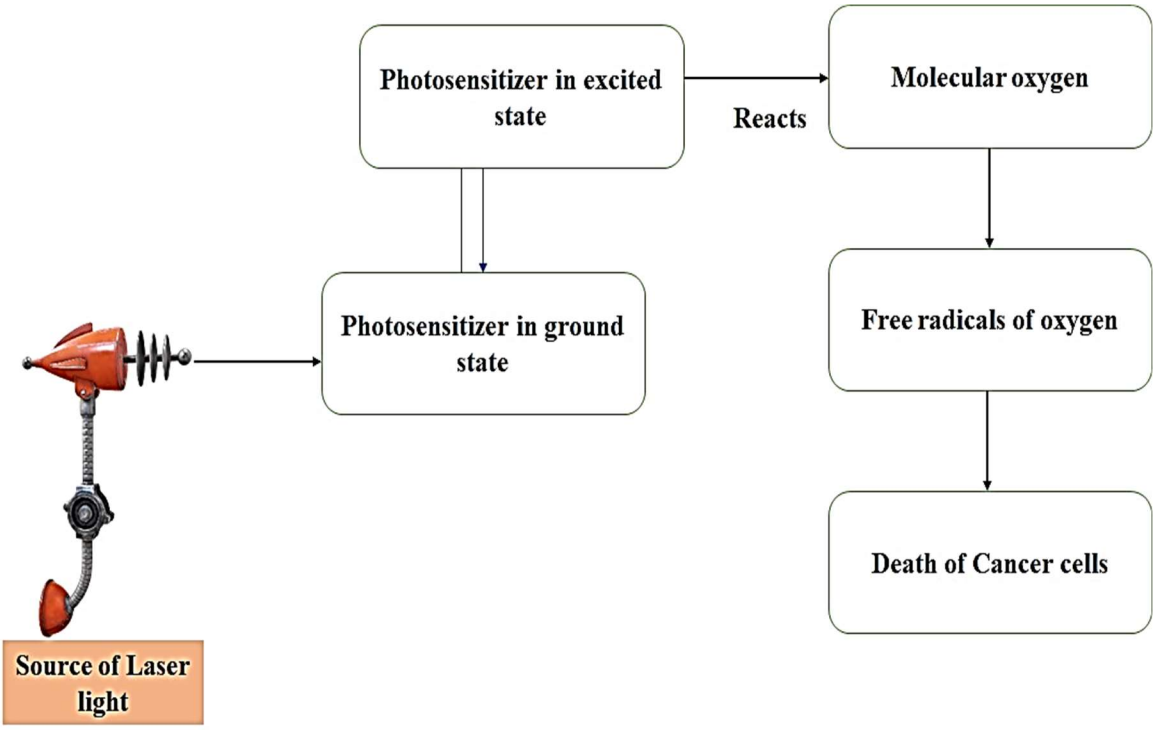


Figure 5: Photodynamic therapy of lung cancer[5]

To compensate and deal with the numerous disadvantages shown by the other types of therapies in treatment of cancer the nanotechnology is being employed as an ideal candidate for the targeted drug delivery to the cancerous cells. Nanotechnology based therapies employs nanoparticles for drug delivery. Because of diverse properties and characteristics nanoparticles are the best option for delivering the medication at a specific location in the body, the application of nanotechnology to cancer management, diagnosis, and treatment has grown significantly in the last several years. When compared to conventional therapies, treatments or therapies that use nanotechnology are advantageous because, first of all, the drug is transported to a specific location only, preventing toxicity towards healthy cells, and there is also greater absorption of the dosage forms, which is less noticeable than with conventional dosage forms[10]. For targeted medication delivery, nanoparticles are frequently used. Biodegradable or non-biodegradable polymers make up nanoparticles. When compared to larger molecules, nanoparticles (NPs) have a better bioavailability because cells absorb them more quickly because to their improved physicochemical and biological features. Nanoparticles are often used in research to examine their potential use in medicine due to their presence of nanoscale dimensions and a sizable surface area. Targeted drug delivery, where nanoparticles are utilised as a carrier to convey medication to a specific region in the body, is the most alluring field of nanotechnology use.

2. INHALABLE NANOPARTICLES FOR TARGETING:

In comparison of the conventional chemotherapy which usually delivers the drug to a cancerous site , the inhalation therapy deliver the anti-cancerous drugs to a specific target site i.e, tumors

which not only increases the effectiveness of the applied therapy for also reduces the occurrence of the side effects.

There are various advantages of the inhalation therapy which are as follows[11]:

1. Avoidance of first pass metabolism.
2. It is highly patient compliant.
3. There is a presence of least dosage.
4. No hypersensitivity reaction.
5. Less toxicities.
6. Non-invasive
7. Presence of biocompatibility

Despite of number of advantages, there are also a number of possible disadvantages to inhalable lung cancer therapy that have limited its practical use. After inhalation, chemotherapeutics are more locally localised in the lung, increasing the risk of pulmonary injury. Additionally, as soon as the therapeutic drug has been placed in the lung, removal of it begins right away. This rapid degradation frequently necessitates numerous daily inhalations, which unavoidably has an impact on patient compliance.

In order to deal with the disadvantages of conventional inhalation therapy many types of new therapies has been developed in which the inhalable polymeric nanocarrier based therapy is commonly used for lung cancer therapy.

Lung cancer treatment has successfully drawn attention recently to the use of inhalable nanocarriers for pulmonary medication delivery as shown by table 1, because nanocarriers have high capacity to join with the anti-cancer drug and also there is a controlled release of drug along with they are biodegradable, has high ability to convert into aerosols and they also avoid the clearance presented to them by the mucillary of the lungs[12]. Thus they have high retention time in the respiratory tract which overall increase the efficacy of the therapy to treat the lung cancer.

Table 1: Different types of nanocarrier and their observation

Polymeric Nanocarrier	Drug	Observation	Reference
Polylactide-tocopheryl Polyethylene glycol 1000 Succinate based nanosystem	Crizotinib	Superior anticancer efficacy and cytotoxic effect towards $NCIH_{3122}$ lung cancer cells in dose dependent manner.	[13]
PeGlyted PLGA based Nanoparticles	Docetaxel	Enhanced tumor targeted drug delivery with limited side effect and increased cytoxicity towards A549 cancer cells.	[14]

Chiton coated PLGA Nanoparticles.	Itraconazole	High cytoxicity and cell death in H1299 cell lines with cancerous cells being stopped at G_0/G_1 and G_2/M phase of cycle cell.	[15]
Poly(d,l-lactide-co-Glycolide) chitosan Composite	Paclitaxel and Topotocan	Concentration dependent toxicity of NSCLC line NCI-H460.	[16]
PLGA nanoparticle	Irinotecan and Stattic	Increased cytotoxicity and anti-cancerous efficiency in in-vitro.	[17]
PLGA TWEEN 80 Copolymer nanoparticle	Pacitaxel	Enhanced level of absorption of PLGA-TWEEN 80 in Paclitaxel resistant lung cancer line A549/T due to which there is higher level of cytotoxicity.	[18]
Biomimetic Nanoparticle	Docetaxel	Enhanced EPR and suppression in growth of tumor cells in in-vitro with best tumor targeting ability.	[19]
PLGA nanoparticles	Suberoylanilide Hydroxamic acid	Dominant antineoplastic activity as compared to free suberoylanilide Hydroxamic acid on Lung cancer cell lines in A549.	[20]
Chitosan coated PLGA/PCL Nanoparticle	Silibinin	Improved cytotoxicity and bioavailability of silibinin.	[21]
PLGA Nanoparticles	Epirubicin and Paclitaxel	Enhanced anticancer activity in comparison to native drug.	[22]

PeGylated Eudragrit Nanoparticles	Oseltamivir	ESR-OSE 2 trigger apoptosis intrinsically and highly selective to human lung adenocarcinoma cell lines.	[23]
Polydopamine Polylactide TPGS nanoparticles	Crizotinib	Inhibition of PC-9 cell viability and promotion of cell apoptosis with dominant cytotoxicity in in-vitro as well as in-vivo.	[24]
PLA Nanoparticles	Docetaxel	Decrease in Metastatic tumor area.	[25]
Monoclonal antibody Conjugated docetaxel Loaded PLGA nanoparticles	Docetaxel	Significant reduction in tumor growth.	[26]
Antibody conjugated PLGA Nanoparticles	Paclitaxel Palmitate	Better inhibition of tumor growth.	[27]
Cetuximab conjugated To Temozolomide Loaded PLGA NPs	Cetuximab and temozolomide	High absorption, cytotoxicity, apoptosis effect as compared to free drug.	[28]
Wheat germ agglutin Conjugated PLGA Nanoparticles loaded with Paclitaxel and isopropyl Myristate.	Paclitaxel and isopropyl myristate	WIT-NP showed more in-vitro cytotoxicity towards A549 and H1299 cells.	[29]
PLGA Nanoparticles	Paclitaxel	Enhanced antitumor effect with less side effects.	[30]

Aptamer coated paclitaxel-Polylactide nanoconjugates	Paclitaxel	Effective targeting of cancer cells.	[31]
Chitosan cross linker-γ- poly (glutamic acid) Nanoparticle Loaded with docetaxel	Docetaxel	Enhanced antiproliferative activity.	[32]

Nanoparticles represent one of the most useful agents in the pulmonary drug delivery as they have numerous advantages that makes them a prime choice for targeted medication delivery in cases of lung cancer or other tumours, however despite of several advantages that they offer in lung cancer therapy they still possess a challenge for the targeted drug delivery in the pulmonary region i.e, lung due to the three main factors which are mainly of clearance type[11]:

01. Enzymatic clearance
02. Respiratory clearance
03. Fast systemic clearance

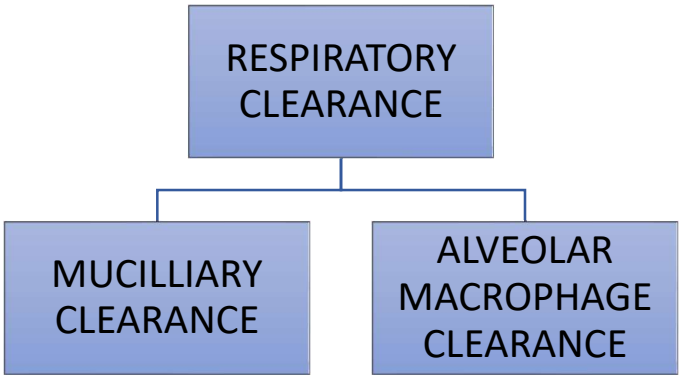
2.1. ENZYMATIC CLEARANCE:

Many of the drugs which are administered through the pulmonary route get degraded due to the presence of the several types of enzymes for example cytochrome p450, lung peptidases and proteases etc. Out of the types of enzymes that are present in the lung cytochrome p450 presents itself as primary degrading enzyme as well as detoxification enzyme for number of pulmonary drugs for example anti-asthmatic drugs. Protein based drugs for example anti-diabetic agent i.e, Insulin get degraded by the lung peptidases as well as proteases[11] . Clearance offered by the pulmonary enzymes provides a hurdle in the administration of pulmonary drug as due to it the retention time of the pulmonary drug gets low that contributes to the medication's limited bioavailability. Enzymatic clearance in lung is dependent on various factors such as patient age, disease condition, gender and polymorphism of various enzymes may increase or decrease their degrading activity towards the administered pulmonary drug. Although degradation shown by the pulmonary enzymes is of low in extent but due to their important role in the degradation of the drug the enzymatic clearance is being studied and investigated extensively in a number of studies.

2.2. RESPIRATORY CLEARANCE:

Respiratory clearance is the natural first line of defense which is protective in nature for removing the inhaled foreign particles from the lungs in order to prevent the interaction of the foreign particle

with the lungs tissues and due to this there is a hurdle in the bioavailability of the pulmonary drug. Respiratory clearance is classified into two categories i.e, Mucilliary clearance and Alveolar macrophage clearance.



Mucilliary clearance as shown in figure 6, represents the prime and the most important route of clearance and elimination of foreign particles from the lungs. It is mainly formed by the lines of epithelial cells covering the upper pulmonary tract. The lines of epithelial cells is also known as the mucocilliary escalator whose main function is to eliminate the foreign particles with the help of the mucus and also with the process of coughing. The mechanism by which mucilliary clearance eliminates the foreign particles is that the particles greater than the size of 6 µm are eliminated with the process of engulfing by the epithelial cells and removing with the help of cough. The most important point about the mucilliary clearance is that small particles are able to successfully bypass it as they are deposited in the alveolar region.

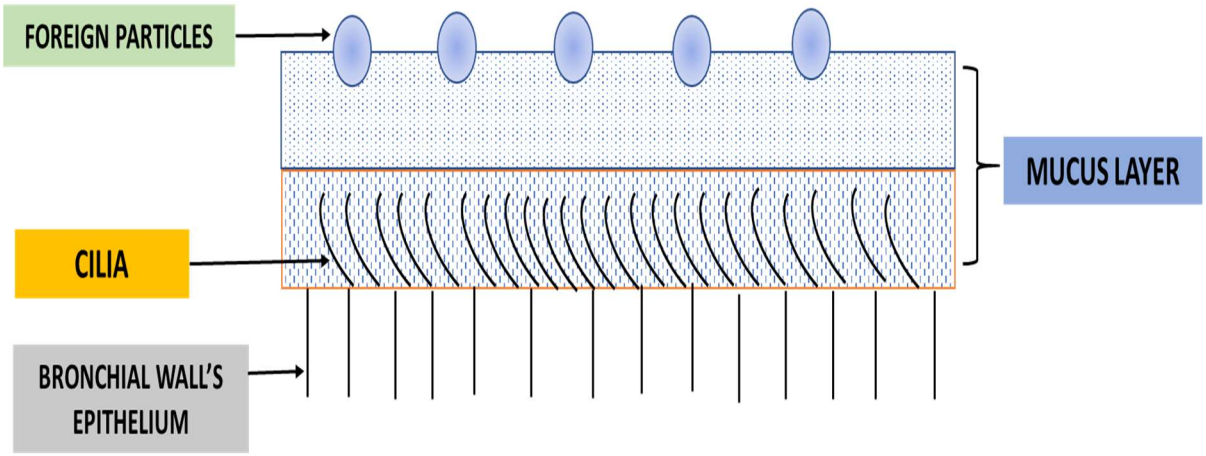


Figure 6: Mucilliary clearance

Kirch et al. used an ex-vivo and an in silico strategy to analyse micro and nanoparticles in order to determine how mucocilliary clearance is dependent on size, shape, and charge. Their research demonstrates that, in contrast to horizontal transport facilitated by mucilliary clearance, the mucocilliary clearance of different kinds of particles—micro or nano—regardless of their size, shape, or charge upon vertical penetration into the mucus layer[33] .

Woods et al. developed albumin based nanoparticle formulation and investigated them for their in-vivo biocompatibility, clearance and biodistribution in mouse model. Their study shows that albumin based nanoparticles could effectively achieve concentration in the lung tissues with low amount of formulation being eliminated by the mucocilliary clearance present in the lungs of the mouse[34].

The second type of clearance present in the lungs is the alveolar macrophage clearance. Alveolar macrophage as depicted in figure 7, originate from monocytes and are phagocytic cells that are typically found in the lung's alveolar area where they eliminate the inhalable administered drugs through xenobiotic clearance due to which their bioavailability as well as retention time in the pulmonary region gets diminished which ultimately leads to the failure of the therapy. Alveolar macrophage plays an important role as they provide innate immunity which provides protection to the lungs against various types of inflammation and cancer.

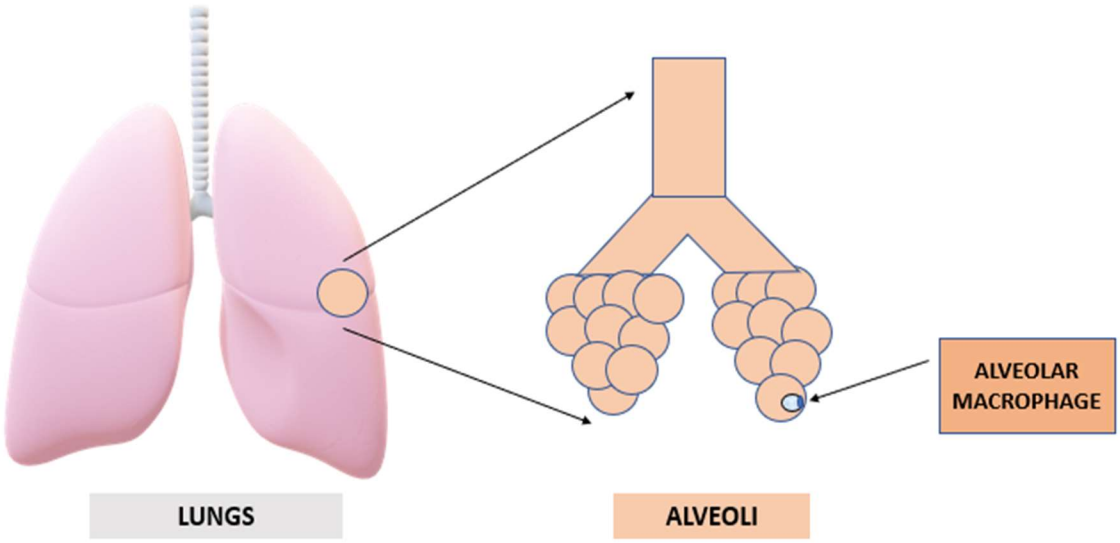


Figure 7: Alveolar macrophage

Lehr et al. used magnetite nanoparticles, which ranged in diameter from 110 to 180 and were coated with various polymers, to investigate the impact of surfactant protein A (SP-A) on the relationship of nanoparticles with alveolar macrophage uptake. Their research unequivocally shows that surfactant protein A-coated nanoparticles are being absorbed at a higher rate[35].

The uptake of pulmonary administered drugs by the alveolar macrophage is also dependent on their particle size and surface modification done with the help of the mannose.

2.3. FAST SYSTEMIC ABSORPTION:

One of the biggest hurdle which is faced by the inhalable nanoparticles is the fast systemic absorption in the lungs. Because of the lungs' enormous vascularity and wide surface area,

inhalable formulations are quickly absorbed into the systemic circulation when given to the lungs[36]. Due to this phenomenon there is also a appearance of undesirable side effects in other tissue other than lungs tissues by the inhalable administered drugs. The best strategy to prevent this is to localize the drugs only at the lungs regions so that its therapeutic effects gets increases and also there is a less appearance of side effects on the other tissues. The systemic absorption of the drugs administered through pulmonary route depends upon the drugs lipid solubility. Inhalable drugs are absorbed or removed depending on the drug's composition as well as how it interacts with the lung's surfactant, causing inhalable medicines to transfer from the air to the blood.
The molecules which are of low in molecular weight with good lipophilicity are absorbed more rapidly in the systemic circulation whereas the rate of systemic circulation absorption is directly dependent upon the molecular weight and the lipophilic nature of the carrier[37].

3. FACTORS AFFECTING THE TOXICITY OF INHALED NP'S:

Investigation of the toxicity of inhaled nanoparticles is day by day becoming very important as it gives idea about the safety profile of formulation which are being administered to the lungs. It is widely acknowledged that nanoparticles can be hazardous to human body cells in healthy conditions., toxicity is one of the most crucial factors to consider when choosing nanoparticles for medication delivery and there are many factors on which it is depicted as shown in figure 8.

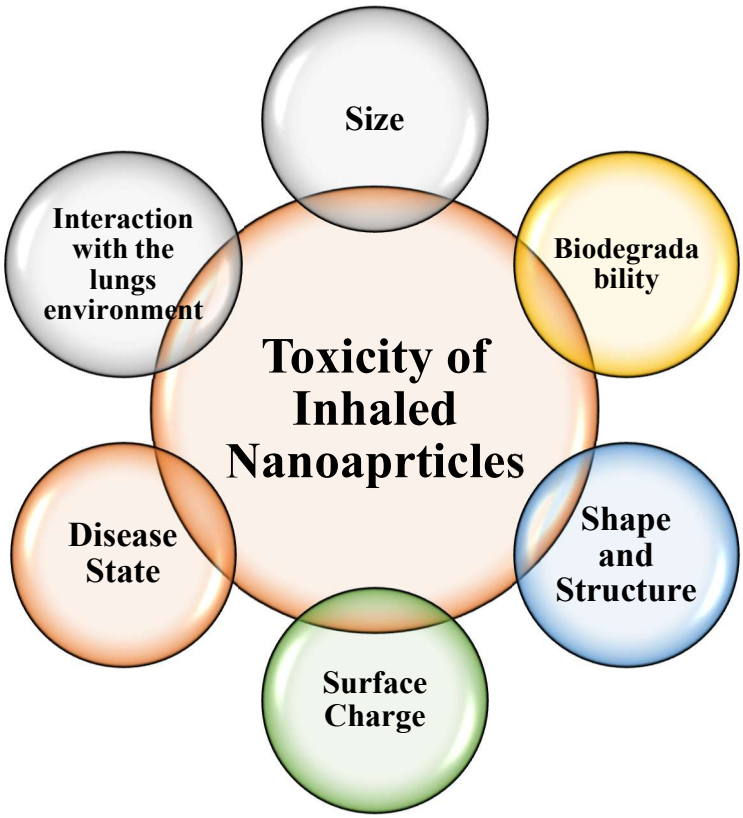


Figure 8: Factors affecting toxicity of inhaled nanoparticles

3.1. SIZE OF NP'S:

The most significant factor influencing the location and amount of nanoparticle deposition in the lungs following delivery is their size. For example, Large-sized nanoparticles are deposited in the upper part of the respiratory tract, whereas tiny and fine-sized ones are deposited at the terminal sections of pulmonary tract. Thus, it is implied that the deposition of the nanoparticles is directly proportional or directly related to the inhaled nanoparticle's size range. The area of deposition and toxicity level of inhaled nanoparticles are determined by their size in the particular lung region. For example, small-sized nanoparticles have been shown to cause cytotoxicity and other harmful effects on normal, healthy cells in comparison to larger range-sized nanoparticles due to enormous surface area.

Nanoparticles have the capacity to efficiently overcome membrane barriers that helps them to move towards the bloodstream, and have cellular as well as molecular effects on organs and tissues. The impact of nanoparticles (NPs) on the biological milieu and the subsequent harmful outcomes are closely linked to their small size distribution, high surface area to mass ratio (SA/MR) and surface properties. Nanoparticles have the capacity to penetrate cellular compartments, cell membranes and inflict toxicity and cellular damage. Adverse reactions can also be formed due to the nanoparticles extraordinarily huge SA/MR. The same chemical's surface reactivity, adsorption capabilities, and potential toxicity will all rise with its surface area[38].

Morimoto et al., conducted a study in which they carried out evaluation of the inhalation toxicity of the nanoparticles which are carbon derived. For this they compared toxicity upon inhalation produced by the commercial nanomaterials with that of carbon based nanoparticles i.e., carbon nanotubes and fullerenes. In their study they assessed toxicity of nanoparticles with the help of pulmonary inflammation and reported that among the various physical as well as chemical properties, the nanoparticles size has a significant impact on deciding its toxicity as the particle with small size generates huge surface area which is linked to the lung inflammation and can be evaluated through the calculation of the rate of neutrophils in bronchoalveolar lavage fluid, however the nanoparticles which has large size do not cause any inflammation infact they resulted into the increase in the thickness of the wall of the alveoli with less number of granulomatous lesions and thus resulted into less toxicity[39].

Hougaard et al., investigated the development of toxicity caused upon inhalation of the nanoparticles by the mother towards the pregnancy and the developing fetus. In their study they had gone through numerous data and reported that when the nanoparticles which were fine i.e., small in size inhaled by the mother, there is a possibility that inhaled nanoparticles can reach to the developing fetus through moving and can have harmful effects linked to respiratory tract to placenta development. However in conclusion they suggested that there is still low number of knowledge and studies that can make a linkage between the inhaled nanoparticles and the toxicity produce by them towards the developing fetus but altogether there is a possibility that the inhalation of the fine nanoparticles can cause toxicity towards the fetus which is of major medical concern and can't be ignored[40].

In one study the nanoparticles size is regarded as the one of the main parameters that defines how the nanoparticles can deposited in the lungs and can create toxicity in the lungs upon inhalation. The extent to which these particles are ingested by the macrophages are dependent upon the size[41]. A study was done to assess the cytotoxicity that comes from nanoparticles. The findings demonstrated that a variety of factors, such as the size, shape, and morphology of the particles along with ion dissolution rate, affect a nanoparticle's ability to cause cancer. Furthermore, when nanoparticles come into touch with cells, they raise intracellular calcium homeostasis and oxidative stress levels, which can cause damage and even death to the cells[42].

3.2. BIODEGRADABILITY OF NP'S:

Biodegradability of the nanoparticles refer to that nanoparticles which are made up of polymers that can be easily absorbed and cleared away from the body. Biodegradable nanoparticles are one of the most used carriers in the lung cancer treatment as they offer numerous advantages:

01. Increased dissolution rate.
02. Increased solubility
03. Large surface areas
04. Excellent transfer of medication into targeted tissues.

Biodegradability of the inhaled nanoparticles determines their level of toxicity exerted in the lungs. Generally biodegradable nanoparticles are more preferred as they are easily tolerated by the body and also doesn't cause any side effect in addition to detrimental effects on healthy cells. Nanoparticles on other hand which are made up from the non-biodegradable polymers creates irritancy along with toxicity in the lungs region.

A study was conducted to find out about the toxicity of the biodegradable nanoparticles administered through pulmonary route and comparison was done with that of non-biodegradable nanoparticles. In this study there was a coating of nanoparticles prepared by poly (D, L-lactide-co-glycolide) with various polymers like chitosan, polyvinyl alcohol , poloxamer and evaluated them for their biodistribution with the help of the in-vivo fluorescence imaging technique and concluded that the nanoparticles which were made up from the biodegradable polymers do not create any type of inflammation in the mice lungs after inhalation as compared to the non-biodegradable one that makes biodegradable nanoparticles safe for use with least toxicity[43].

Hu et al., assessed the toxicity produced by the biodegradable chitosan nanoparticles with the help of zebrafish embryo model. In their they incubated embryos of zebrafish with different concentrations of the biodegradable nanoparticles and discovered that the embryos which were incubated with the biodegradable nanoparticles had very low hatching rate with increased death rate along with it they have bent spine with high amount of oxidative stress due to the formation of the oxygen free radicals and disformed body. Thus they suggested that there is an toxicity associated with the biodegradable nanoparticles which has to be taken in consideration[44].

Alsmadi et al., prepared chitosan-alginate nanocarriers loaded with cisplatin and evaluated it for the toxicity as well the drug loading. In their study they found out that the dug loading on the

biodegradable nanocarrier was although very high but they causes toxicity in the lungs alon with further toxicity in the liver as confirmed by the animal toxicity studies done on the rat model[45].

3.3. SHAPE AND STRUCTURE OF NP'S:

Nanoparticles are available in number of varieties of shape and structures with distinguished properties and affects. Toxicity of inhaled nanoparticles also depends upon the shape and structure as different levels of toxicity is exerted upon the normal cells by the nanoparticles having different types of shape as well structure, for example inhaled nanoparticles having certain types of the shape and structure will exert more toxicity as compared to that ones possessing other morphological properties. Shape as well as structure is an important characteristic of the nanoparticles that defines its safety profile along with the cytoxicity that it produce in the normal cells.

In one study it was found out that shape as well as structure of nanoparticles could be linked to the toxicity that they produce as in some case the nanoparticles shape could affect the interaction with which they interact with several body cells[46].

In a one study numbers of different types of nanocarriers were developed and the effect of shape and structure on lung deposition is monitored. It was found out that there was a difference in patterns of deposition in lungs shown by the lipids based as well as non-lipid based nanoparticles having different types of shapes with best accumulation shown by the lipid based nanoparticles[47].

3.4. CHARGE ON THE SURFACE OF THE NP'S:

Charge present on the surface of the inhaled nanoparticles determine their extent of tolerability as well as toxicity in the lungs. The inhaled nanoparticles which are negatively charged produce less levels of the toxicity as compared to the positively charged ones. Anionic inhaled nanoparticles doesn't create any irritancy and are also well tolerated by the lungs tissues as compared to the cationic ones.

Surface charge of the nanoparticle may be readily adjusted with the assistance of the connected functional groups. Compared to negatively charged nanoparticles, positively charged ones are more toxic because they are more likely to attach to the negatively charged cell membrane and be absorbed through endocytosis. When the surface charge changed, so did the nanoparticle dispersion in vivo.

In one study there was a preparation of positive, negative as well as neutral charged nanoparticles which were coated with various types of polymers. In the study it was found that in vitro lung toxicity of biodegradable nanoparticles was independent of the surface charge with low levels of toxicity in the lungs[48].

Chuang et al., conducted research to determine how soot nanoparticle surface charge affected the toxicity that mice may inhale. They found out that the positive charged nanoparticles produced more cytotoxicity in the mice lungs with increased permeability and were more toxic as compared to the negatively charged soot nanoparticles which causes least amount of toxicity in mice lungs and are comparable more safer than positive charged nanoparticles[49].

3.5. DISEASE STATE AND CONCENTRATION OF NP'S AT TARGET SITE:

The patient's level of illness determines both the toxicity and deposition of inhaled nanoparticles at the target region. For examples there is a more deposition of inhaled nanoparticles in the lungs of the patient suffering from the respiratory diseases as compared to the healthy patient's lungs. Due to the increase in the deposition of the nanoparticles there will be an increased levels of toxicity in the lungs[50].

3.6. INTERACTION OF NP'S WITH THE LUNGS ENVIRONMENT:

There is limited information or minimal knowledge accessible regarding how inhaled nanoparticles interact with the lungs' environment. Surfactant film is present in the lungs and is crucial to both the expansion and compression cycles of the respiratory system. Surfactant proteins and pulmonary surfactants form the first line of defence against inhaled nanomedicines. Pulmonary surfactants form the surface active film at the respiratory air–liquid interface. A number of times, interactions between nanoparticles and the lung's surfactant layer led to potentially deadly situations[51].

Conclusion:

Lung cancer is one of the most common types of cancer that claim the lives of many afflicted patients, with a low survival rate. There are two primary forms of lung cancer: small cell and non-small cell. Non-small cell lung cancer accounts for the majority of instances in both categories. The least common and rarest type of lung cancer is small cell lung carcinoma. There are many therapies available for lung cancer which are chemotherapy, immunotherapy, Gene therapy, photodynamic therapy and the nanotechnology. All of the methods are dependent upon the type of malignancy and also the stage of the lung cancer. In chemotherapy there is a use of the chemotherapeutic agents to treat the cancer. One of the most popular approaches for treating lung cancer is chemotherapy; however, it has a number of drawbacks, such as poor drug availability and targeting, toxic effects on healthy cells from anti-cancer medications, and adverse effects on the body's metabolism. In immunotherapy there is a use of the body immune system for fight against the cancerous cell for example in order to destroy the cancerous cells a immunoactive agents is administered that blocks the series of chains which prevents the growth of the cancerous cells. Gene therapy is a relatively new type of the method of treatment of the lung cancer in which there is a delivery of the healthy genes with two approaches i.e., in-vivo and ex-vivo into the healthy cells for purpose of the treatment and management of the disease. Because it has fewer adverse effects than other forms of therapy, gene therapy is beneficial and successful forms of treatment that is being used globally. Photodynamic method is a very known method for the treatment of the cancerous cells, in this method a source of laser light is used for the activation of the photosensitizer compound that leads to free radicals formation of the oxygen that leads to the destruction of the cancer cells. The primary drawback of this approach is the photosensitizer's poor solubility, which limits the application of photodynamic treatment. However to deal with this problem photodynamic therapy is often used in combination with the chemotherapy that

effectively kills the cancerous cells. Other than the available therapies which are used to treat the cancer, nanotechnology is the most promising and effective type of the treatment in which delivery of anti-cancer drugs to malignant cells is accomplished by the use of nanoparticles based on nanotechnology. As compared to the conventional methods there is less or no toxicity seen in the nanotechnology therapy with high biocompatibility, high bioavailability and efficiency. In recent times there is a rise of a inhalable nanoparticles for the targeting in which there is a use of the polymeric nanoparticles to deliver the medication to the desired location. This approach is fairly good as it offers numbers of advantages for example there is a avoidance of the first pass metabolism, low toxicity with good biocompatibility etc. Although there is a high efficiency in drug targeting but there is also number of challenges which are faced by the nanoparticles which affects their bioavailability in the systemic circulation for example in enzymatic clearance there is a degradation of the drug by the enzymes present in the lungs, medication elimination from the respiratory system with the aid of mucocilliary clearance and the fast absorption in the systemic circulation which creates difficulty in the stable localization of the drug. All of these clearance mechanism are offered by the lungs that makes the localization and bioavailability little bit complicated. Along with it in numerous studies it has been shown that the nanoparticles are associated with the certain level of toxicity towards the normal cells which are influenced by number of factors like nanoparticle's size, shape, structure, biodegradability, disease state and the interaction with environment of the lungs. For example: nanoparticles having different types of size, shape, structure, biodegradability are having varied levels of toxicity as some of them will create low toxicity while others ones will create high toxicity. Toxicity also increases as in case of diseased state of lungs and association with the lungs environment. However by controlling these factors there can be efficient and effective drug targeting which will prevents the growth of the cancerous cells and thus lung cancer can be treated in the efficient manner.

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