Inhalable hybrid nanocarriers for respiratory disorders

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1 Inhalable nanocarriers and their specific requirements

Pulmonary route offers various outstanding features when studied in comparison with the oral and parenteral routes. It offers a highly vascularized area with a thin blood-alveolar barrier. The route also possesses increased selectivity, reduced systemic side effects, and low administered dose [1].

Inhalation drug delivery has long been used in the treatment of tuberculosis, asthma, bronchitis, cystic fibrosis (CF), chronic obstructive pulmonary disease (COPD) [2], and systemic diseases like osteoporosis, pain, and diabetes. It is particularly useful in drugs with low bioavailability and in reducing the dose with reference to oral administration. It offers a noninvasive route for drug delivery increasing patient acceptability. One of the major challenges in oral systems is achieving delivery to the site desired and avoiding its side effects. Inhalable delivery overcomes these challenges by achieving site specific delivery and overcoming side effects such as decline in lung and kidney functions due to prolonged exposure subsequent to oral therapy. The inhalable formulations are delivered as a solution, suspension, or dry powder [3].

Nanoparticles (NP) possess promising targeting ability and have high cell uptake characteristics when administered through vascular routes. Nanoparticles show rapid clearance as they are coughed out after pulmonary administration. To overcome this problem, they are incorporated in large microparticles. Microparticles with appropriate aerodynamic characters (1–5 μm) allow drug delivery to lung tumors [4].

The different anatomical barriers to successful pulmonary delivery are as follows:

(i) The mucus layer/surfactant layer (~5–10 μm thick) poses a barrier to the deposited drug. It has to be quickly dissolved into this mucus layer before enzymatic degradation of the drug or else there would be rapid mucociliary clearance; hence, permeation enhancers must act rapidly to improve the bioavailability of the active ingredient.

(ii) The epithelial layer consists of pseudo-stratified columnar cells interconnected via tight junctions. Most of the molecules are absorbed through transcellular diffusion (small lipophilic molecules partition between the membranes via concentration gradient), and polar molecules follow paracellular diffusion, but the tight junction poses a barrier to the absorption of drug molecules.

(iii) Capillary endothelium is of importance to systemically targeted drugs but does not favor locally acting drugs [5, 6].

The different barriers to pulmonary delivery are listed in Fig. 1.

Lungs achieve slow clearance of nanoparticles. The NP escape mucociliary and phagocytic inactivation. They achieve controlled release. The major hurdles in delivery through nanoparticle are poor particle size distribution, instability, and not-so-good loading efficiency. Hybrid nanoparticles are comparatively new class of nanoparticles with the beneficial effects of both lipids and polymers. Hybrid nanoparticles possess good loading efficacy, structural integrity, cell targeting properties, and better cellular affinity. It is also beneficial in drug delivery of both hydrophilic and hydrophobic drugs [7]. Pulmonary administration of nanoparticles also reduces the drug dose to about 5% of the initial dose [8].

Drug release from these hybrid systems is affected by the thickness of the lipid layer in the case of polymeric cores and lipidic shell-type hybrid systems. As the thickness of the lipid layer decreases, the size is reduced, but the release increases as the water permeation is increased and the dissolution, in turn, increases for hydrophilic drugs. When hybrid systems are formulated with a polymeric shell and lipid core, the clearance from the lung decreases as the polymeric shell protects the core from macrophage uptake, thereby increasing their residence time [9]. Particles inhaled through inhalation devices are deposited in the airways through sedimentation under gravity, Brownian diffusion, and inertial impaction. Large particles more than 5 μm deposit in the throat and upper respiratory tract due to high mass and inertia and are eliminated through spitting or swallowing. Particles between 1 and 5 μm travel up to the lower airways by gravitational sedimentation. Particles smaller than 1 μm are deposited in the alveoli by Brownian motion but are mostly eliminated as they do not get sufficient time to adhere leading to exhalation [3].

Inhalable micro- and nanocarriers deliver the drug or active ingredient to the lung epithelium and basal layers for quicker onset of action. NP that is below 300 nm is delivered directly to the basal epithelium and avoids phagocytosis. Endocytosis of NP occurs between a range of 50–500 nm. Dry nebulized nanoparticles have low deposition values. To achieve better results, they can be nebulized by dispersing them in normal saline. Nowadays, apart from delivering drugs, research is undergoing to deliver miRNA and antisense oligonucleotides that work by inhibiting protein expression of various inflammatory conditions.

Inflammatory lung disorders can be described as COPD, CF, and asthma. Bronchial epithelium, the first in line of defense as presented by the airway, secretes IL-8 in response to toll-like receptor-4 activation. As these proinflammatory

Mechanical barriers
- Impaction of inhaled drug and droplets in nose and mouth
- Mucociliary clearance
- Pathophysiological condition
- Impaction losses in large airways further restricting delivery to peripheral lungs region

Chemical barriers
- Proteolysis enzymes causes drug degradation
- Effects of surfactants

Immunological barriers
- Alveolar macrophages uptake of Xenobiotics

Behavioral barriers
- Non-compliance with treatment regimen
- Poor delivery device

Strategies to overcome these barriers
- Preventing degradation of drugs
- Enhancing barrier permeability
- Disruption of liquid bilayer
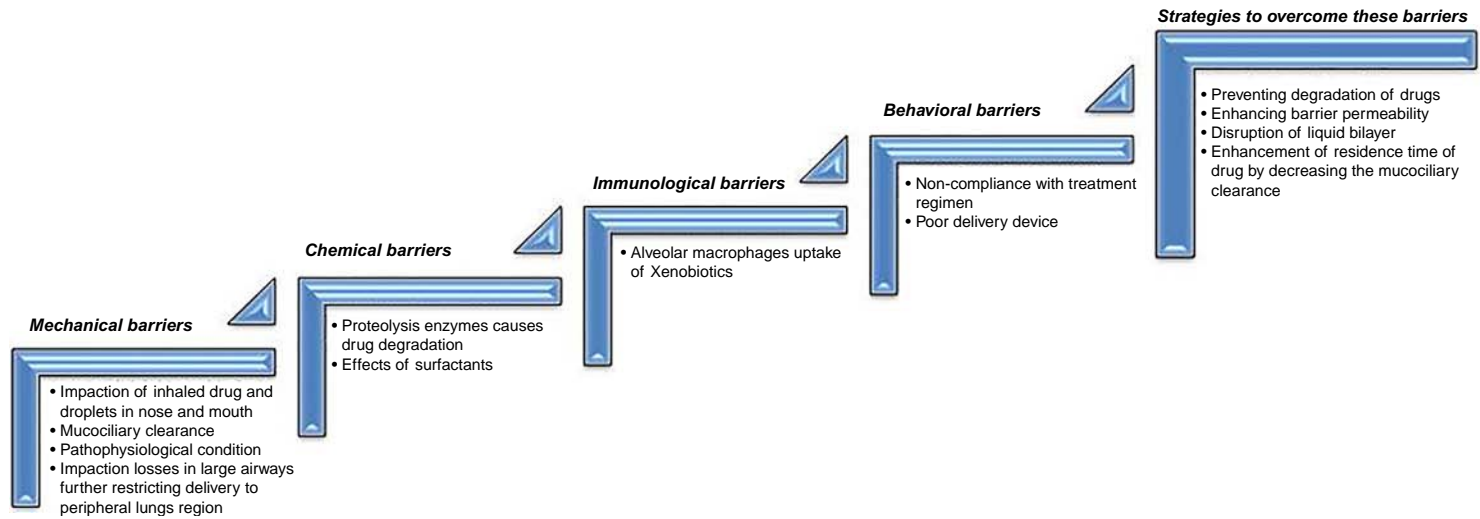- Enhancement of residence time of drug by decreasing the mucociliary clearance

FIG. 1

Barriers to pulmonary drug delivery.

cytokines are released, they start neutrophil infiltration at the site of release and all of proteases and oxidants start damaging the epithelium and begin losing in tissue function and start tissue transformation. miR-17 downregulates the secretion of IL-8 secreted in response to lipopolysaccharide by more than 40% [9–11]. Vencken et al. designed and prepared hybrid nanoparticles for targeting bronchial epithelial cells loading them with miR-17 to downregulate proinflammatory chemokine IL-8. miRNA delivery through nanoparticles which opens up various avenues for disease targeting [9].

It has been reported that miRNA are involved in various pulmonary disorders such as COPD, asthma, and lung cancer [11]. Targets for miRNA involved in lung diseases are IL-6, IL-10, IL-12A, IL-13, IFNB1, TLR4, TGF-β pathway, phosphoinositide 3-kinase (PI3K)/Akt pathway, and glycogen synthase kinase 3 beta (GSK3B). The miRNA involved are miR-21, miR-25, miR-26A, miR-106A, miR-126, miR-127, miR-133A, miR-145, miR-146A, miR-192, miR-199A, miR-221, and miR-485 [10]. miRNA possess a low molecular weight and small size that enable them to be efficiently given as drugs. The miRNA targeting is done by two mechanisms, by direct downregulation using miRNA antagonists or by using miRNA sponges to sequester misexpressed miRNA. The second approach is used in miRNA targeting [10]. The various challenges and approaches to overcome miRNA targeting are given in Fig. 2.

Antigen-presenting cells are commonly called dendritic cells that are of immense importance in immune response related to its regulation and initiation. The dendritic cells (DC) continuously sample the inhaled air for antigens and present them to the specific T cells in the regional lymph nodes. Thereby, they activate the T cells and present them the processed peptides. They also activate memory T-cell responses in the lungs. They are quite sensitive to environmental factors such as allergens, pollutants, microbes, and tissue damage products [12]. The miRNA is nowadays utilized as biomarker. DC hold popularity as antitumor agents. DC possess antitumor effects

Challenges to miRNA targeting	Approaches to overcome challenges
1. miRNA mimics and antagonists are degraded in the blood circulation.	1. Optimize the particle size, surface charge and chemical modification of the miRNAs or delivering them locally.
2. Poor permeation in tumor tissues	2. Ligand targeting and attaching cell-penetrating moieties.
3. Aggregation in endosomes of naked miRNAs end up in inefficient gene silecing and off target effects.	3. Fusogenic peptides are used to overcome intracellular deposition

FIG. 2

Challenges and approaches to overcome miRNA targeting.

that are affected by trivial DC count, low antigen presentation efficacy, and reduced ability of DC to migrate into the tumor mass. Apart from improving the antigen-presenting efficacy of DC, blocking the signal between DC and tumor cells is also beneficial in developing antitumor therapy. Wand et al. reported that to support tumor growth, lung cancers restrict functional DCs from that region. DC-derived exosomes are efficiently used in immunotherapy in nonsmall cell lung cancer [13].

2 Types of hybrid nanocarriers

When a NP utilizes the multifunctionality given to it by way of different materials of construction, it becomes hybrid. Depending upon the properties required for a system, a suitable selection can be made. Hybrid nanoparticles of the core-shell type in the nanorange are composed of the polymeric layer and a lipidic layer. Hybrid nanoparticles were prepared to reduce the limitations of lipidic and polymeric systems. These are solid submicron particles composed of the lipid and the polymer containing various bioactives such as proteins, genes, targeting ligands, and drugs, which can be encapsulated, covalently attached, and entrapped. Hybrid nanoparticles are used to overcome the biobarriers limiting oral drug absorption, that is, acid hydrolysis, pH differences, enzymatic degradation, mucosal barriers, and variable transit time. Lipids provide an endless opportunity as an excipient enabling formulation of solid lipid nanoparticle, self-emulsifying systems, nanoemulsions, nanostructured lipid carriers, and liposomes. Lipidic systems can be used efficiently in formulating poorly water-soluble drugs as they provide a lipophilic microenvironment for enhancing drug solubilization and preventing P-glycoprotein (P-gp) efflux, and avoid the first-pass metabolism, reduces hepatic metabolism by promoting lymphatic drug transport and lipidic systems, and protect encapsulated drugs from digestive enzymes in GIT.

Inclusion of a polymeric nanocarrier can be utilized to deliver compounds not easily delivered via lipidic systems. Polymeric systems are more stable in GI transit and provide the versatility of a natural, synthetic, or semisynthetic alternative. An advance in polymer sciences enables superior control over the properties and architecture of these carriers facilitating controlled delivery although issues regarding their inadequate encapsulation and burst release still pop up from time to time [14]. Hybrid nanoparticles of core-shell type can be classified as.

2.1 Core-coated nanoparticles

2.1.1 Lipid-core/polymer-shell systems

Lipid-core/polymer-shell (LC-PS) systems include a lipid core (cholesterol, DPPC, DSPE-PEG2000) enclosed by one or multiple polymeric coats (PEG, chitosan, polyacrylic acid, and polyallylamine). The core holds the active ingredient, while the coating stabilizes the lipid core to overcome biological obstacles. Significant work has been done on linking nanocarriers such as liposomes, SLN or NLC with chitosan, and PEG like multifunctional polymers [3–6].

2.1.1.1 Chitosan-coated lipid nanoparticles

Incubation method is the preferred method for preparing chitosan-coated lipid nanoparticles, that is, uncoated lipid nanoparticles are prepared first, and then the prepared nanoparticles are incubated in an aqueous chitosan solution. The chitosan self-assembles at the interface of oil and water (o/w) through electrostatic interactions during incubation. Alternatively, glutaraldehyde can be utilized as the cross-linking agent for stabilization. Chitosan-coated systems are beneficial in terms of efficiently loading hydrophobic drugs in nanocolloidal systems. The chitosan coated formulation due to its positive charge possessed better uptake and targeting ability [15]. Garcia et al. developed chitosan-coated lipidic nanoparticles of tripalmitin and lecithin and isolated them using ultracentrifugation. The negatively charged nanoparticles possessed a positive charge after being coated by chitosan. The chitosan-coated NP remained unaltered in simulated gastric and intestinal media and proved that it is suitable for oral use [16].

2.1.1.2 PEGylated lipid nanoparticles

PEGylated nanoparticles possess a longer circulation half-life because they escape capture and phagocytosis by various organs. PEGylated lipid nanoparticles are prepared by adding PEG esters in the lipid phase. Thin-film hydration method is frequently used in its preparation. Dipalmitoyl phosphatidylcholine (DPPC), distearoyl phosphatidylethanolamine-polyethylene glycol 2000 (DSPE-PEG2000), and cholesterol are the lipids of choice for PEGylated lipid nanoparticles. PEGylated SLN are prepared by emulsification and can be purified by ultracentrifugation. A blend of PEG-stearic acid and tripalmitin is solubilized in an organic solvent, followed by sonication, in an aqueous surfactant solution. The organic solvent gets evaporated during stirring, and the final PEG-SLN is collected and purified by ultracentrifugation [17]. PEGylated NLC (PEG-NLC) can also be prepared by substituting tripalmitin with liquid medium-chain triglyceride (Miglyol 812) [16, 18].

2.1.1.3 Layerosomes

Polyelectrolyte-stabilized liposomes or layerosomes are prepared by a multiple coatings of polyelectrolyte (positive and negative charged), utilizing the layer-by-layer approach. The coatings so applied on the liposomal surface preserve the original structure and protect it from the physiological damage. Layering helps in incorporating various materials in the system and in its overall stabilization through ionic interactions [19]. The liposomal core consisting of cholesterol and phospholipid core achieve a positive charge on inclusion of stearyl amine. Anionic polymers, namely, polyacrylic acid (PAA) are then made use of in coating liposomes followed by another coat of polyallylamine hydrochloride (PAH) cationic polymer. Transmission electron microscopy is used to characterize layerosomes. Layerosomes range from 200 to 500 nm, and it depends on the size of crude or uncoated liposomes and the mass ratio amidst polymer and lipids [20].

2.1.2 Polymer-core/lipid-shell systems

In the polymer-core/lipid-shell systems, polymer core is delimited by unit coat or several coats of lipid. The hydrophobic nature of the shell inhibits water infiltration toward the core. Core-shell system modifies polymer degradation, prevents drug movement, and sustains drug release, as the polymer provides structural integrity to the shell. The drug may be captured within the core or simultaneously in core and in the adjacent lipid layer, depending upon the nature of drug(s) [21–25].

2.1.2.1 Chitosan lipid nanoparticles

Lipidic carriers are reported in the literature to augment the oral administration of biomacromolecules to the systemic circulation via intestinal lymphatic system, thereby evading degradation by first-pass metabolism. Enclosing hydrophilic drugs in the lipid system promotes transport via the lymphatic system. A hybrid nanoparticle is utilized for various purposes. The use of cationic polymer increases the loading efficiency of drug (heparin) in the lipid carrier, and chitosan is recognized to improve the passage of heparin across the intestinal membrane through tight junctions. Chitosan when used as a constituent of the hybrid system increases the entrapment efficiency of lipid nanoparticle [26].

2.1.2.2 PLGA-phospholipid nanoparticles

Sandwich-like poly(lactic-*co*-glycolic acid) (PLGA)-soybean phosphatidylcholine (SPC)-PEG systems with three functional components have been reported in the literature:

  (i) Internal core (hydrophobic PLGA).
 (ii) Intermediary (amphiphilic SPC layer).
(iii) External shell (hydrophilic PEG).

The hydrophilic PEG shell improves the steadiness of NP in physiological environment and minimizes the mucin adhesive interfaces [7, 27–29].

2.2 **Matrix-type polymer-lipid hybrid systems**

2.2.1 Polymerized liposomes

Polymerized liposomes (PL) possess features similar to liposomes, wherein the covalent bonds link the phospholipid bilayers. PL are classically created from lipids, which can be polymerized by the thin-film hydration method. Polymerization is used to stabilize the lipid bilayer [30, 31].

O'Brein et al., in 1985, prepared polymerized liposomes from reactive lipids containing diacetylene, methacryloyl, and dieneoyl groups. Complete polymerization was not observed in diacetylene and methacryloyl lipids while moderate decrease in permeability of water-soluble compound (glucose) was observed in methacryloyl groups. Dienoyl lipids can be efficiently polymerized, and maximal reduction in membrane permeability is achieved as assessed by glucose permeation [30].

2.2.2 Nano-in-micro-type hybrid

A lipidic nanocarrier composed of solid-state medium enhances the formulation stability and facilitates various desirable biopharmaceutical functions. Nano-in-micro-type silica-lipid hybrid microparticles have been reported in the literature. Foreseeable and precise lipid digestion can be achieved by altering the internal nano-structures including surface area and porosity. Lately, spray drying and incubation methods have been used in PLGA-lipid hybrid (PLH) systems. They are prepared from Miglyol and PLGA NP. Chitosan-zein nano-in-micro-type formulations have also been reported for gene delivery [32].

Hybrid nanoparticles have been used to overcome the bio barriers limiting oral drug absorption, that is, acid and enzymatic degradation, pH differences, mucosal barricades, and variable transit time. Lipids provide an endless opportunity as an excipient enabling formulation of SLN, self-emulsifying systems, nanoemulsions, NLC, and liposomes. Lipidic systems can be used efficiently in formulation of hydrophobic drugs as they provide a lipophilic micro-environment for enhancing drug solubilization, averting P-glycoprotein (P-gp) efflux and dodging the first-pass metabolism as well as reducing hepatic metabolism by promoting lymphatic drug transport. Lipidic systems also protect encapsulated drugs from the degradative effect of the digestive enzymes in GIT.

Inclusion of a polymeric nanocarrier can be used to deliver compounds not delivered via lipidic systems. Compared with their lipidic counterparts, polymeric systems are more stable in GI transit and provide the versatility of a natural, synthetic, or semisynthetic alternative. Developments in polymer sciences enable good control over the properties and architecture of these carriers, facilitating controlled delivery.

However, issues regarding their adequate encapsulation and burst release still surface from time to time [33].

3 Method of preparation

The preparation of hybrid nanoparticles falls under two broad categories: the two-step method and the single-step method.

3.1 Two-step method

This involves independent preparation of core and shell components, which may then be combined by either direct hydration, extrusion, or sonication. Positively charged lipid vesicles and negatively charged polymeric nanoparticles fuse by electrostatic magnetisms. Dry lipid films are hydrated by polymeric dispersions or the dispersions can be added to preformed lipid vesicles, followed by vortexing and subsequent heating to arrange lipids onto the particle surface. The formulation is finally centrifuged to remove nonadsorbed lipids, micelles, or free polymeric nanoparticles, as the case may be [34, 35].

3.2 Single-step method

This method involves synchronizing nanoprecipitation with self-assembly, simultaneously. Modifications to this single-step method have also been reported, which include modified solvent extraction/evaporation or nanoprecipitation method respectively [36].

3.2.1 Modified solvent extraction/evaporation method

Firstly the polymer and drug are dissolved in a water-immiscible solvent (chloroform, ethyl acetate, dichloromethane, etc.) followed by mixing lipid in aqueous phase by sonication. Rotary evaporator can be utilized for removal of organic solvents. The product is further centrifuged followed by controlled washing. The product is dried by a suitable method like lyophilization to obtain a free-flowing dry powder [7, 18, 37].

3.2.2 Modified nanoprecipitation

A water-miscible organic solvent (acetone and acetonitrile) is used to solubilize the polymer and hydrophobic drugs. Dropwise addition of organic solution to aqueous dispersion of lipid or PEG-lipid conjugate is carried out. The blend is then vortexed and sonicated to achieve nanosized particles [14, 38].

4 Targeting strategies for hybrid systems

Pulmonary drug delivery is mainly aimed at passive targeting of tumor sites via enhanced permeation and retention (EPR) effect rather than active targeting via overexpressed receptors. Particles in the range of 100–150 nm are internalized better than microparticles of size 3–5 μm. Therefore size uniformity is a major concern in passive targeting as it plays an important role in deep lung deposition and internalization of the delivery system [39]. Pulmonary delivery of drugs via active targeting is achieved by the coupling of the drug to carrier molecules through a bioreceptive bond. Extensive studies are however required to establish the efficacy of these targeting strategies.

4.1 Size-based targeting

The size and shape of the NP formulation plays a significant part in pulmonary drug targeting. The anatomy of the airways and ventilation parameters also determine the drug delivery and its time of residence in the respiratory tract [40]. Very small particles are exhaled, and very large particles are removed by mucociliary machineries. Therefore there is a size range that determines the extent to which a formulation may reach the desired site of action. Drug delivery to deep lung tissues is dependent on size [41, 42]. Respirable particles between 1 and 5 μm are suitable for achieving significant drug concentrations. Small size and hydrophilic molecules are passively taken up by epithelial cells, and insoluble vectors are taken up by macrophages and

cleared. Alveolar macrophages do not recognize particles less than 70 nm on the surface of the lungs and allow them access to pulmonary interstitium and further to the capillary blood flow [3, 39].

Calcium carbonate microparticles prepared from vaterite polymorph possess suitable properties for drug delivery such as uniform size, and narrow size distribution, and spherical geometry as assessed by BET, SEM, and TEM in various studies. Alginate, when used in conjunction with calcium carbonate, reduces its toxicity and aids in the formation of a biocompatible formulation. These hybrid microstructures are capable of further modification through changes in polymer content and microsurface changes in porosity. These microsystems possess good drug loading capability. Islan et al. prepared spherical microparticles in the range of 3–5 μm, which is ideal for pulmonary delivery. As evidenced from the in vivo data, the microparticles reached 7.4 times the concentration of pure drug solution in the lung at a dose of 0.7 mg and at 1.4 mg, the lung levels were 2.8 times higher than pure drug [42]. Hybrid systems can be efficiently used to incorporate nuclease that helps in the breakdown of DNA chains, which are products of cell lysis and lead to mucus accumulation. The reduction in viscoelasticity imparted by nuclease improves the antimicrobial efficacy of drugs [43].

4.2 Heat triggered drug release

Hybrid nanoparticles containing lipids have been prepared in various studies for their diagnostic and colloidal stabilization properties. Localized laser heat generation can be utilized efficiently as absorption of light leads to the oscillation of surface electrons and generation of heat. This simple mechanism can be used in hybrid systems that are effectively made with the purpose of releasing the drug with respect to change in temperature. Hybrid nanoparticles releasing the drug in response to external stimuli were successfully prepared by Ahmady et al. Various formulations were prepared to contain gold, silver, and iron oxide in the hybrid formulation containing thermosensitive liposomes. The presence of metals in the formulation makes it stimulus responsive. The controlled drug release from the formulation continued for 60 min at mild heating conditions while maintaining good drug retention. The authors also provide support to the use of these NP in the theranostic application [44].

4.3 Downregulation of proinflammatory chemokines/oncoproteins

It has been reported that miRNA are involved in gene regulation in eukaryotes, and they are a group of small noncoding RNAs. They can target multiple sites and multiple genes within a signaling network. They also function as regulators, in the advancement and expansion of lung diseases. Variations in their number in blood, inflammatory cells and tissues act as disease modifiers and drivers. They act as biomarker tools as well, for the detection of diseases. In some diseases, miRNA act as disease drivers, but in the majority, they only maintain signaling pathway and gene expression. Knockout models for miRNA do not exist or are not published [11].

Proinflammatory chemokines such as interleukin (IL)-8 are secreted by human bronchial epithelial cells to retort lipopolysaccharide as a stimulant. To study its effect on the treatment of respiratory disorders, modulation of miRNAs was studied by Sebastian et al. They studied the role of miRNA-17 in secretion of IL-8. Nebulized hybrid particles containing miR-17down regulated LPS-induced IL-8 secretion by 40% in epithelial cells. Hybrid nanocarriers containing DOTAP-PLGA are efficient carriers for miRNA delivery for inflammatory conditions [9].

The miRNA delivery to cancer cells via aptamer-functionalized hybrid nanoparticles for lung cancer was successfully achieved by Perepelyuk et al. To efficiently carry miRNA-29b to MUC1-expressing cancer cells, bioconjugate system was prepared. A549 cells showed significant downregulation of oncoproteins DNMT3b and MCL1, and this further led to apoptosis and better antiproliferative effect [45].

Novel calcium phosphate-polymer hybrid nanoparticle systems were reported by Zhou et al. Hydrophilic miRNA and hydrophobic drugs were encapsulated in this system by coprecipitation in water-in-oil emulsion followed by coating with anionic lipid. The system delivered both the drug and miRNA to the target site and inhibited the proliferative effect of miR221/222 and enhanced the therapeutic effect of paclitaxel [46].

4.4 Dendritic cell targeted

Dendritic cell targeting is nowadays being used in monovalent and polyvalent vaccine delivery. The current approaches use bifunctional fusion protein (truncated core streptavidin fused to anti-DEC-205-single chain antibody) in conjunction with biotinylated PLGA nanoparticles (containing antigen) as the delivery system is biodegradable and can be used without adjuvants also. It also dodges a postformulation modification that has a detrimental effect on the antigen. The process involved is also quite simple as it requires a simple mixing of the two components (targeting ligand with nanoparticles). It utilizes the DEC-205 as the target moiety. In vitro studies showed a twofold increase in receptor-mediated uptake when compared with nontargeted nanoparticles [47].

Migdal et al., prepared hybrid nanoparticles containing para amino benzoic acid, and titanium dioxide internalized in dendritic cells was found to be noncytotoxic. Cellular uptake occurs through macro pinocytosis. NP were not present in the nucleus as seen through confocal microscopy. The NP remained in contact with cytoplasmic vesicles and cellular membrane without colocalizing with clathrin-coated vesicles. The nanoparticles are nonimmunogenic and do not induce oxidative stress [48].

Raghuvanshi et al. targeted plasmid DNA, through loaded biotinylated nanoparticles containing chitosan for immunization against SARS-CoV as antigen. The nanoparticles were prepared by the coacervation process and evaluated for nuclease digestion and plasmid DNA loading. The formulation being noninvasive is efficiently delivered via receptor mediation through the nasal route. The dendrimer targeting ability toward DEC-205 is imparted by the bifunctional fusion protein. Intranasal administration enhanced IgG and nasal IgA antibodies. Intramuscular route was also

evaluated for delivery of vaccines, which revealed its superiority for IgG response over the intranasal route [49].

5 Applications

Inhalable hybrid nanocarriers have varied applications in drug delivery for respiratory disorders. The inhalable nanocarriers that are below 300 nm are rapidly deposited to the basal epithelial cells and provide for site-specific delivery and avoid phagocytosis. Hybrid microcarriers (1–5 μm) allow for passive targeting to lungs. Hybrid nanocarriers can effectively deliver miRNA for treatment of inflammatory lung conditions and in lung cancer [9, 45]. Dendritic cell targeting (in inflammation) can be achieved by a preparing a hybrid between targeting ligand and PLGA NP. Cystic fibrosis can be targeted by silica-coated silver NP containing antibiotic. Colloidal hybrid systems can be used for imaging, diagnostics, and drug delivery. Hybrid nanocarriers are mostly useful in treating lung cancers [50].

Hybrid nanoparticles are nowadays used in various fields of pharmacotherapy and theranostics, tumor being the front-runner followed by gene delivery [51], peptide [52, 53], protein [54], vaccines [55], diagnostics [56–59], and materials science [60–63]. The different applications of hybrid formulations are listed in Table 1.

6 Future scope

A hybrid nanoparticle with a suitable target offers a novel approach for a rational design for effective therapeutic drug delivery. In inflammatory disorders, oral delivery of drugs leads to poor patient compliance and more of dose dumping. The route that is mostly preferred for inflammatory conditions is the pulmonary route as it offers the advantage of immediate delivery of the drug to the site and a lesser systemic side effect. The only concern in pulmonary delivery is that the drug once delivered cannot be reversed. Hybrid nanoformulations are nowadays preferred due to the flexibility in formulation procedures and the advantage of codrug delivery. This system also reduces the concern for interaction in terms of codelivery as both the drugs are present in their respective phases. The added benefits now are advances in drug delivery with novel systems that aim to deliver si RNA, miRNA, vaccines, and antivirals. These normally require sophisticated carriers that deliver these agents directly to the target site, preventing the degradation of gene/vaccine. The hybrid carriers can be suitably modulated to keep all these properties intact. As with core-shell systems, the formulator can efficiently select the core and shell material to either actively target the formulation or avoid the RES uptake mechanism and aim to amplify the circulation time of the nanoformulation so that it keeps releasing the drug at a predetermined rate without being taken up by the immune system. As discussed in the previous sections, these systems efficiently target and treat various therapeutic indications including tumors, colorectal disorders, Alzheimer's disease, psoriasis, lung disorders,

Table 1 Applications of various hybrid nanoparticles.

Type	Indication/site	API	Lipid/polymer	References
Aptamer-functionalized hybrid nanoparticles	Breast cancer	Doxorubicin, siRNA	DOTAP, cholesterol, PLGA, PEG	[64]
Calcium phosphate-polymer hybrid nanoparticle	Breast cancer	miRNA 221 and 222 and paclitaxel	Dioleoyl phosphatidic acid, calcium phosphate	[46]
Colloidal hybrids	Imaging/drug delivery		N-vinylcaprolactum, FePt NP	[65]
DNA/RNA hybrid	Ovarian cancer	Doxorubicin	Annexin A2, Endo28, phi29 packaging RNA	[66]
Hollow silica hybrid	Solid tumor	Arsenic trioxide	Distearoyl phosphoethanolamine-PEG (DSPE-PEG), distearoyl phosphatidylcholine (DSPC), distearoyl phosphoethanolamine-PEG-NHS (DSPE-PEG-NHS), cholesterol	[67]
Hybrid		Ibuprofen	N-isopropylacrylamide (NIPAM), porous silica NP	[68]
Hybrid	Cystic fibrosis	Levofloxacin, DNAse	Calcium carbonate, alginate	[42]
Hybrid	Psoriasis	Tacrolimus	Hyaluronic acid, cholesterol, nicotinamide	[69]
Hybrid liposome	Lung cancer	Doxorubicin	Phospholipid (DPPC) and Poloxamer 188	[50]
Hydrogel core surfactant shell	Lung	siRNA	Curosurf	[70]
Immunohybrid	Colorectal tumor	Oxliplatin	Chitosan, lipid	[35]
In situ hybrid	HIV	Nevirapine	Gelol (plyceryl monostearate), plurol stearique (polyglyceryl distearate), Lutrol F68	[71]
Inorganic-organic hybrid	Multiple sclerosis	Betamethasone	Zirconium dioxide	[72]
Lipid-dendrimer hybrid	Antibacterial	Vancomycin	Compritol 888 ATO, G4 PAMAM-succinamic acid dendrimer, Kolliphor RH-40	[73]
Lipid-polymer hybrid		siRNA	Dipalmitoyl phosphatidylcholine (DPPC), (PLGA)	[74]
Lipid-polymer hybrid	Anesthesia	Bupivacaine	Lecithin PLGA	[75]

Table 1 Applications of various hybrid nanoparticles—cont'd

Type	Indication/site	API	Lipid/polymer	References
Lipid-polymer hybrid	Benign prostatic hyperplasia	Lonidamide	L-α-Phosphatidyl choline, PLGA, DSPE-PEG-COOH	[34]
Lipid-polymer hybrid	Brain tumor	Pemetrexed	PLGA, L-alpha-phosphatidylcholine, trimyristin	[76]
Lipid-polymer hybrid	Cancer	Erlotinib	(DSPE-PEG2000), hydrogenated soy phosphatidylcholine (HSPC), and polycaprolactone	[77]
Lipid-polymer hybrid	Cancer	Paclitaxel	Poly(ε-caprolactone), poly(ε-caprolactone)-poly(ethylene glycol)-poly(ε-caprolactone) (PCL-PEG-PCL), (DSPE-PEG2000)	[23]
Lipid-polymer hybrid	Cervical cancer	Cisplatin and curcumin codelivery	Cholesterol, PLGA, PEG-DSPE	[78]
Lipid-polymer hybrid	Gene delivery		Cationic lipids, PLGA	[79]
Lipid-polymer hybrid	Head and neck cancer	Cisplatin and DNA	1,2-Dioleoyloxy-3-trimethylammonium-propane (DOTAP), PLGA	[80]
Lipid-polymer hybrid	Inflammatory lung disease	miRNA	(PLGA), 1,2-dioleoyloxy-3-trimethylammonium propane (DOTAP)	[9]
Lipid-polymer hybrid	Nasal	Tenofovir disoproxil fumarate	Lauric acid, pemulen polymer	[81]
Lipid-polymer hybrid	Ovarian cancer	Methotrexate		[82]
Lipid-polymer hybrid	Prostate cancer	Docetaxel (DTX), curcumin	PLGA, lecithin, PEG-DSPE	[83]
Lipid-polymer hybrid	Squamous cell carcinoma	Doxorubicin, triptolide	Soybean lecithin, monomethoxy-poly(ethylene glycol)-S-S-hexadecyl (mPEG-S-S-C16), and PLGA	[84]
Lipid-polymer hybrid	Tuberculosis	Isoniazid, ciprofloxacin		[7]
Lipid-polymer hybrid	Vaccine	Nicotine	PLGA	[85]
Lipid-polymer hybrid	Viral reservoirs	Pemetrexed	PLGA	[76]
Lipid-polymer hybrid		Lysozyme	Tripalmitin, lecithin, polycaprolactone	[86]
Lipid-protein hybrid	Tumor	Paclitaxel, vorinostat	Albumin, histone	[87]
Mesoporous silica nanoparticles	Cancer	Methotrexate	Poly 4-vinyl pyridine	[88]

Nano-in-micro	Gene delivery	DNA	Zein, chitosan	[32]
Nanolipomer	Schizophrenia	Paliperidone	Poly-ε-caprolactone, Lipoid S75, Gelucire 50/13, polyvinyl alcohol	[89]
Organic-inorganic	Ocular		Chitosan, glutathione, valine	[90]
Polymer-lipid hybrid		Verapamil	Dextran sulfate	[91]
Polymer-lipid hybrid	Breast cancer	Doxorubicin, mitomycin C	Epoxidized soyabean oil	[92]
Polymer-lipid hybrid	Cancer	Doxorubicin	Soyabean oil	[93]
Polymer-lipid hybrid	Cancer	Doxorubicin	Stearic acid, Pluronic F68, HPESO (hydrolyzed polymer of epoxidized soybean oil)	[94]
Polymer-lipid hybrid	Cancer	Doxorubicin	Stearic acid, tristearin, epoxidized soyabean oil	[95]
Polymer-lipid hybrid	Cancer	Doxorubicin	PLGA, DSPE-PEGCOOH, lecithin	[96]
Polymer-lipid hybrid	Cancer	LMW heparin	Chitosan	[26]
Polymer-lipid hybrid	Cancer, atherosclerotic plaque	Paclitaxel	Iron oxide, PLGA, 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-*N*-[maleimide(polyethylene glycol)- 2000] (ammonium salt) (DSPE-PEG-Mal), 1,2-dioleoylsn-glycero-3-phosphoethanolamine-*N*-carboxyfluorescein (CFPE), soybean lecithin	[97]
Polymer-lipid hybrid	Cancer, inflammation	Daunorubicin, lornoxicam	PLGA, soya lecithin	[98]
Polymer-lipid hybrid	Gene delivery		Poly(ethylene glycol)-distearoyl phosphatidylethanolamine (PEG-DSPE)	[99]
Polymer-lipid hybrid	Gene delivery	siRNA	Polyethylenimine	[100]
Polymer-lipid-polymer hybrid	Acne	Dapsone	Carbopol, HPMC, glyceryl monostearate, isopropyl myristate	[22]
Polymer-polymer	Colon	Doxorubicin hydrochloride	Enoxaparin sodium, PLGA	[101]
Silica-coated silver	Cystic fibrosis	Ciprofloxacin	Chitosan	[43]
Silver hybrid	Orthopedic applications	Naproxen	Chitosan, silver nanoparticles	[102]

and atherosclerosis. They are now also used in diagnostics and theranostics for the effective delivery of contrast agents and fluorescent dyes. The future scope for this formulation should aim at delivering the therapeutics to tubercle nodules and chronic inflammatory disorders, which occur as a result of antibiotic resistance developed due to misuse/overuse of antibiotics. The pulmonary route and the complications offered in the way can be very easily modulated by the hybrid systems to overcome and heal the damaged tissue in affected areas, without being concerned about the excessive dose and related side effects.

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