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Pulmonary Drug Delivery: Role and Application of Lipid Carriers

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ABSTRACT
The present review describes all the aspect of pulmonary drug delivery system and recent advancement. It deals with the delivery of drugs in important disease conditions like asthma, COPD, lung cancer and cystic fibrosis. These disorders required prolonged delivery of the drug through pulmonary route. Various drug loaded lipid formulation like spherulites, lipid nanoparticles, exosomes, solid lipid nanoparticles, nano structured lipid carriers, Janus particles, liposomes, self-micro-emulsifying drug delivery system, lipospheres and RBS derived nanovesicles are discussed. The pulmonary drug delivery system offers important system to deliver the drug to the targeted site.

Keywords: Pulmonary drug delivery system, Lipid carriers, Polymeric carriers, lipid nanoparticles, liposomes, spherulites, exosomes, solid lipid nanoparticles, nano structured lipid carriers, Janus particles, self-micro-emulsifying drug delivery system, SMEDDS, lipospheres, RBS derived nanovesicles, Dendrimers, nanocapsules, nanospheres

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INTRODUCTION

An effective treatment depends on the techniques on how the drug is delivered and the quantity or the dose of the drug that is given, concentration above or below the prescribed dose can be toxic or of no therapeutic use. The effectiveness of the drug and its treatment can be achieved by controlling pharmacokinetics, pharmacodynamics, immunogenicity, and bio recognition, these along with interdisciplinary approach such as polymer science, pharmaceutical technology, bio-conjugate chemistry, and molecular biology, are often called novel/advanced drug delivery systems. There exist different drug delivery system and drug targeting system that are currently being developed to reduce the drug loss and drug degradation with increased efficacy (1).

Pulmonary drug delivery system has attracted large scientific and biomedical interest as the pulmonary route has several advantages over the systemic delivery of the same drug in treating respiratory diseases like asthma, chronic obstructive broncho-pneumopathy due to the capability of the lungs in absorbing pharmaceuticals either for the local or systemic delivery. Systemic absorption can also be achieved through alveolar administration of therapeutic agents and is proved to be more beneficial. Through inhalation the deposition of the drug in lungs is rapid with little side effects when compared through other route of administration, because of high permeability, large absorptive surface area of lungs and is with good supply of blood. Pulmonary route is gaining more attention as non-invasive administration of the therapeutic agents to both the local and systemic delivery (2-4).Though pulmonary route it is likely to target drugs to specific cell like macrophages, lymphocytes, neutrophils, endothelial cells or epithelial cell or the cell organelles, here the nature of the material used in the drugs affect the rate of uptake. It has been observed that the alveolar epithelium of the distal lungs is the absorption site for most of the therapeutic agents and other molecules (5-8). Up to now, the delivery of drug through pulmonary means was to treat asthma and Chronic obstructive pulmonary disease (COPD), but recent advancements and research development in the technologies this route is not confined in treating respiratory related disease only, several literature have reported the therapeutic use of pulmonary route in other areas such as diabetes, virus infection and cancer (9) pulmonary hypertension, systemic use of insulin, human growth hormone and oxytocin (10-16).

Benefits of the pulmonary drug delivery:

- As mentioned earlier, Lungs has a large surface area (approximately 100 m^2) for the absorption or deposition of the therapeutic agents, and it is supplied with blood that paves the way for systemic delivery of the agents.
- Prevents the degradation of the drug in the GI tract and bypass the first pass metabolism in liver due to decrease in the activity of enzymes involved in drug metabolism (6)
- Limits the penetration of the drugs into the blood and thereby limits the accumulation into the healthy organs
- In majority of the cases the use of systemic delivery of drugs to treat lung diseases proved to be of low efficacy rate and with severe side effects on the healthy organs
- The action of the drug is rapid through inhalation (in min.) as compared to the oral dose (which may take hours)

Challenges faced by pulmonary route.

- Low efficiency of inhalation system
- Less drug mass per puff
- Poor formulation stability for drug
- Improper dosing reproducibility

To ensure increase in the efficiency of the treatment, the pharmaceutical agents must target the disease cell and decrease the exposure of the toxic drug to the healthy organs, its ideal to give the therapeutically active agent directly through inhalation. An ideal pulmonary formulation must ensure that the drug is targeting specifically to the disease and limiting the exposure to the surrounding healthy cells and with decrease saturation in the circulatory fluid (circulation).

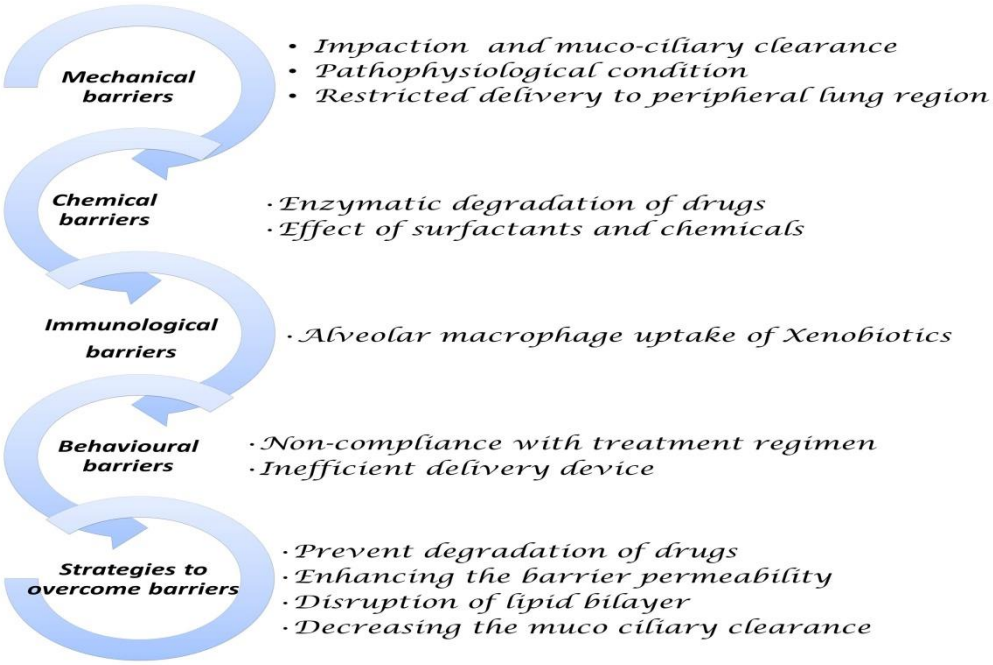

Fig. 1: Different barriers to be considered during the design of Pulmonary Drug Delivery Systems**.**

Drugs can be administered by pulmonary route using two main techniques

- Aerosol inhalation - there is uniform distribution of the drug, with greater penetration of the drug into the peripheral and the alveolar region of the lung. But the exact dosage of the substance inhaled is difficult to measure and is more cost effective
- Intra-tracheal instillation – is simple, less expensive and has uniform distribution of drugs.

The devices used in the inhalation process.

- Metered dose inhalers (MDI) – used in the treatment of the asthma and COPD, where the fine particle of the medicine with size of 5 microns is directly inhaled into the airways (17-19).
- Dry powder inhalers - as these drugs are often highly soluble, it readily dissolves in the fluid layer lining of lung before passing into the type I alveolar cells, the interstitial space and the capillary endothelium. It's more stable, dose control per puff (high or low), can be used in both soluble and insoluble drugs, low contamination like growth or microbes. Whereas it has to overcome some of the issues the control of the moisture, use of efficient powder, reproducible powder filling and developing an efficient aerosol
- Nebulizer – mainly two types of nebulizers are available the ultrasonic and air jet. The jet nebulizers are used in treating patients with pulmonary disease; the outgoing air is being saturated with solvents due to aerosols and cools the drug solution in the nebulizer with remaining volume with increase in solute particles. Whereas the ultrasonic is more effective and very compact so easy to use, but in case of protein and suspensions it cannot be used. The development of mesh nebulizer which uses low frequency waves that decreases the chance of denaturation of protein not achieved by other aerosol therapy. Like any other nebulizer mesh nebulizer has issue of clogging the mesh when viscous drugs or suspensions are used.

Transepithelial transport of drugs:

A thorough knowledge on the lungs both in the healthy and in disease state is required to develop a drug for administration through pulmonary route. More than 40 different types of cell make up the human lungs (10) . The human respiratory system comprises of main regions – the conducting airways and the respiratory region. The airways are divided into nasal cavity and its sinuses, the nasopharynx, oropharynx, larynx, trachea, bronchi, and bronchioles, and the respiratory regions consist of respiratory bronchioles, alveolar ducts, and alveolar sacs. The delivery of drugs through trans-epithelium is challenged by two differences in the region. The transport of drug in the upper airways is limited due to its small surface area and lower blood flow. In addition to the small surface area and low blood supply 90% of the drug particles transported in upper region is removed due to its high filtering capacity, moreover the inhaled substances are deposited on the mucus layer that coats the wall of the airways, which is secreted by the goblet and sub mucosal gland cells (12) . 95% of the lung's surface area is the smaller airways and the alveolar space, which is directly connected to the systemic circulation via pulmonary circulation. Regardless of this, the transport of the trans-epithelial drugs is most probably governed by morphology of the alveolar epithelium, the pulmonary blood-gas barrier system, and size of pores and tight junction depth of alveolar and endothelial cells (13).

Properties of nanoparticles for effective lung deposition:

There are several factors for the deposition of NP's to the alveolus such as: Particle size; geometric size shape and aerodynamic diameter; behaviour and surface chemistry.

The deposition area of the particles with aerodynamic diameter more than 5µm due to lower inertia tends to settle down in upper respiratory tract i.e larynx and trachea and above 10µm are settled more before and those of near to 20µm failed to enter nasal cavity.

The particles having smaller aero diameter tends to move fast and travel more due to high inertia and reaches to alveolus. Interestingly the rate of airflow reduces the deposition of particles in the lower respiratory tract, but this effect is lost with particle of small aerodynamic diameter i.e. 10µm. For lower inertial transport small aero dynamic radius is required i. e. in Broncho-alveolar region whereas for larger particles there is impaction and sedimentation. Eventually, gravitation pull counts a lot in alveolar deposition other than impaction for the particles having aerodynamic diameter 3 µm. thus, there exist more particles in the gravity line of alveolus. Liposomal accumulation in lungs for diameter 0.2 µm was found 10X more than that of particles with 0.6 µm.

Various nanocarriers and polymeric particles used in pulmonary drug delivery system are presented in Figure 2.

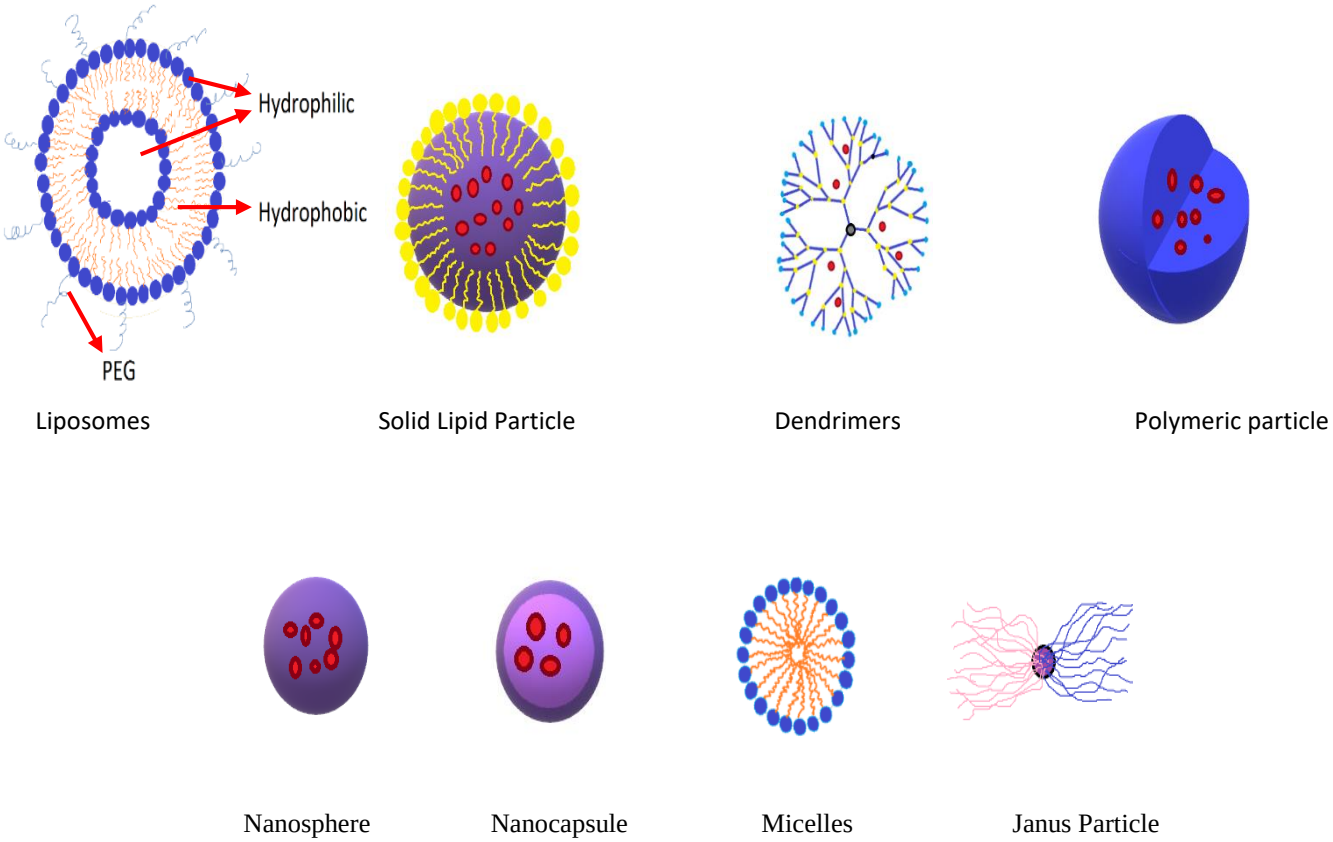

Fig. 2: Lipid and polymeric carrier used in pulmonary drug delivery system

Important Pulmonary disorders

Asthma

One of the common type of chronic inflammatory lung disease is the asthma that occurs in the airways leading to the lungs and affects more than 300 million people worldwide (22). It makes the person difficult to breathe and carry out the physical activities, it sometimes makes the person suffering impossible to carry out the work. In Asthma the lining of the airways swells, tightening the muscle around them and secrete extra mucus causing the narrowing of the airways which makes the person breathing difficult and cause coughing, wheezing and shortness of breath. The chronic inflammation of the airways may be due to the hyper responsive behaviour towards the triggers like viruses, allergens and exercise leading to the frequent cycles of wheezing, coughing, chest tightness and pain and make breathing difficult. Symptoms vary from person to person, and the intensity, it is associated with obstruction of airflow within the lungs that is reversible either spontaneously or with appropriate treatment such as that lead to the dilation of the bronchioles or

giving bronchodilators(23). At present the focus of treatment for asthma is to eliminate the inflammation by corticosteroids (CSs) and the bronchodilators (BDs). CS is a strong anti - inflammatory and immunosuppressive medicine that induce anti – inflammatory response or reduce the inflammation by suppressing the pro – inflammatory genes (24, 25). CS treatments are effective in controlling the asthma however it is difficult to treat people with severe asthma , treating people with severe asthma requires high dose of CS along with second controller or suppress the systemic CS, or in which case it may remain uncontrollable (26). In People with severe asthma CS insensitivity may occur contributing to the severity of the disease (27). In addition long term use of systemic CS therapy may have adverse effect like diabetes, osteoporosis, suppression of adrenal gland and may lead to cardiovascular diseases (24, 27, 28). Liposomes are self-assembled structure constructed from the phospholipid bilayer which is amphipathic in nature, it is spherical with aqueous core region (29), and due to its amphipathic nature it is a suitable candidate to carry the drugs with different molecular regions towards water. Hence it is one of the suitable candidate in the combination therapy to treat CILD (28) One of the main problem associated with the liposomes is its instability and short time in circulation of blood (10), which can be solved by the modification of the surface with the ligands. Surface modification increases the instability, permeability circulation, muco-adhesiveness and cellular uptake (30).

Coating the liposomes with the mucoadhesive coating like chitosan, Carbopol or hydraulic acid gives muco-adhesiveness to the liposomes which is one of the most important features when treating Asthma or COPD as both these disease secrete mucous (31, 32). In 2003 Konduri and his co-workers developed a stealth liposome, which is more stable than the unmodified version with budesonide in order to decrease the administration of CSs in patients who have side effects to CS (33). Generally patients suffering from CILD are prescribed combination of CS and BD as these combinations of CS and β2 antagonists (LABAs) have greater efficiency in the controlling asthma (34, 35). Parikh and his co-workers stated that the when the two drugs were administered in combination they have synergistic effect on the inflammation at the target site as these drugs increases or enhances the biochemical and pharmacological effect of each other (34) in might be stated that when these drugs are delivered in combination through liposome platforms at the same time it may increase the efficiency of the treatment. Generally in the primary treatment of the asthma the patients are treated with the smooth muscle relaxant that target the beta-2 (β2)-adrenergic receptor (2) where salbutamol is usually used and is available in both oral and in inhaled form ((24). Generally, the inhaled form of salbutamol is used in case the inhaled therapy fails intravenous (IV) administration is suggested (25).

Chronic obstructive pulmonary disease (COPD)

COPD is a growing health problem in the population worldwide with death as many as or as that of lung cancer, the etymology of the disease is not much studied although it is one of the global health problems. It's a new term and refers to old diseases like bronchitis, asthmatics bronchitis, chronic-bronchitis and emphysema (36). COPD is a chronic inflammatory disease, with limited air flow and increase in the secretion of the mucus and with progressive decline in the function of the lung. The etiology of the disease depends on the genetic predisposition, age, pollution exposure and cigarette smoking. At present the treatment includes inhaled corticosteroids, anticholinergics, and β2-agonists. These treatments are effective in minimizing the symptoms, but these treatments cannot cure the disease (37). Liposomes are the vehicles that are developed or designed from the materials that are biocompatible and biodegradable in lungs. These are phospholipid that act as vehicle for the delivery of drugs for small molecules like peptides and nucleic acid, enclosing hydrophilic drug within in the interior aqueous core and lipophilic drugs into to the phospholipid bilayer (38). To treat disease like asthma, COPD and pulmonary infection several drugs that are approved have been formulated again in a wide ranges of doses with the help or by using lipid based carriers (like lipid microparticles, liposomes and co – suspensions formulations) these drugs include as salbutamol, formoterol, glycopyrronium, chromones, budesonide, gentamicin, tobramycin, and ciprofloxacin(38).

Studies have suggested that SLMs smaller size is one of the options for the delivery of the drugs to lungs as they can deposit in the secondary bronchi. Erika Amore and his co-workers (39) reported that fluticasone propionate (FP)-loaded SLMs are more effective in controlling oxidative stress then when treated alone with FP. In this scenario, a potential multifunctional polymeric vesicle composed of PLGA and PEG has been suggested for the delivery of COPD drugs such as prednisolone (corticosteroid) and theophylline (bronchodilator). (40). Furthermore, dimethyl fumarate, an antioxidant Nrf2 activator, is capable of reaching the lower airways to treat inflammation in this region (41). Commonly prescribed medications for both asthma and COPD are inhaled corticosteroids (i.e., anti-inflammatory), bronchodilators, leukotriene receptor antagonists, mast cell inhibitors, anticholinergics, muscarinic antagonists and methyl xanthine preparations (42, 43).

Solid lipid microparticles by melt-emulsification/spray-drying processes as carriers for pulmonary drug delivery have been developed by Ignjatovic et al.(44) using design of experiments. Obtained dry powders for inhalation (DPIs) were evaluated in terms of SLMs size distribution, morphology, true density, drug content, solid state characterization studies, in vitro aerosol performance and in vitro drug release. SLMs micrographs indicated spherical, porous particles. Selected powders showed satisfactory aerosol performance with a mean mass aerodynamic diameter of around 3 μm and acceptable fine particle fraction (FPF). Addition of trehalose positively affected SLMs aerodynamic properties. The results of in vitro dissolution testing indicated that salbutamol sulfate release from the tested SLMs formulations was modified, in comparison to

the raw drug release. The SLMs in a form of DPIs were successfully developed and numerous factors that affects SLMs properties were identified in this study.

Lung cancer

One of the most common and cancer related death in both men and women word wide is the lung cancer (45, 46). Although treatments like chemotherapy and radiotherapy are successful in treating lung cancer, some patients develop recurrence of disease with increase in the resistance to the therapy. Hence there is a need to develop a new therapeutic strategy to deal with such type of disease. One approach is the nanotechnology that has made significant advancement for example the LBNPs (lipid based nanoparticles), Nanocrystals (Kumar et al.106) bromo-noscapine NE (47), lipophilic diferuloylmethane NE (48), CUR-water-Free-NE (49), and docetaxel-NE (50) showed increased antitumor activity in A-549 cells. One of the strategies used in order to achieve promising result in the lung cancer therapy is combination of drugs or the codelivery of the drug. Studies carried out *in-vivo* on non-small cell lung cancer using aerosolized celecoxib encapsulated nanolipid carriers (Cxb – NLC) as a single and in combination with intravenously administered Docetaxel (Doc) showed significant reduction in the tumour(51). Chengsong and his colleagues (52) studied the synergistic effect of co – delivery of doxorubicin (DOX) and β-elemene (ELE), pH-sensitive nanostructured lipid carriers (NLC)(DOX/ ELE Hyd NLCs) on the inhibition of lung tumour and growth of the tumour, they found that the synergistic effect of the drugs inhibited the lung tumour and its growth. In similar study carried out by (53) on Paclitaxel (PTX) and doxorubicin (DOX) by NLC in vivo and in vitro NCL-H460 and NCL-H460 cell-treated mice lung cancer model. Showed that the synergistic effect of PTX and DOX by NLC inhibited the growth of lung tumour and killed the cancer cells. Kaur and her co-workers(54) used NLCs loaded with paclitaxel (PTX) using different variety of surfactants using Box-Behnken design, they concluded that delivery of drug through pulmonary route is more effective than any other route for lungs as maximum amount of the drug was observed in lungs.

Lung cancer and metastases are major concerns worldwide. Although systemic chemotherapy is the recommended treatment, it is associated with various disadvantages, including nonselective drug distribution and systemic toxicity. The pulmonary route ensures the localized delivery of drugs to the lung. Enhanced stability, high aerosolization performance, better particle size distribution, improved penetration, sustained release of the drug, and minimal excipients usage makes drug nanocrystal an ideal candidate for pulmonary delivery. Besides, drug nanocrystals may provide selective cellular internalization with minimum clearance and maximum deposition. Furthermore, surface modified nanocrystals and nanocrystals in nanocarriers can exhibit a more prolonged, and site-specific release of the drug to cancer cells in the lungs (55).

Cystic fibrosis

Cystic fibrosis (CF) is a genetic disorder disease that is caused by the mutation in CFTR gene (Cystic fibrosis trans membrane conductance regulator). This gene codes for the protein that forms ion channel in the epithelial cell of many organ, hence this gene is of importance, if there is defect in gene it may translate into different protein resulting in the obstruction of the bronchial due to the accumulation and secretion of the mucous in the airways. This creates a hospitable environment for the growth of the microbes, especially the *Pseudomonas aeruginosa* and *Staphilococcus aureus* (56-58). Therefore, CF requires continues administration of bronchodilators, mucolytics and antibiotics. At present majority of the treatments that are given deals with the symptoms but none of them addresses or is concern in reducing the progression or curing the disease. To remove the obstruction of the airways the mucous must be remove so that it clears the airways. This is achieved by administration of bronchodilators, mucolytic and by chest physical therapy (59). There are several issues that are to be addressed in treating CF. Synthesis of NPs using different materials shapes and sizes and can be tuned accordingly to overcome all the issues faced in free drug delivery.

One of the most common way of treating this disease is administration of antibiotics by inhalation especially Tobramycin. In its free from tobramycin cannot achieve its therapeutical level so in order to enhance the delivery of the drug , nanostructured lipid carriers loaded with tobramycin (tb- NLC) was developed by Moreno-Sastre and his colleagues (60), tb – NLC was developed to address the issue of bypassing the mucosal membrane and increase the retention of tobramycin. The core of the NP was made of solid lipid Precirol ATO 5 (NLC P) or with a mixture of Precirol ATO 5 and Compritol ATO 888 (NLC PC) another solid lipid. Their result showed that both the NLC P and NLC PC showed 80% of drug release in first 24 hr and sustained release for up to 96 hr, they also reported that in both NLC P and NLC PC 100 % of the drug that was loaded was released. In addition to this they also showed that NLC had same MIC to that of the free drug. In an experiment carried out by Garbuzenko *et al.* (61). They tested the nanostructured lipid carrier (NLC) loaded with drugs both in vitro on the normal and CF human bronchial epithelial cells and in vivo on homozygote/homozygote bi – transgenic mice with CF. Their result showed that the NLC had a high capacity for the drug holding efficiency which was internalized in the cytoplasm of the cells. They found that the drugs loaded in the NLC were able to restore the expression and function of the CFTR protein. Both the drugs lumacaftor and ivacaftor delivered into the lungs by the lipid nanocarrier was effective in the treating the CF.

Lipidic formulations and their applications

Spherulites

Spherulites were developed as an alternative to liposomes. They are used in oligonucleotide, enzyme delivery, drug detoxifications and as microreactors with high encapsulation efficiencies. These are concentric multilamellar structures with

alternating layers of aqueous medium which confers it high dispersion stability and is devoid of a large aqueous core that is present in liposomes. They are prepared by a process involving controlled hydration of surfactant or lipid lamellar phases (62). Spherulites are prepared by dispersion of lipid film in aqueous phase containing drug followed by controlled shearing and extrusion (63).

For pulmonary drug delivery Dhande *et al.* (2018) prepared Vinorelbine tartrate spherulites targeting non-small cell lung cancer consisting of cholesterol, soybean phosphatidylcholine, mannitol and potassium oleate. The PEGylated and non-PEGylated spherulites possessed good efficiency of more than 95% and a 48h drug release profile. The surface functionalized i.e., PEGylated spherulites were present in the lungs at higher concentration than non-PEGylated spherulites as revealed by gamma scintigraphy results (63).

Dhande *et al.* (2017) prepared radiolabelled Gemcitabine hydrochloride (GCH) spherulites targeting non-small cell lung cancer. The technetium radiolabeled formulation was used to study bio distribution in Sprague-Dawley rats. PEGylated spherulites exhibited better sustained release of GCH followed by non-PEGylated and plain GCH. The formulation possessed much higher cytotoxicity and apoptosis at lesser concentration than GCH solution. Gamma scintigraphy showed that GCH-loaded PEGylated spherulites were able to localize better within lungs in higher concentration than non-PEGylated followed by plain GCH (64).

Lipid nanocapsules

Lipid nano-capsules are not affected structurally or functionally during nebulization and are the front-runners for pulmonary delivery with highly bio-compatible aerosol system. They possess better retention in lungs and consistent repartition in lungs. Core-shell type systems have also been developed for nanocapsules. These nanocapsules have been efficiently used for treatment of asthma, non-small cell lung cancer and for delivering peptides (65).

Hureaux *et al.* (2017) formulated paclitaxel loaded nanocapsules and studied various toxicity aspects as well as bio distribution of endotracheal sprays. Analysis of bronchoalveolar fluid showed a transient alveolar inflammation lasting 7 days with a peak between day 2 and day 4. The lesions subsided gradually leaving no histological lesion on day 60, suggesting the safety of nanocapsules (66).

Inhalable fluticasone propionate (FP) nanocapsules were prepared for treating asthma by Umerska *et al.* (2015). Fluticasone is used in first-line therapy for the effective management of pulmonary diseases. They studied the drug-related influences in the formulation design and the behaviour of nanocapsules with different intimidating conditions of nebulization. Fluticasone was proficiently encapsulated with a yield of up to 97%, comparable to marketed formulations. Fluticasone showed no leakage from the formulation and no phase separation was observed after nebulization. Larger nanocapsules (100nm) contained a lesser amount of surfactant and a large amount of oil, provided improved drug loading capability and superior stability during nebulization than smaller 30 or 60 nm nanocapsules (67).

Erlotinib was formulated in a core shell type nanocapsule formulation for treatment of non-small cell lung cancer by Kim *et al.* (2017). They formulated PEGylated nanocapsules with a diameter of 200 nm and a net 20mV negative surface charge. PEGylation efficiently controlled the drug release from the core whereas acidic pH accelerated the release of drug due to presence of poly (L-aspartic acid). They possess a dose dependent cytotoxicity on lung cancer cells as shown by NCI-H358 and HCC-827. Nanocapsules showed a better tumour regression i.e., a 5times and 2times smaller tumour volume when compared to control and free erlotinib (68) .

Exosomes

Exosomes are intercellular transporters that deliver their content to exosome recipient cells and are intermediaries of cell-cell communication. They are vesicular systems containing proteins, lipid and nucleic acids. They can be used as biomarker detectors, as cell free delivery system for targeting cells, a drug delivery system for treatment of cardiovascular diseases, pulmonary hypertension, cancer (69-71) .

They have been found in body fluids of various individuals and in patients as cargos of several molecules including miRNAs. They also possess the ability to modulate gene expression post-transcription and can also be used in stem cell therapy (72-75) .

Aqil *et al.* (2017) developed exosomes for delivering Curcumin for lung and breast cancer. Milk derived exosomes were utilised as carriers of curcumin. The formulation remained stable for ant proliferative activity, particle size and drug load during a period of 6 months when stored at -80°C. The uptake of exosomes by cancer cells was deciphered as caveolae/clathrin-mediated endocytosis. The formulation showed no systemic toxicity. Exosomal curcumin administered orally to Sprague-Dawley rats exhibited enhanced activity with 3-5 times higher levels in different organs. Anti-inflammatory activity was measured in lung and breast cancer cell line with NF-kappa-B activation. Nude mice with cervical CaSki tumour xenograft were utilised to demonstrate *in-vivo* anti-tumour activity of exosomal formulation. Significant inhibition of cervical tumour xenograft was observed in exosomal formulation when compared to curcumin through dietary route (76).

Solid lipid nanoparticles

Solid lipid nanoparticles were introduced in early 1990s as colloidal carriers between 10-1000nm and consist of physiological lipid dispersed in surfactant solution with high drug loading efficacy, small size and high surface area. They possess controlled drug release characteristics and better targeting efficacies. They were introduced as an alternative to traditional colloidal carriers like liposomes, emulsions and polymeric nano and micro particles. The lipid chosen for formulation were solid at room temperature and are chemically inert with high melting point. To improve the drug compatibility with lipid matrix, conjugation approaches were found to be useful for hydrophilic substances.

The small size of SLNs helps in better pulmonary action as particles reach deep lung sites, leading to better accumulation at the site of action as well as

in lung cancer cases. The SLNs possess better activity systemically as well as locally (77, 78). Shah *et al.* (2016) studied the mechanism of cellular uptake of SLNs and found that the process is energy-dependent, and endocytosis of SLNs depends upon clathrin-mediated mechanisms (79). Burke *et al.* (2019) prepared microencapsulated SLNs of 200 nm, and zeta potential around +15 mV for safe pulmonary gene delivery. Microencapsulation helped in protection of pDNA from degradation. Plasmid stability and integrity were confirmed by electrophoretic analysis. The pDNA-loaded SLN were capable to transfect the pulmonary cell lines (Calu-3 and A549) and possess low cytotoxicity (80).

Polymeric nanoparticles (NPs) have received much attention as promising carrier systems in lung cancer and brain metastases (81). The feasibility of using inhaled cholesterol-PEG co-modified poly (n-butyl) cyanoacrylate NPs (CLS-PEG NPs) of docetaxel (DTX) for sustained pulmonary drug delivery in cancer metastasis was reported by Hu et al. In vitro inhalation evaluation data indicated that the inhalation formulation had better inhalation capability. Compared with intravenous (IV) administration, pharmacokinetic data suggested that the inhalation formulation prolonged plasma concentration of DTX for greater than 24 h and is more quickly and completely absorbed into the rat lung after intratracheal (IT) administration. The freeze- and spray-dried powders have the potential for pulmonary sustained release, and they also have the potential to be used as a novel treatment for the delivery of drugs that pass through the air–blood barrier and enter the brain and are efficient carriers for the treatment of brain metastasis.

Nafee *et al.* (2014) developed antibiotic free SLNs for quorum sensing inhibitors (QSI). They aimed at targeting *Pseudomonas aeruginosa* as one of the causative organisms of cystic fibrosis. It is manifested as biofilms which counteract the immune response and decrease the susceptibility of organism to antibiotics. QSI incorporated SLNs were prepared and were characterised for mucus penetration successfully using confocal microscopy equipped with 3D imaging. Acute toxicity studies were carried out on Calu-3 cells with no signs of toxicity. Next generation impactor was used to study the lung deposition which occurred mostly in bronchial region and nebulisation efficiency. Anti-virulence efficacy was measured by estimating the amount of pyocyanin exhibited by plain SLNs also without QSI (82).

Zhao *et al.* (2017) successfully achieved pulmonary delivery of Yuxingcao essential oil (YEO) loaded SLNs. The SLNs achieved a 48h sustained release. The SLNs were administered through a nebuliser and through intratracheal administration of YEO solution to rats. SLNs prolonged pulmonary retention to 24h and increased the AUC values by 4.5 -7.7 folds compared to intratracheal administration and 257-438 times the intravenous solution. They revealed that YEO loaded SLNs sustain YEO inhalation delivery and also improves local bioavailability thus representing a promising inhalable carrier to attain once daily application (83).

Pandey *et al.* (2015) prepared a lactoferrin conjugated SLNs containing Paclitaxel for targeting lung cancer. Lactoferrin secreted by exocrine glands is a multifunctional protein and is important for immune response. Bronchial epithelial cells are characterised by the presence of lactoferrin receptors on its apical surface and is utilised for targeting strategies. The SLNs were functionalised with lactoferrin using carbodiimide reaction. Higher anticancer activity was observed in case of functionalised SLNs when compared to plain SLNs and pure drug as deciphered by the cytotoxicity data on BEAS-2B cells. The bio distribution data also showed that the functionalised formulation was better taken up by the lungs as compared to plain SLNs and pure drug (84) .

Gasper *et al.* (2016) prepared SLNs containing rifabutin. Systemic administration of the drug is difficult due to off-target toxicity to cells and tissues which are uninfected. Delivery of drugs in nano-formulation minimises the toxicity and maximises the efficacy to the infected cells. SLNs can endure harsh conditions as well as release the drug completely. The delivery system achieved low toxicity as assessed by viability assays on A549 and Calu-3 cells (85).

Rosiere *et al.* (2018) prepared inhalable folate grafted PEG conjugated chitosan SLNs for treatment of lung tumours to improve selectivity for cancer cells, tumour penetration and allows for a sufficient lung residence time. The folate grafted SLN entered folate receptor (FR) overexpressed HeLa and M109-HiFR cells in vitro and M109 tumours in vivo after pulmonary delivery. It significantly decreased the in vitro half-maximum inhibitory concentrations of paclitaxel in M109-HiFR cells. During in vivo pulmonary delivery, the folate grafted SLN had encouraging pharmacokinetic profile, with 7h pulmonary exposure to paclitaxel and limited systemic distribution (86).

Pan et al (2021) reported the new type of self-assembled Ptx-SA drug-loaded nano-meters based on the carrier-free concept fiber. they found that the drug-loaded fiber has better cellophilicity, anti-tumor effect in vitro and in vivo than naked drug, and may be mediated by regulating the expression of related proteins. At present, nanomedicines mainly include lipid nanoparticles, polymer nanoparticles granules, gold nanoparticles, magnetic nanoparticles, mesoporous silica, and other dosage forms. The use of nanomaterials as carriers in the treatment of lung cancer has unique advantages in achieving targeted drug delivery, slow-release drugs, and improvement of poorly soluble drugs and peptide drugs show obvious advantages in terms of bioavailability and reduction of adverse reactions, and have broad research and development prospects (87).

Acosta *et al.* (2021) reported the Inhalable Nanoparticles/Microparticles of an AMPK and Nrf2 Activator for Targeted Pulmonary Drug Delivery as Dry Powder Inhalers. Metformin is an activator of the AMPK and Nrf2 pathways which are important in the pathology of several complex pulmonary diseases with unmet medical needs. The nanoparticles were prepared using the organic solution advanced spray drying method without using water. *In vitro* cell assays were conducted to

test safety in 2D human pulmonary cell lines and in 3D small airway epithelia comprising primary cells at the air-liquid interface (ALI). The authors described that the therapeutic advantages of metformin dried powder nanoparticles for the treatment of a number of pulmonary diseases including pulmonary vascular diseases such as pulmonary hypertension (Figure 3) (88).

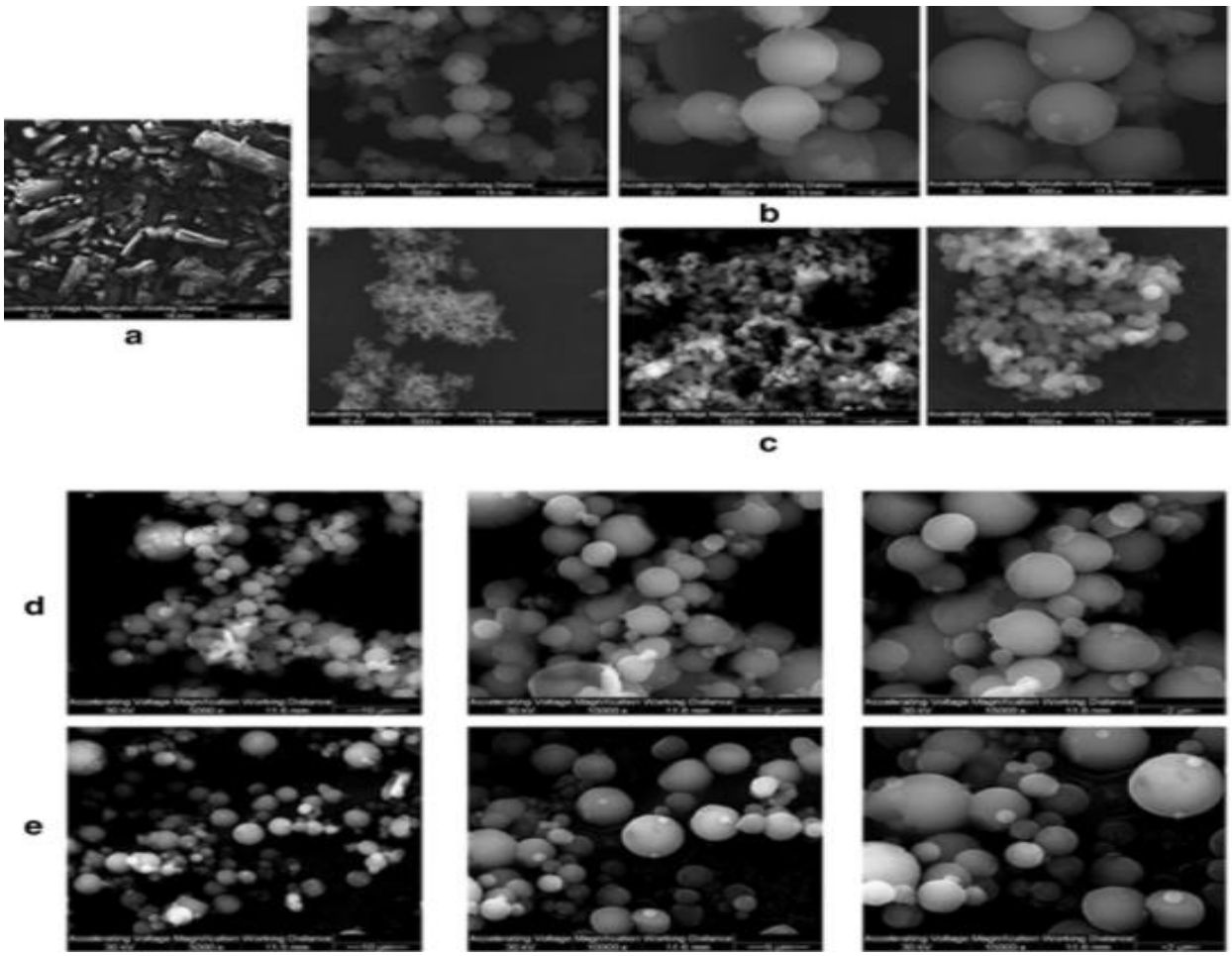

Fig. 3: SEM micrographs of (**a)** raw metformin HCl, (**b)** SD metformin (25% pump rate), (**c)** SD metformin (50% PR), (**d)** SD metformin (75% PR), and (**e)** SD metformin (100% PR), [Acosta MF, Abrahamson MD, Encinas-Basurto D, Fineman JR, Black SM, Mansour HM. Inhalable Nanoparticles/Microparticles of an AMPK and Nrf2 Activator for Targeted Pulmonary Drug Delivery as Dry Powder Inhalers. AAPS J. 2020;23(1):2.].

The inhaled delivery of nanomedicines has attracted much attention in the treatment of lung diseases or systemic diseases. Less information's are available regarding their ADME. Liu et al (2020) reported and summarised the physicochemical properties affecting the fate of nanoparticles after deposition in the lung. Physiochemical properties affecting the clearance and translocation of nanoparticles (including particle size, surface charge and surface hydrophilicity). Better understanding of the fate of nanoparticles in the lung will broaden their application in inhalation for a better therapeutic effect in the future (89).

Nano-structured lipid carriers (NLC)

NLCs are composed of a solid and a lipid phase dispersed in an aqueous surfactant. The major advantage of using a lipidic vehicle for drug administration includes easy and safe administration of gene and various other drugs which are unstable in aqueous environment. Use of lipid carriers helps in better compatibility of the system, low toxicity, better drug entrapment and freedom in selection of different modes of drug administration. These NLCs can effectively target pulmonary aspergillosis (90), lung cancer (91), tuberculosis (92), acute lung injury (93), cystic fibrosis (94).

β-elemene and Doxorubicin containing pH sensitive NLC were prepared by hot homogenization and sonication. The formulation exhibited synergistic anticancer effect. It also exhibited significantly improved tumour inhibition and cytotoxicity when compared to non-pH responsive and single drug loaded formulation (52). Paclitaxel and Doxorubicin co-loaded NLC were prepared by melt emulsification technique. The formulation has strong anti-tumour efficacy and better tumour targeting potential. The cytotoxicity was assessed on NCL-H460 cell line (53).

Inhalable NLC containing prostaglandin E2 was formulated for idiopathic pulmonary fibrosis. The formulation with and without siRNA targeted MMP3, CCL12 and HIF1 Alpha mRNAs. Idiopathic pulmonary fibrosis model was developed by administering bleomycin (1.5U/kg) intratracheally. NLC prepared in conjunction with siRNA prevented

animal mortality, reduced body mass, restricted lung damage limited mRNA disturbance and protein expression (95).

Transfectin modified NLC prepared by Han *et al.* (2014) exhibited better gene transfection efficiency than SLN containing doxorubicin (DOX) and enhanced green fluorescence protein plasmid (pEGFP). The results were found to be due to combination effect of chemotherapy and gene therapy. Transfectin improved the lung targeting efficacy of the formulation (96).

Zhang *et al.* (2017) prepared Transfectin and Hyaluronic acid modified NLCs containing plasmid enhances green fluorescence protein and found that the dual targeting system worked better than the single ligand targeted system(97).

Janus particles

Anisotropic nanoparticles or 'Janus' particles can deliver hydrophilic as well as hydrophobic drug molecules in one complex system. They possess a large surface area to volume ratio for better adjustment of ligands and protective coatings. They can be prepared by modified double emulsion solvent evaporation method. Janus particles are neither cytotoxic nor genotoxic as determined by various methods and therefore can be easily used for treating other diseases as well.

Olga *et al.* (2014) prepared inhalable Janus particles for treatment of lung cancer. The particles were accumulated in the mice lungs for 24h. Curcumin and Doxorubicin were efficiently entrapped in this self-assembled particulate system and prevented tumour progression. The dual drug-loading capacity of these particles also plays an important part in synergistic action of drugs. The Janus particles can be effectively used in delivery of various other combination of hydrophilic and hydrophobic drug combinations and reduce multiple drug dosing schedules (98).

Liposomes

Liposomes are vesicular structures composed of lipidic bilayer. They are efficient carriers for drug delivery via pulmonary route as they remain stable and safe during administration. Liposomes can be loaded with hydrophilic as well as hydrophobic drugs for controlled drug delivery. The drug release occurs via diffusion through the bilayer. Liposomes can be modified for targeted action. Guo *et al.* (2015) prepared theragnostic liposomes containing a photo thermal agent and folate as ligand. The liposomal preparation owes its efficacy to bubble generation by thermal triggering. A near IR thermal source was utilized to produce heat and generate bubbles of carbon dioxide by releasing entrapped ammonium bicarbonate, folate helped in efficient binding of the formulation to the target tumour. The bubbling helped in creating defects in the lipid bilayer and lead to efficient release of drug from the system. The liposomes exhibited enhanced circulation time and targeted human epidermoid carcinoma cells. Liposomes showed no side effects and inhibited tumours in nude mice efficiently (99).

Omer *et al.* (2018) studied pulmonary delivery of drugs using spray dried proliposomes loaded with salbutamol sulphate (SS). These proliposomes were formulated using a range of lipid to carrier ratio and consisted of carbohydrate carriers (lactose monohydrate or mannitol) and lipids (soyaphosphatidylcholine and cholesterol; 1:1). The lipid phase consisted in a ratio 1:1 of soy phosphatidylcholine (SPC) and cholesterol and the lipid carrier consisted in a ratio of 1:2, 1:4, 1:6, 1:8 or 1:10 w/w. the morphology of the proliposome particles studied using scanning electron microscope showed that the particles were irregular in shape in mannitol-based particles irrespective of its lipid to carrier ratio, whereas LMH – based particles were irregular in shape and rough with no uniformity in the size. Further the inertial impaction studies conducted using two – stage impinge (TSI), revealed that the fine particle fraction (FPF) values were higher in mannitol-based formulations with 52.6% and was attributed to its flowing properties due to its uniform size, smooth spherical shape. Transmission electron microscopy studies revealed that the liposomes generated from hydration of mannitol-based formulations showed a combination unilamellar (LUVs) and oligolamellar vesicles (OLVs), while proliposomes with LMH had structures worm like and with rich vesicle clusters. Carrier to lipid ratio affected the vesicle size, the vesicle size decreased on increasing the lipid to carrier ratio. The Zeta potential in the liposomes in all formulations was slightly negative indicating that the surface charges of the vesicles were unaffected by lipid to carrier ratio and carrier type used in the formulations. The drug entrapment efficiency (EE) differed slightly depending on the formulations, due to the lipid formulation entrapment efficiency was higher 37.76% for LMH base proliposomes with a lipid to carrier a ratio of 1:2. Omer and his co-worker concluded that spray drying can be used to produce inhalable proliposome microparticles that can generate liposome upon contact with aqueous phase (100).

Gomez *et al. (2020)* have reported the design, develop and characterize inhalable proliposomal microparticles/nanoparticles of Amphotericin B (AmB) with synthetic phospholipids, dipalmitoyl-phosphatidylcholine (DPPC) and dipalmitoyl-phosphatidylglycerol (DPPG) which are lung surfactant-mimic phospholipids. Gomez et al. (101)

Solid self-micro-emulsifying drug delivery system (SMEDDS)

SMEDDS is mostly used for delivery of drugs with solubility issues and make the drug available in solubilised form by avoiding the dissolution step. Ishak *et al.* (2015) prepared Solid SMEDDS to deliver drugs to lungs for treatment of lung cancer. Atorvastatin was formulated as SMEDDS using lecithin and TPGS. The formulation was tested for cytotoxicity on lung cancer cell line and lecithin (1) and TPGS (3) was found to be adequately encouraging. 70% respirable SMEDDS were successfully prepared and effective results were obtained (102).

Lipospheres

They are composed of solidified lipid core with a drug enriched phospholipid layer; it achieves tensile strength due to presence of plasticisers such as PEGs. Lipospheres are mostly affected morphologically owing to choose of excipients. Lipids surface charge and size affect the stability and integrity. They protect the drug moiety from hydrolysis, substantiate the shelf life enabling high

bioavailability, prolonged plasma levels and avoids side effects of oral administration (103).

Singh *et al.* prepared rifampicin lipospheres using spray dried method and achieved higher deposition rates at 3, 4 and 5 stages there by simulating the pathway of human lung. The formulation got deposited in the lower regions of the lung. Pharmacokinetics study showed prolonged availability of the drug in the lungs and the targeting efficacy was found to be much higher at 8.03 than the aqueous rifampicin solution and exhibited lesser drug in non-target tissues. Adhesion to airway epithelium prevented the mucociliary clearance of the formulation and exhibited a decent potential to reach deep tissues in the lung for clearance of tubercular infection (104).

RBC derived nanovesicles

Vesicular systems prepared with RBC's have advantage of being biodegradable, non-immunogenic, longer circulation, avoids the opsonisation of nanoparticles and improves therapeutic efficacy and pharmacokinetic properties. They have an average size of 100-200 nm with a bilayer structure rich in cholesterol, lipid raft, proteins, haemoglobin, phospholipids and acetyl cholinesterase. They are mostly used as stealth nanoparticles to minimise their clearance by reticuloendothelial system (105).

Contrasting from liposomes, hydrophobic moieties are partitioned inside the lipophilic casing, rather than an aqueous core with a hydrophilic drug. Malhotra *et al.* prepared camptothecin encapsulated nanovesicles and modified it with amphiphilic fluorophore. The prepared vesicle remained stable and was non phagocytic in presence of serum and exhibited less macrophage stimulation to supress cytokine release. The drug released over a time span of 24 h from these nanovesicles. The nanovesicles showed higher toxicity when compared to free drug as they were internalised by the carcinoma cells. Parenteral administration in Balb/c mice exhibited a longer circulation time of 48 h and insignificant accumulation in vital organs. These nano-vesicles show great potential to be developed as personalised medicine (106) .

CONCLUSION

The pulmonary diseases can be better treated by the pulmonary drug delivery systems as the system is directly delivering the drug to the pulmonary system. Diseases like asthma, COPD, lung cancer and cystic fibrosis requires extra precaution to receive better results, which can be solved by pulmonary delivery system. The pulmonary drug delivery system delivers the drug directly to the system without hepatic first pass metabolism of the potent drugs. It can be concluded that the new drugs acting on pulmonary system, which are having solubility problem can be directly delivers to the system by the pulmonary drug delivery system.

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