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Conceptual Paper

Nanoparticles for Pulmonary Therapies

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In the last few years, nanoscale materials (1-100 nm) have received noticeable attention by virtue of their impressive and unusual chemical, catalytic, thermal, mechanical, electric, and electronic properties which differ significantly from bulk material. Nanoparticles with controlled size and composition are of fundamental and technological interest as they provide solutions to the areas of medicine, solar energy conversion, catalysis, and water treatment [1].

Over the past few decades, applications of nanotechnology have attracted attention in the field of medical science. However, there are rare reports whatsoever in literature about the clinical application of nanotechnology in therapeutics and diagnostics, as well as the scope of multiple promising nanomedicine for future use in the field of pulmonary medicine needed. It is also very important to understand the adverse effects of various nanomaterials on the pulmonary system. The main advantage of nanoparticles is the capability of targeted drug delivery due to small size and can reach almost any region of the human organism. Surface modified or drug coated nanoparticles either by a variety of linker molecules or by encapsulation can achieve passive target through enhanced permeability and retention effect [2].

Lung cancer is the second most common cancer worldwide, representing 14% of newly reported cases. The majority (85%) of lung cancer cases is classified as non-small cell lung cancer (NSCLC), with the remaining classified as small cell lung cancer (SCLS). The American Cancer Society estimates that there were more than 200000 new cases of lung cancer and approximately 150000 deaths in 2017 in the United States alone, making it the deadliest among all types of cancer [3]. Lin., *et al.* [4] describes DNA loaded polyethylenimine nanoparticles as vectors for genes in order to treat lipopolysaccharide induced acute lung injury in mice. It is mentioned in their study that the 5-day survival rate improved from 28 % to 64 % by performing intravenous injection of the DNA loaded polyethylenimine. It is due to the involvement of beta 2-Adrenic Receptor genes in the nanoparticles that can cause a short lived transgene expression in alveolar epithelia cells. Kumar., *et al.* [5] evaluated the *in vitro* cytotoxicity of the Ag nanoparticles against human cancer cell lines A-549 from lung at different concentrations (0.01 - 20 μM). It showed that, there was no effect of Ag nanoparticles on cell proliferation of lung A-549. These results suggest that the new silver nanoparticles might be used as safe drug carriers. In addition to the toxicity analysis was performed on A549 lung cancer cells and normal peripheral lymphocytes with silver nanoparticles coated with saponins and glycosides using *Albizia adianthifolia* leaf extract. The results showed that the proliferation rates for normal cell lines were not altered but A549 cellular viability reduced to to 21% at 10 g/mL and 73% at 50 g/mL [6].

On the other hand, oxidative stress-inducing agent like $KBrO_3$, BEAS-2B cells pretreated with the CeO_2 nanoparticles showed reduction in DNA damage and can cause less intracellular reactive oxygen species (ROS) as a compared to non-pretreated cells. So, CeO_2 nanoparticles may be used as an anti-genotoxic and antioxidant agents in the pulmonary system [7]. Furthermore, Lai., *et al.* [8] reported the use of ZnO and Fe_2O_3 in terms of creating oxidative stress on BEAS- 2B and A549 lung cell lines. They observed that the 39 nm sized Fe_2O_3 nanoparticles were distributed in the cytoplasm, whereas the 63 nm sized ZnO nanoparticles were trapped endosome. The ZnO

nanoparticles also caused ROS production as well as cell apoptosis, cell cycle arrest, mitochondrial dysfunction and glucose metabolism perturbation [8].

Bendale., *et al.* [9] concluded an acute cytotoxic effect of PtNPs in lung (A549) cancer cell. Pandey., *et al.* [10] demonstrated that the antitubercular drugs as pyrazinamide, isoniazid, and rifampicin encapsulated in poly (DL-lactide-co-glycolide) nanoparticles inhaled by tuberculosis infected guinea pigs showed better bioavailability and higher efficiency than oral drug medication [10]. Another study by Trivedi., *et al.* [11] tested the effect of pirfenidone loaded nanoparticles efficacy in the treatment of mice with bleomycin-induced pulmonary fibrosis. The pirfenidone loaded nanoparticles exhibited higher anti-fibrotic efficacy than dissolved pirfenidone [11]. Another interesting example involved the evaluation of cytotoxic effects of smart releasing NPs synthesized using cytochrome C (Cyt C) and hyaluronic acid (HA) [12]. Another interesting study by Figueroa., *et al.* [12] reported the cytotoxic effects of smart releasing nanoparticles synthesized using hyaluronic acid and cytochrome C. The results indicated 20% reduction of A549 human lung adenocarcinoma cellular viability in 6 h with concentration 0.16 mg/mL (cytochrome C).

Kosheleva., *et al.* [13] discovered that the combined treatment of ultrasound and gold nanoparticles exerted a high cytotoxic effect on A549 lung cancer cells and also suggested that gold nanoparticle-assisted thermotherapy could cause targeted cancer cell ablation, without damaging surrounding noncancerous cells. Additionally, Folic acid-modified dendrimer entrapped gold nanoparticles were evaluated for targeted computed tomography imaging whereas, Gadolinium- DOTA nanoparticles enhance magnetic resonance diagnostics of lung tissue [14]. Nanomaterials and other substances transported from the blood to the kidneys and liver seems to be size dependent, primarily excreted into the surrounding water through urine and feces, respectively. Biodistribution of nanoparticles in organisms preferred on intravenous injection. Recent studies confirm that neutral or anionic nanoparticles having diameter of 34 nm or less has significant uptake by different organs in mice in comparison to bigger and positively charged nanoparticles [14].

In future, nanoparticles will replace conventional therapeutic agents in respiratory diseases due to their functionality, low toxicity, ease of processing, and low cost. It is only a matter of time before new nano based drugs will reach in the field of targeted drug delivery, gene therapy, and hyperthermia etc., and offer great potential for modern drugs.

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