

Nanoparticulate Delivery Systems for the Effective Treatment of COPD

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Abstract:

Globally is chronic obstructive pulmonary disease (COPD) distinct of the trendy ubiquitous obstructive lung diseases by 4th prime motive of death. Development of Reactive Oxygen Species (ROS), majorly contributes to COPD, by airway-obstruction, oxidative hassle, inflammation, hyper-secretions, cellular senescence. Standard anti-oxidant, bronchodilator and corticosteroids based therapies, are typically used to improve the impact of COPD conditions. Due to numerous linked repercussions like unsuitable drug pharmacokinetics & low diffusion, these therapies are limited. Recently nanocarriers gains more attention with its own advantageous to treat COPD. Spotlight of this review, We have summarize on advancement of nanocarrier based treatment options for COPD; nanoparticles, liposomes, nanospheres and dendrimer formulations for lung specific delivery of drugs including siRNA through intravenous and nebulization for the effective management of COPD. Nanotechnology has created considerable significance, many nanocarriers are safe with little side effects. In further, researches based on targeted delivery mechanisms of nanocarriers are warranted.

KEYWORDS: nanoparticles; liposomes; nanospheres; dendrimers; nanocarriers

INTRODUCTION

COPD (Chronic obstructive pulmonary disease) is a rising life menacing lung disease which results in serious illness and exacerbations predisposition as well as breathlessness. COPD is ranking 4th worldwide in causing the death of patients progressively in accordance to medical reports. COPD symptoms are on exertion increasingly intensifying with tenacious breathlessness, ultimately results in breathlessness in the time of rest. It may be camouflaged and life-threatening (Qureshi et al., 2014).

The mechanism of inhalation and exhale through the two bronchi to lungs from trachea and alveolus. The alveolus are soft elastic tissue comprises of smaller capillaries helps to exchange the oxygen from air to blood streams through small blood vessels and similarly the metabolic waste exhaled. In the patients suffering from COPD, lungs are inflamed, over-expanded and their elasticity is lost with permanent damage to the alveoli as well as to the bronchi and bronchioles that resulted in certain air trapping in lungs during exhalation (Passi et al., 2020). The major cause of this airways obstructions are cigarette smoke, chronic bronchitis, emphysema, and other irritants, genetics, exposure to fumes from burning fuel, exposure to chemicals and dust, alpha-1-antitrypsin deficiency people with asthma.

The diagnostic test for COPD includes arterial blood gas analysis, CT scan, chest x-ray, and pulmonary function test etc., helps to determine the extent of lung damage by severe COPD. The medications that are commonly used to treat COPD are bronchodilators and antibiotics. The bronchodilator medications generally come with inhaler, which helps in breath shortness and relieving coughing which makes breathing at ease (Domej et al., 2014). However the long term use of these drug substances with higher dose leads to potential adverse events like poor disease control associated with dose tolerance, exacerbation and asthma related sudden death (<https://pubmed.ncbi.nlm.nih.gov>). The use of antibiotics for respiratory infections with COPD, such as acute bronchitis, pneumonia, and influenza, may aggravate the symptoms and worsening COPD episodes and that should be avoided due to their limitations of adverse effects and antibiotic resistance.

The conventional therapeutics strategies are mostly based and dependent on antioxidant and anti-inflammatory properties. Generally to get better COPD impacts, conventional antioxidant pharmacological therapies are utilized because they might comprises of linked consequences like unsuitable drug pharmacokinetics and low diffusion rate.

Other lungs therapies like lung volume reduction surgery are beneficial for various patients with severe or moderate COPD (Komalla et al., 2020). But it is expensive and needs hospitalization with the risk of air leakage from lung tissue in some patients, bleeding, pneumonia infection and stroke. Now a day's nanotechnology based drug delivery systems gained a great interest to overcome such above stated issues with the effective COPD treatment. In this review, we have discussed about the potential of nanocarriers such as nanoparticles, liposome and dendrimer formulations containing COPD drugs to the lung specific delivery including siRNA delivery through intravenous and nebulisation for the effective management of COPD (Yhee et al., 2016) pathogenesis of COPD shown in fig 1.

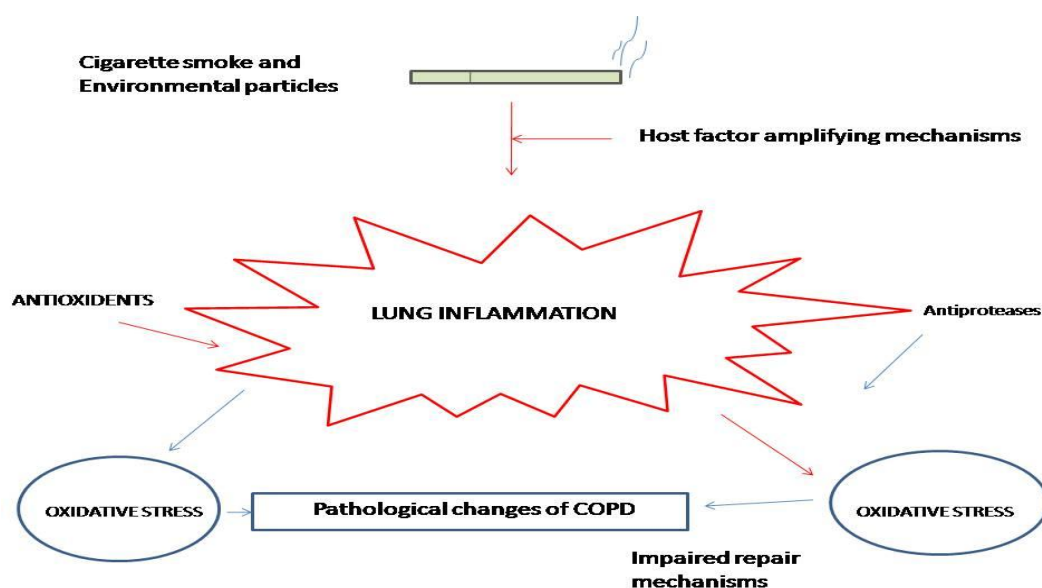


Figure 1: Pathogenesis of COPD

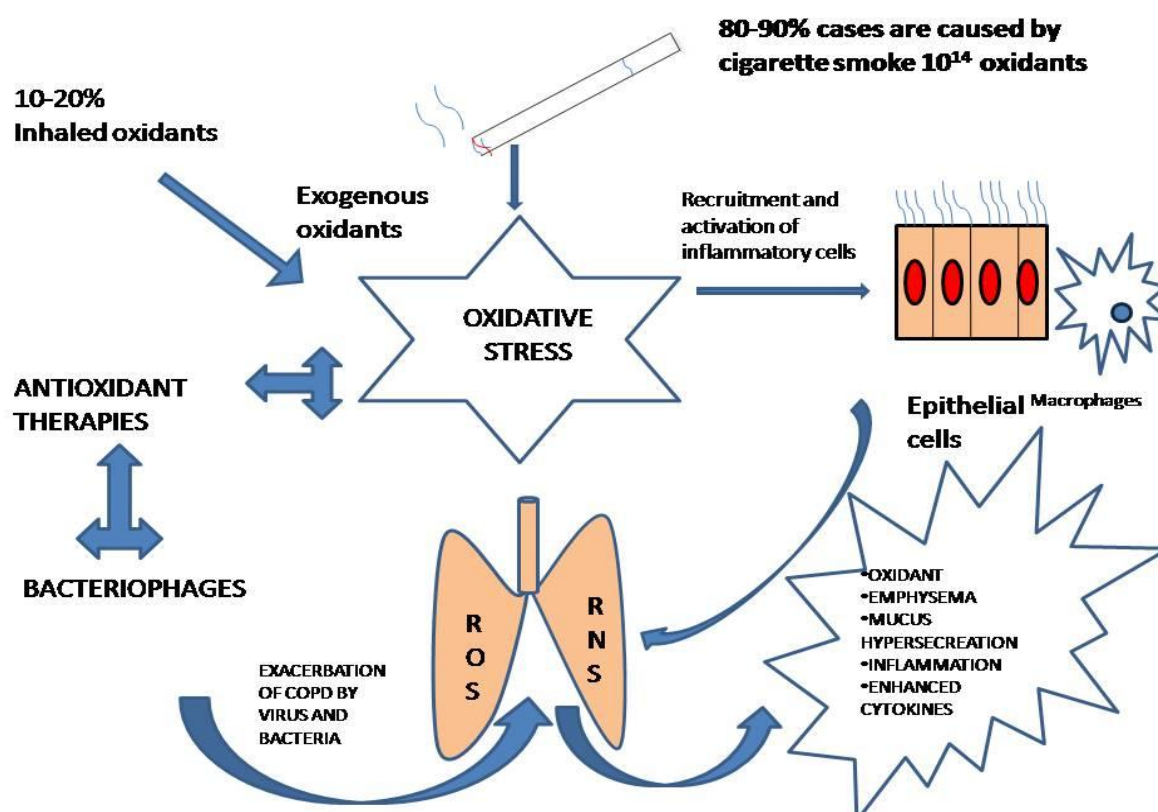


Figure 2: factors that influence pathogenesis

Free radicals and oxidative stress in COPD

Since in the late 1960s the discovery of ROS (Reactive Oxygen Species) we knew that life can be threatened as well as supported by oxygen as well as in aerobic life it is also essential for energy enervation, in the oxidant-antioxidant balance possibly harmful disturbance is resulted due to oxidative stress(Xu Y et al.,) .

These oxidative strains arise when the supply of antioxidants overwhelms free radicals as well as other reactive species. Reactive nitrogen species, inflammatory reactive oxygen species (ROS) and their counterpart antioxidants are important both for host defence and physiological signalling. Due to the disturbance in the normal steady-state and the disparities among antioxidants and oxidants, it can cause pathological reactions that cause numerous respiratory and non-respiratory diseases, especially COPD (chronic pulmonary obstructive diseases) that is explained and showed in fig 2.

Body tissue damage can also be the source of ROS created enzymatic ally from inflammatory, immune and respiratory cells based on the exposure length and degree.

It is very unfortunate to say that, the existing methods of therapy are not sufficient to avoid chronic inflammation of the airways and cannot yet significantly change the trajectory of COPD. Efficient preventive steps for antioxidants in COPD as well as other respiratory disease are urgent in the management and prevention of local and systemic oxygen bursts. How Smoking and other noxious agents affect the cells as well as cell mediators is shown in fig 3.

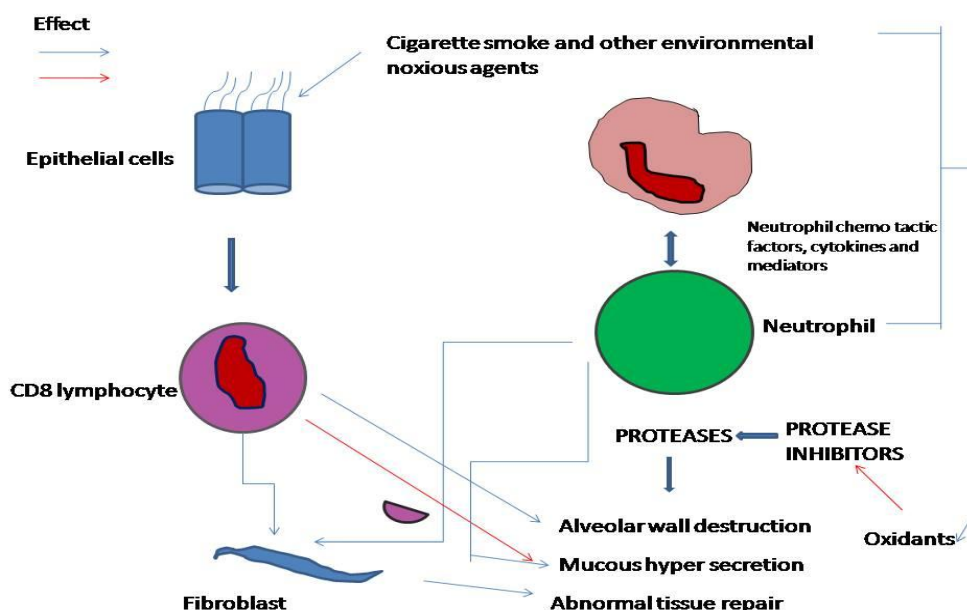


Figure 3: Inflammatory cells and mediators in COPD

New perspectives in nanotherapeutics for chronic respiratory diseases

The recent advancements in the field of stem cell research and nanotechnology emphasized on chronic respiratory diseases. In recent times, there does not exist any therapies which can be used for entirely curing the COPD pathogenesis. There are a variety of nanocarriers for improving efficiency and decreasing the toxicity of the drugs. Smart multifunctional drug carriers' development has allowed by utilizing the targeting ligands. The "smart technology" translation in clinical objective, one must consider the cost/benefit ratio, e.g. a large number of targeting ligands necessity and recognition as well as accepting the nanoparticles toxicity as well as how immune system is affected by them. Requirement for the fabrication of novel nano materials those exhibiting mechanism of lung clearance as well as after its deposition on lung. The stem cell and gene therapy approach combination along with nanotechnology provides the ideal scope for chronic airway disease therapeutics as well as COPD's efficient approach development.

Nanotechnology approaches for inhalation treatment of lung diseases

Nanocarrier based inhalation therapy has become an attractive alternative drug delivery is pulmonary drug delivery(Kuzmov et al., 2015). For several pharmaceutical agents' systemic delivery, possessing larger areas for the therapeutics depositions as well as higher vascularisation. Inhalation drug delivery has bypassing advantage the first-pass metabolism as well as in the gastrointestinal tract, preventing the active components degradation. Regardless of such striking benefits, therapeutics systemic inhalation delivery is not utilized widely. Risks are – drugs higher lung toxicity as well as lung macrophages delegates it, drug-induced lung injury risks, and health care workers occupational exposure in nebulising drugs limits interest for the systemic drug delivery for the inhalation route. Low efficacy and potentially serious detrimental side effects on other organs are seen in most instances through the usage of systematic delivery of pharmaceuticals to cure lung diseases. It seems normal to

administer therapeutics directly to the lungs through inhalation in order to improve the effectiveness of the treatment of multiple lung disorders and limit the sensitivity of healthy organs to possibly dangerous medications. Local inhalation distribution directly to the diseased cells can provide an optimal drug composition and inhalation delivery process, minimise the exposure to safe lung cells, and restrict drug entry into the bloodstream.

Therefore we showed our interest in nano technological-based drug delivery which is less toxic as well as target specific which would reduce the unnecessary toxicity of healthy organs.

Table 1: Here we summarised the few potential Nanoparticulate Delivery Systems for the Effective Treatment of COPD

TYPES	NANOCARRIER COMPOSITION	DRUGS	METHOD OF PREPARATION	SIZE	ROUTE OF ADMINISTRATION	MODE OF ACTION
LIPOSOMES	Phospholipids and cholesterol	NAC	Reverse phase evaporation and spray drying	~100 nm	Inhalation	Against TBARS production
	DPPE	α-Tocopherol	Solvent evaporation method	-	Intraperitoneal, injection	Reduce acute inflammatory, cell influx and suppress collagen formation in lung tissue
	Chitosan, hyaluronan, and phospholipids	Curcumin	Sonication, stirring	130 nm	A549 cells	Cell relative metabolic activity ≥ 80% after treated with hydrogen peroxide
Solid lipid nanoparticle	Lipid and surfactant lipid	Proanthocyanidins	Melt-emulsion method	243 nm	H441 cells Inhalation	reduce ROS production
Inorganic nanoparticles	gold nanoparticles	Au	-----	21 nm	Inhalation	AuNP can be used as nanocarrier (rapid binding to the alveolar epithelium)
Polymer nanoparticles	PHEA-PLA-PEG2000	FP	HPH (freeze drying)	161.3 ± 4.14.0 nm	immortalized normal bronchial epithelial cell line	Improve drug permeation through the mucus layer,
	PAMAM dendrimers (PEGylated)	-----	-----	5.1–9.9 nm	Pulmonary delivery pharyngeal	Enhance dendrimer reaching the endothelial cells and systemic circulation. P.A. administration promotes the

	d or not)				aspiration (P.A.) technique	passive targeting of dendrimers to lymph nodes
Dendrimers						
	TEE modified PAMAM dendrimers	siRNA	Vortex	257 nm	Inhalation	Target lung alveolar epithelial A549 cells and silence genes
	PAMAM dendrimer	TNF- α siRNA	Vortex	127–153 nm	RAW264.7 cells, intranasal in acute lung inflammation model	Gene silence (targeted TNF- α)
Polymer hybrid nanoparticles	PLGA and DOTAP	siRNA	DESE	Below 250 nm	H1299 cells	Gene silence (targeted TNF- α)s

Liposomal drug delivery for COPD

In the fast-moving field of nanomedicine, liposomes and methods of liposome-dependent drug delivery are a promising provider. Thanks to their unusual structural features, physiological characteristics and biological properties, liposomes are increasingly interested in the scientific field. These flexible lipid blood vesicles are a special treatment, targeting, diagnosis, imaging and theranostic tool (van Rijt et al., 2010). Inhalable pulmonary liposomes have special benefits when they are formulated from endogenous surfactant-like phospholipids (Parmar et al., 2012).

For the airway inflammation COPD treatment, phospholipids-dependent formulations have utilized. The major hallmark of all chronic respiratory diseases is inflammation and it can be managed by some inhaled corticosteroids (Singh, A.p et al., 2019). The limitation is long-term use can cause various side effects and adverse effect, therefore, for non-steroidal anti-inflammatory therapies; a medical need is required in tackling airway inflammation. A ray of hope to reduced inflammation in several inflammatory conditions is shown by phospholipids. The cell membranes building blocks are considered to be included in significant physiological functions like chemo taxis, exocytosis, cytokinesis, cholesterol transport, and signal transduction (Patil JS et al 2015). In the pulmonary surfactant, gastric mucosa, and cell structure, most abundant phospholipids are Phosphatidylcholine (PC). Changes of PC in pulmonary/plasma surfactant have been described in respiratory diseases patients (Willis et al., 2012).

DOPC (Liposome generated with the DOPC and the cholesterol molar ratio of 1.5:1, by the thin-film hydration process(Mehta Pet al ., 2019)

For one hour, the solvent was lowered to 79%. At 70%, PBS was applied to the thin film to keep it hydrated.) Liposomes consist of subsequently greater encapsulation efficiency, larger vesicle size, and soft membrane.

After TNF stimulation, the therapy of liposome successfully decreased IL-6 levels In-vivo, comprising of the in-vitro results, decreased overall immune cell counts in the bronchi alveolar fluid in the ovalbumin model of airway allergic inflammation and reduced the respiratory hyper reaction and hence reduced the effects.

In another way for the delivery of drugs using liposomes to reduce the symptoms of COPD is hybrid lipid-polymer nanoparticles with the release potential of anti-bio film drug delivery caused by rhamno lipid. The usage of lipid polymer nanoparticles for the encapsulation of medicines has demonstrated potential options for liposomal use, as they also exhibit superior physicochemical stability as well as the affinity of bio films and the capacity of liposomes to sputum penetrate.

Antibiotic liberated from liposomes is activated by virulence factors of *P. aeruginosa*, its surfactant rhamnolipid that bacteria frequently generate to preserve its bio film architecture and is rarely present in patients with sputum.

The discharge caused decreases the sputum antibiotic degradation, thus increasing the bio film colonies sensitivity to the antibiotic and thus enhance the antibacterial efficacy. Calcein was successfully showed for the model drug when a BCS Class III medication was released from lipid-polymer hybrid nanoparticles caused by the presence of rhamnolipid from *P. aeruginosa* bio film cell. An early explosion of calcein release is observed after the nanoparticles are revealed at a concentration near their clinically observed significance in rhamnolipid. The preliminary explosion of the release of calcein can be suppressed by an additional lipid layer in the hybrid nanoparticles, by an electrostatic adsorption of lipid vesicles. However, owing to their high lipid membrane permeability the release of rhamnolipid is not observed with drugs of BCS Class I.

Inhalable Dendrimers for pulmonary delivery to treat COPD

For the pulmonary disorders treatment, dendrimers too have shown great ability as inhalable drug delivery substitutions. A finer dendrimer carrier is needed to recognise persistent efforts from diverse scientific disciplines which provide the best inhalable translation platform for accelerating bench to bed translation. The overall effectiveness of inhaled dendrimers would be dependent not only on the conception or creation of multiple new dendrimers but on solving existing information gaps. In this rapidly growing field of nanomedicine dendrimers as well as dendrimer-dependent delivery system are possible biomedicine.

In recent times in the scientific domain dendrimers are drawing attention because of their biological attributes, physiological properties, and unique structural features. Unique platforms are provided by such multifunctional nonmaterial for theranostics, diagnostics, imaging, and targeting. The dendrimers pulmonary applications including special prominence

on DPI(dry powder inhalers),nebulizers,SMI(soft mist inhalers), and pMDIs(pressurized metered-dose inhalers), the scientific disciplines range, acquired knowledge, and present proficiency's profound strength is trusted that are presently functioning in that area that might be developed for continuing the significant actions in contrast to pulmonary disorder .

Poly (amidoamine) Dendrimer Nanocarriers for siRNA Delivery

Important a siRNA (small interfering RNA)-dependent therapy shown great promises in treating several widespread pulmonary disorders that includes cystic fibrosis, asthma, and lung cancer.

However, development in this field is hindered by the absence of right carrier systems which can laboriously provide siRNA to lung epithelial cells and also by the challenge to establish OI (Oral Inhalation) formulations for the regional control of siRNA and its pulmonary carriers.

Abilities of 4th generation amine-terminated poly (amidoamine) (PAMAM) dendrimer (G4NH₂) –siRNA complexes (dendriplexes) for silencing the improved green fluorescent protein (eGFP) gene on A549 lung alveolar epithelial cells stably expressing eGFP.

Dendriplex composition and its aerosol properties in portable OI systems using the propellant. Dendriplexes were not shown to have a good N/P-ratio feature of size and gene silencing capabilities.

In hydrofluoroalkane (HFA)-dependent pressurised metered dose inhalers (pMDIs) on safe dendriplex dispersions embedded in mannitol as well as in water-soluble and biodegradable co-oligomer. They have very desirable aerosol properties and are conducive to deposition in the deep lung of breathable fractions of up to 77%. In specific, SiRNA formulated as dendriplexes in pMDIs has been shown to maintain its integrity following the method of particulate preparation and long-term HFA exposures (Conti DS et al.,2014).

After the discussion about siRNA let throw some light on polymeric nanoparticles for miRNA delivery to COPD treatment.

According to the present therapeutics strategies that are used for reducing COPD like oxygen, inhaled corticosteroids, antibiotics, and bronchodilators not been shown to correct or delay the COPD's long term advancements. Small non-coding RNA molecules that are the Mature microRNAs (miRNAs) which down-regulate gene expressions, at the beginning with the acute translational repression then afterward through steady-state mRNA destabilization (Conti DS et al., 2014) .

This miR146a was adsorbed onto nanoparticles (NPs), PGA-co-PDL, poly (glycerol adipate-co- ω -pentadecalactone) for reducing expression of target gene IRAK1.A549 cell lines were observed with miR-146a loaded cationic NPs internalization which utilizes co focal microscopy and fluorescence. For that reason, miR-146a, PGA-co-PDL potent NPs are used as a delivery systems in COPD treatment (Velino et al., 2019)

In another study little more effective way used to deliver siRNA through inhalable siRNA-loaded nano-embedded microparticles.

SiRNA (Small interfering RNA) dependent medicines are capable for treating various lung diseases. In addition to economic methods of developing the finished product, however,

proficient delivery mechanisms and the production of safe dosage types are needed for inhalation therapy. In preparation for the siRNA dendrimer nano complexes 3D-printed micromixer was designed (Walworth et al 2016).

They were eventually extracted in dry powders for inhalation by spray drying into micro particles. Usage of a disposable micromixer for nanocomplex preparation with an overall hydrodynamic diameter similar to that of manual mixing nanocomplexes, but with a reduced delivery area and a minimal variance batch to batch. The prepared nanocomplexes were like those created by bulk mixing, greater size control and a small batch-to-batch difference. Depending on the stabiliser form, the physical stability of nanocomplexes in microparticles varies (Sharma et al., 2018)

A synthesis of trehalose and inulin resulted in greater physical stability, as is obvious from the retained nanocomplex measurements. On resuspension, the nanocomplex was reconstituted under optimised conditions, and RAW264.7 macrophages demonstrated increased transfection and cellular uptake (Chowdhury et al., 2017)

The biodegradability of the carrier is also important, so biodegradable polyester dendrimers transport and cellular internalization on a pulmonary epithelium model as well as its development in pMDIs, the generation's end product as well as degradable surface PEGylation, polyester-dependent dendrimers nanocarriers on interacting with pulmonary epithelium's *in-vitro* model and for assessing the abilities in formulating these carriers in portable oral-inhalation device that are propellant-dependent for determining their abilities for drugs systemic and local delivery as well as across lungs (Xu et al., 2020)

All the dendrimers as well as their elements were compatible with pulmonary epithelium model, with toxicity profile much more favourable as compared to non-degradable, polyamidoamine dendrimers (PAMAM).

To increase nanocarriers solvation by the hydrofluoroalkane propellant utilized in pMDI is done by the help of PEGylation which results in formulations with aerosol quality and excellent dispersibility (Seshadri et al., 2018)

Macromolecules degradation profiles were assessed in biological relevances pH values as well as for the nanocarriers elimination, convenient hydrolysis is determined (da Silva et al., 2017)

Potential of nanosphere for COPD Treatment

pH-dependent nanospheres development for nebulisation. The cytotoxicity, aerodynamic and in-vitro diffusion studies (Mehta et al., 2020)

HPMCP nanospheres, that are loaded with Beclomethasone dipropionate, promising formulation were developed with solvent evaporation approach where the stabilizer used is PEG 400²⁶. Since, it is water-insoluble drug, it is combined with HPMCP nanosphere with a basic pH solubility for the successful targeted drug delivery in the lungs and reduces the cytotoxicity and capabilities of immediate release (McKenzie et al., 2015)

To determine the safety characterization studies redone like drug loading, entrapment efficiency, PDI, and zeta potential, in stability, in vitro cytotoxicity, aerodynamic, and in vitro diffusion studies, it has been observed to be stable, safe with considerable solubility enhancement as well as bypassing liver (Purr et al., 2019). Colloidal medication delivery system is the most frequently studied system for managed drug delivery to particular corporal organs (Lungs). Polymeric nanosuspension delivers the hydrophobic medication to the plum with greater deposition effectiveness (Inkrottet al., 2016).

. These beclomethasone dipropionate (BDP) loaded HPMC nanosphere phthalates were found to be healthy, stable and significantly soluble, with a first pass effect avoided and the inhalation by nebulisation was successfully prepared.

One of the promising treatments for chronic pulmonary diseases is by gene therapies localized aerosol delivery (Yao et al., 2014).

The drug administration by inhalational features multiplies the advantages that include improved patient compliance and acceptability (Nasrin et al., 2020)

Advantageous spray-dried formulations of solutions provide better stability and shelf life as well. After spray drying the nucleic acid integrity and bioactivity were conserved as well as the reconstitution of those polyplexes from the dry powder developed by trehalose however as a stabilizer, mannitol is not used . Studies like transfection and cellular uptake studies performed in lung presented that in comparison to non-spray-dried polyplexes, better or equivalent performance is noticed from redispersed trehalose particles. With this, we get the confirmation that nucleic acid contained spray-dried NEM formulations can be developed with some distinguished characteristics for inhalation therapy that will be optimal

Inorganic nanoparticles used in the treatment of COPD

Although nanoparticles are the topic of discussion for the treating the COPD but it has some history behind it .in this present times nanomedicines holds promising stands for the sustained and controlled drug delivery with diverse therapeutic agents. The administration is via various methods like pulmonary inhalation, oral administration, or intravenous injection.

Because of its special physiological and anatomical characteristics and the limited contacts between its target position and other organs, the use of nanocarriers by intravenous or oral routes is still under study. This device provides an appealing alternative for oral or intravenous routes. Most of these most commonly-used nanoparticles are polymeric nanoparticles and liposome nanoparticles, nano-solid nanoparticles and submicron emulsions, which serve for treating chronic pulmonary conditions . It gives the benefit of long-term drug release in the pulmonary tissue that decreases the dose frequency and increases patient conformity (Singh et al., 2019)

One of the recent promising models is the model which includes dimethyl fumarate comprised inhalable dry powder . Through this new system lower airways can be reached by most particles and drugs. Hence provides an anti-inflammatory response. Furthermore, great promise has been shown by treatment, specifically in enhancing COPD patients' life quality.

In lung tissue, due to sustained drug release advantages, nanocarrier results in enhanced patient compliance as well as decreased dosing frequency (Ganguly et al., 2019).

Conclusion

Here in this context, we discussed few key and most important viewpoints for COPD in nanotherapeutics, their treatments aspects, and also highlighting various current researches in this area. By summarizing the nanoparticles, dendrimers, liposomes, gene therapy with its possible beneficial effects in the treatment of COPD diseases. As the effective treatment option, nanotechnology has created considerable significance. Preclinical trials using NPs indicate gifted development, although ongoing literature indicates many nanocarriers are safe to use with little side effects and adverse reactions. In the other hand, substantial obstacles already require to prevail before clinical research can use nanotherapeutic strategies. Further research based on the understanding and recoveries of the mechanisms of action of NPs are warranted in further improving sensible strategies to clinical studies.

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