A review paper of pulmonary drug delivery system

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Abstract:

Due to limitations associated with the conventional treatment of various chronic diseases, a growing attention has been paid to the development of targeted drug delivery systems. Thanks for direct delivery to lung both for local and systemic treatment, pulmonary drug delivery route has gained much importance in the present research field and also in market. This review aims to discuss the mechanisms of pulmonary drug administration, the device used, and the techniques used to improve the performance. This review also points out the pros and cons of pulmonary delivery route and several products used in real world.

Introduction:

To alleviate and treat diseases, oral, parenteral and pulmonary delivery methods are the most frequently used administration routes for patients and medical practitioners. [1] With high solute permeability, a large surface area for absorption, and limited proteolytic activity the lungs attract scientists and become a prospective route for drug delivery. Additionally, high therapeutic ratio, increased selectivity, lower administered dose and reduced side effects are also benefit of pulmonary delivery. [2] [3]

What's more, for locally applied drugs, the systemic side effects could be reduced for minimized systemic exposure by targeting to the desired site (especially for drugs with a narrow therapeutic window). [4] The inhalation delivery of therapeutic agents has been known, though poorly understood, for many years. But the pulmonary tends to be considered as very promising and attractive route for the administration of active substances intended to treat local pulmonary (e.g., asthma, chronic obstructive pulmonary disease (COPD), microbial infections) as well as systemic diseases (e.g., diabetes). [5]

Lung anatomy

Our lung plays a vital role in the respiratory system, which is separated into two parts, the left lung and the right lung, and several lobes. They are situated with the thoracic cavity of the chest. Each lung houses structures of both the conducting and respiratory zones. The lungs are enclosed by the pleura, a membrane

that is composed of visceral and parietal pleural layers. The space between these two layers is called the pleural cavity. [6] The mesothelial cells of the pleural membranes created pleural fluid, which serves as both lubricant and as an adhesive to adhere the lungs to the thoracic wall. The major function of the lungs is to perform the inhalation of oxygen and the exhalation of carbon dioxide with air from the atmosphere. To this end, the lungs exchange respiratory gases across a very large epithelial surface area about 70 square meters, which is highly permeable to gases. The left lung consists of two lobes the superior lobe, and the inferior lobe, while the right lung consists of three lobes the superior lobe, middle lobe, and the inferior lobe. The lungs are part of the lower respiratory tract that begins at the trachea and branches into the bronchi and bronchioles, and which receive air breathed in via the conducting zone. The ends of conducting zone are called terminal bronchioles, which is called alveoli. Lungs provide oxygen for blood to transport to other tissues throughout the body.

Pulmonary drug delivery:

The function of the pulmonary circulation is to aid in gas exchanges. The pulmonary artery provides deoxygenated blood to the capillaries that form respiratory membranes with the alveoli, and the pulmonary veins return newly oxygenated blood to the heart for further transport throughout the body. The lungs are innervated by the parasympathetic and sympathetic nervous systems, which coordinate the bronchodilation and bronchoconstriction of the airways. The airway provides a pathway of low resistance to the bulk flow of air into and out of lung periphery where gas exchange occurs. The administration of drug to airway is pulmonary delivery. [7]

The alveolar blood barrier in its simplest form consist a single epithelial cell, a basement membrane, and a single endothelial cell. While this morphologic arrangement readily facilitates the exchange, it can still represent a major barrier to large molecules. Before entering the systemic circulation, solutes must travers a thin layer of fluid, the epithelial lining fluid. Unlike the larger airways, the alveolar region is lined with a surface activated layer consisting of phospholipids. The surfactant lining fluid plays an important role in maintaining alveolar fluid homeostasis and permeability and participates in various defense mechanisms. The secretion lining consists of two layers: s fluid layer of low viscosity, which surrounds the periciliary fluid layer, and a more viscous layer on top, the mucus. The mucus is a protective layer that consists of a complex

mixture of glycoprotein's released primarily by the goblet cells and local glands. The mucus blanket removes inhaled particles from the airways by entrapment and mucociliary transport at a rate that depends on viscosity and elasticity. The lung tissue is highly vascularized, which makes pulmonary targeting difficult because of fast absorption of most drugs.

Studies on pulmonary drug delivery systems have been carried out in recent several decades. There are some advantages and disadvantages of this route over other drug administration ways as shown below:

Advantages:

- Provides local action within the respiratory tract
- Provides rapid drug action
- Provides reduced dose
- Allows for a reduction in systemic side-effects. It can be employed as an alternative route to drug interaction when two or more medications are used concurrently.

Disadvantages:

- The duration of activity is often short-lived due to the rapid removal of drug from the lungs or drug metabolism.
- Necessitates frequent dosing. [8]

The influence of particle parameters:

Various biophysical parameters determine regional drug deposition in human lungs:

- Aerodynamic particle behaviour (size, density, hygroscopicity, shape).
- Breathing pattern of the patients (flow rate, ventilation volume).
- Time of aerosol pulse injection into the breathing cycle.
- Anatomy of the respiratory tract.

Techniques used on making particulate matter for lung delivery:

In recent years, several traditional techniques have been stated to produce pulmonary delivery formulations. Nevertheless, these methods have numerals limitations, such as particle size, size distribution, shape and poor control over powder crystallinity. These problems can be improved by specialized milling techniques. [9]

Spray drying technique:

One way that pharmaceutical manufacturing process used to efficiently produce respirable colloidal particles in the solid state is spray drying. [10] In 1980s, spray drying appears as an alternative means of producing fine particles for pulmonary delivery. Among the process, the feed solution is supplied at room temperature and pumped to the nozzle where it is atomized by the nozzle gas. Then the drying process happened in a special chamber by preheated drying gas which can remove water moisture from the atomized solution system. By using spray drying, we can produce particles with above 2μm size and have a better control on particle formation which directly increase large scale production. [11] As no mechanical high energy input, spray drying can be a suitable method for thermolabile materials like proteins and peptides. the particle after spray drying is uniform in morphology. [12]

Spray freeze drying method:

After spray drying technology, in early 1990s, spray freeze drying method come to our sight. Known as its name, this method combines spray-drying and freeze-drying process together which is a more advanced particle engineering method. The drug solution after spraying lyophilized by liquid nitrogen. This method produces light and porous particles and high fine particle fraction with improved aerosol performance and almost 100% yield at subambient temperatures. [13] Thermolabile protein and peptide substances such as insulin and plasmid DNA can also be produced into dry powder inhalation products. [14] However, the biggest drawback is it is an expensive process only for producing cost drug.

Supercritical fluid technology:

This method is mainly about the controlled crystallization of drugs from dispersion in supercritical fluids. It has been used in pharmaceutical field for production of microparticles, nanoparticles, and liposomes. This is

also used for the production of particulate pulmonary drug delivery systems including protein and peptides, and also used to improve the formulation properties of certain drug candidates. [15]

Solvent precipitation method:

This method involves sono-crystallization and microprecipitation by opposing liquid jets, which allows us to directly control crystallization process to produce crystalline drug particles with narrow size distribution. [16] By using antisolvents, aqueous solution can be rapidly precipitate into inhalable particles. In market, various anti-asthmatic drugs were prepared using the sono-crystallization technique.

Double emulsion/solvent evaporation technique:

This method involves preparation of oil/water emulsion with subsequent removal of oil phase through evaporation. After diffusing out of the polymer phase and into the aqueous phase, the organic solvent then is evaporated forming drug loaded polymeric nanoparticles. Following this method, biodegradable polymers have been intensively exploited as carriers for respiratory solid drug nanoparticles.

Particle replication in nonwetting templates (PRINT):

PRINT is a top-down particle fabrication technique which is able to produce uniform-sized organic micro and nanoparticles with complete control of size, shape and surface functionality [17] and helps in loading of small organic therapeutic, proteins, peptides, oligonucleotides, siRNA contrast agents, radiotracers and flurophores. [17]

Equipment of pulmonary drug delivery: Aerosol delivery:

The equipment for delivering in pulmonary administration plays an important role in the success of this system. Recently, great efforts have been made in the development of advanced devices. However, equipment is much less explored than powder formulations. [4] To select a proper device for delivery of drugs to the lungs is a big thing in the formulation design. If we want the drug delivered to a special locate of lungs, then the delivery equipment must be capable enough to generate and deliver the particles or droplets of specific aerodynamic

diameter. Till now, both in science view and market, nebulizers, metered dose inhalers (MDI), and dry powder inhalers (DPI) are the most popular devices used for respiratory delivery.

Nebulization is a drug delivery device used to administer medication in the form of a mist inhaled into the lungs. It is commonly used for the treatment of cystic fibrosis, asthma, chronic obstructive pulmonary disease (COPD)and other respiratory. diseases or disorders. Based on oxygen, compressed air or ultrasonic power, nebulizers break up medication solutions and suspensions into small aerosol droplets or particles which can be directly inhaled form the mouthpiece of the device. Nebulizers can generate droplets in the 2-5μm range. With its high dose delivery capacity and easily to produce for industry, nebulizers developed well. There are several types of nebulizers available, namely jet nebulizers, ultrasonic nebulizers, vibrating mesh nebulizers.

Jet nebulizer is the most prevalent used nebulizer, also called atomizers. [18] Jet nebulizers are connected by tubing to a compressor, that causes compressed air or oxygen to flow at high velocity through liquid medicine to turn it into an aerosol, which is then inhaled by the patient. The main advantage of the jet nebulizer is its low operational cost. Compared to other competing inhalers and nebulizers, the biggest drawback should be the noise and heavy weight. Maxin which is the trade name of jet nebulizers are more common in industry.

Ultrasonic wave nebulizer is a portable nebulizer, which was invented in 1965. [19] The technology behind is to have an electronic oscillator generate a high frequency ultrasonic wave, which causes the mechanical vibration of a piezoelectric element. This vibrating element is in contact with a liquid reservoir and its high frequency vibration is sufficient to produce a vapor mist. [20] Except for its light, another advantage is that the ultrasonic vibration is almost silent. The commercial examples of this type nebulizers are Omron NE-U17 and Beurer Nebulizer IH30. [21]

The creation of ultrasonic vibrating mesh technology (VMT) brings the new era for nebulizer market. With this technology a mesh with 1000-7000 laser drilled holes vibrates at the top of the liquid reservoir, and thereby pressures out a mist of very fine droplets through the holes, which is more efficient than having a vibrating piezoelectric element at the bottom of the liquid reservoir, and thereby make the treatment times shorter. VMT

also solves problems in ultrasonic wave nebulizer, too much liquid waste and undesired heating of the medical liquid. The available VMT in market includes Pari eFlow, [22] Respironics i-Neb, [23] Beurer Nebulizer IH50, [24] and Aerogen Aeroneb. [25] However, there exists a big problem-high price. Scientists now are working to make it cheap enough for patients.

Metered dose inhalers:

Metered Dose Inhaler (MDI) is a handheld device that delivers a specific amount of medication in aerosol form, instead of as a pill or capsule. The MDI consists of a pressurized canister inside a plastic case, with a mouthpiece attached. There is a chemical propellant inside MDI which function is to push medication out of the inhaler. With an MDI, patients can press on the device while inhaling the medication directly into lungs. It is also small and easy to carry and use, which make it anywhere, and anytime. Recent research has found that MDI with spacer are more effective than nebulizers. [26] For children who have acute asthma, MDI with a spacer may provide more advantages. A spacer is an add-on device, which is a tube attached to the inhaler that act as a reservoir or holding chamber and reduce the speed at which the aerosol enters the mouth. [27] With proper use, a spacer can make an inhaler somewhat more effective in delivering medicine. Contrary to nebulizer, MDI can not produce uniform particle size and particle size distribution. And it also requires coordination of actuation and breathing which may be disliked by patients. In spite of its little drawback, MDI still popular for its advantages like compact, patient compliance. With MDI it is easy to achieve multiple doses up to hundreds doses one time and accurate dose delivery (50μg-50mg). Several products have been used widely like Salbutamol, Beclometasone, and Seretide.

Dry powder inhalers:

DPI is an equipment to achieve aerosolization of a dry powder dosage form, which is an alternative to MDI. Some medications can be taken in the form of a dry powder, which is also a handheld device. A DPI delivers medication to the lungs as you inhale through it. It doesn’t contain propellants or other ingredients but just medication. There are plenty of passive breath driven and active power driven single/-multiple dose dry powder inhalers available in market. Actually, dry powder inhalers are the most popular devices used to drug delivery, especially proteins to the lungs. DPIs are commonly used to treat respiratory diseases such as asthma,

bronchitis, emphysema and COPD and it also be used in the treatment of diabetes mellitus. [28] The DPIs may require some procedure to allow a measured dose of powder to be ready for the patient to take. The medication is commonly held either in a capsule for manual loading or a proprietary from inside the inhaler. There is a high requirement for the size of the dose less than a few tens of milligrams is a single breath because larger powder doses may cause provocation of cough. Moreover, insufficient patient inhalation flow rates may lead to reduced dose delivery and incomplete deaggregation of the powder, leading to unsatisfactory device performance, because most DPIs rely on the force of patient inhalation to entrain powder from the device and subsequently break-up the powder into particles that are small enough to reach the lungs. [29] DPIs can be compact-hand held, require little coordination of activation and breathing, and tightly control over particle size and distribution manufacture of powder. Some of the commercially available dry powder inhalers include Acorda Arcus (Civitas/Alkermes/AIR), Spinhaler (Fisons Pharmaceuticals, Rochester, NY) and Rotahaler (GSK, RTP, NC). [5]

Particle deposition and clearance mechanisms in the airways:

The equipment we discussed former are all inhaled orally. There are some three prevalent accepted deposition mechanisms for particles accessing the lung: inertial impaction, gravitational sedimentation and Brownian diffusion. [30] Impaction and sedimentation have dominant roles in the deposition of microparticle and nanoparticle agglomerates. For example, due to their size microparticles with diameters larger 5μm are prefer to deposit in the oropharynx, which results in large gravitation and inertia. Actually, diffusion impact the behavior of nanoparticles mostly, while the role of impaction and sedimentation is neglectable. As for the longtime breath-holding providing for nanoparticle diffusion, it is much helpful to deposition. On the other hand, mucociliary clearance is more important in clearing lung-deposited particles. The ciliated epithelial cells move the mucus together with the particles toward the pharynx, which is ultimately swallowed or expectorated. Mucociliary clearance tends to have the most impact on insoluble particles with geometric diameters larger than 6μm. [31] While small particles prone to alveolar deposition and tend to be phagocytosed by alveolar macrophages, which will be dissolved or maintained much longer in the lung than larger insoluble ones. Particles with 1.5-3.0 μm in size are most sensible to phagocytosis. [32] For locally acting drugs, they can be

transported passively or actively to the capillary blood network and, being absorbed into the systemic circulation, cleared from the lung tissue. [3]

Nowadays, there are several pulmonary delivery products for diabetes in market. Afrezza® is an innovation man made insulin approved by FDA June 2014. It consists of single-use plastic cartridges filled with a white powder containing insulin, which is administered via oral inhalation.

With its great advantages, pulmonary drug delivery system has stand out over other administration routes. However, to date most of the marketed inhalable products are short-acting formulations that require the patient to inhale several times every day, thus reducing patient compliance. Controlled pulmonary drug delivery is a promising system but the formidable airway clearance mechanisms need to be avoided. In the next part, I will introduce polymers for pulmonary drug delivery system to overcome barriers when administration.

Polymers for pulmonary drug delivery:

So far, a large amount of polymeric material has been studied as carriers for pulmonary drug delivery, including natural polymers like chitosan (CS), gelatin, hyaluronic acid (HA), synthetic polymers like poly (lactic acid), oligo (lactic acid), poly (vinyl alcohol) and copolymers like poly (lactic-co-glycolide acid) (PLGA). To be an excellent carrier, good biocompatibility and high biodegradability are the most important properties. CS, HA and PLGA are reported to have promising prospects among different polymers.

As one of the most commonly used natural polymers in pharmaceutics, CS is supposed to be able to improve drug absorption and control drug release attributed to its mucoadhesion and the reversible opening of the intercellular tight junctions [33] [34] [35]

In recent years, scientist who make great efforts on sustained respiratory delivery have been attracted by HA not only because its endogenity to lung milieu and bioadhesion of high molecular weight, but also for its role in diverse inflammatory mediators and agglutination of alveolar macrophages. Rouse et al. studied the interaction and adsorption of HA onto the surface of fluticasone propionate particles and found that the adsorption extent is influenced by HA conformation in solution. [36] What's more, Surendrakumar et al. reported that HA can be employed to prolong insulin release when administered as a dry powder formulation

to the lungs of Beagles. [37] Compared with various polymers mentioned before, PLGA is the most completely exploited in the pulmonary drug delivery field, not only because of its excellent biocompatibility but also owing to tuning its biodegradation and drug release rate via changing its molecular weight, lactide: glucolide ration and chemical structure. [38] Several reviews have summarized in detail the application of PLGA and its derivatives for pulmonary delivery as well as the pros and cons. [39] [40] [41] No matter how well a polymer as a carrier, the long-term presence of polymers in the lung could result in accumulation of polymers and their catabolites, with the potential of causing safety problems. For instance, the degradation duration of PLGA can last from weeks to months, which could lead to lactic and glycolic acid accumulation and, thus, a significant reduction in the microenvironmental pH, especially when frequent dosing is required. [42][43] To avoid compromising the therapeutic benefits of these polymers, such concerns need to be explored thoroughly before inhaled polymeric drug delivery systems reach the clinical stage.

Summary:

As stated before, pulmonary drug delivery system is a promising method for its rapid onset of action, high local concentration by delivery directly to the airways (and hence high therapeutic ratio and increased selectivity), and needle-free systemic delivery of drugs with poor oral bioavailability. With proper use, it is a good medication method especially for locally pulmonary diseases.

Reference:

[1] Liang, Zhenglin, et al. “Recent Advances in Controlled Pulmonary Drug Delivery.” Drug Discovery Today, vol. 20, no. 3, 2015, pp. 380–389.

[2] Pilcer, and Amighi. “Formulation Strategy and Use of Excipients in Pulmonary Drug Delivery.” International Journal of Pharmaceutics, vol. 392, no. 1, 2010, pp. 1–19.

[3] Olsson, B. et al. (2011) Pulmonary drug metabolism, clearance, and absorption. In Controlled Pulmonary Drug Delivery (2nd edn) (Smyth, H.D. and Hickey, A.J., eds), pp. 21–50, Springer

[4] Chan, Hak-Kim K. “Inhalation Drug Delivery Devices and Emerging Technologies.” Expert Opinion on Therapeutic Patents, vol. 13, no. 9, 2003, pp. 1333–1343.

[5] Jaspart, Séverine M, et al. “Solid Lipid Microparticles as a Sustained Release System for Pulmonary Drug Delivery.” European Journal of Pharmaceutics and Biopharmaceutics, vol. 65, no. 1, 2007, pp. 47–56.

[6] Leslie, Kevin O. O, and Mark R. R Wick. “Lung Anatomy.” Practical Pulmonary Pathology: A Diagnostic Approach A Volume in the Pattern Recognition Series, Elsevier, 2017, pp. 1–13.

[7] Martin, Clemence, et al. “Dysfunctional Lung Anatomy and Small Airways Degeneration in COPD.” International Journal of Chronic Obstructive Pulmonary Disease, vol. 8, 2013, pp. 7–13.

[8] Ozer A, Alternative applications for drug delivery: Nasal and pulmonary routes, Nanomaterials and Nanosystems for Biomedical Applications. 2007; 99-112.

[9] Patil JS, Sarasija S. Pulmonary drug delivery strategies: A concise, systematic review. Lung India 2012;29:44-9. Source of Support: Nil, Conflict of Interest: None declared.

[10] Mosén, Kristina, et al. “Particle Formation and Capture During Spray Drying of Inhalable Particles.” Pharmaceutical Development and Technology, vol. 9, no. 4, 2005, pp. 409–417.

[11] White, S, et al. “EXUBERA®: Pharmaceutical Development of a Novel Product for Pulmonary Delivery of Insulin.” Diabetes Technology and Therapeutics, vol. 7, no. 6, 2005, pp. 896–906.

[12] Gilani, Kambiz, et al. “The Effect of Water to Ethanol Feed Ratio on Physical Properties and Aerosolization Behavior of Spray Dried Cromolyn Sodium Particles.” Journal of Pharmaceutical Sciences, vol. 94, no. 5, 2005, pp. 1048–1059.

[13] Bowey, Kristen, and Ronald Neufeld. “Systemic and Mucosal Delivery of Drugs within Polymeric Microparticles Produced by Spray Drying.” BioDrugs, vol. 24, no. 6, 2010, pp. 359–377.

[14] Yu, et al. “Spray Freezing into Liquid Nitrogen for Highly Stable Protein Nanostructured Microparticles.” European Journal of Pharmaceutics and Biopharmaceutics, vol. 58, no. 3, 2004, pp. 529–537.

[15] Chattopadhyay, et al. “Production of Solid Lipid Nanoparticle Suspensions Using Supercritical Fluid Extraction of Emulsions (SFEE) for Pulmonary Delivery Using the AERx System.” Advanced Drug Delivery Reviews, vol. 59, no. 6, 2007, pp. 444–453.

[16] Rasenack N, Steckel H, Mullar BW. Micronization of anti-inflammatory drugs forpulmonary delivery by a controlled crystallization process. J Pharm Sci 2003;92:35-44.

[17] Gratton SE, Pohlaus PD, Lee J, Cho MJ, DeSimon JM. Nanofabricated particles for engineered drug therapies: A preliminary biodistribution study of PRINTTM nanoparticles. J Control Rel 2007;121:10-8.

[18] The Mechanics of Inhaled Pharmaceutical Aerosols: An Introduction. Elsevier Science, 2001.

[19] “NanoMech LLC Files Brazilian Patent Application for Methods and Apparatus for Making Coatings Using Ultrasonic Spray Deposition.” Global IP News. Nanotech Patent News, 2013, pp. Global IP News. Nanotech Patent News, Jul 12, 2013.

[20] Millington, Ben, et al. “A Novel Method for Preparing Proton Exchange Membrane Fuel Cell Electrodes by the Ultrasonic-Spray Technique.(Report).” Journal of Power Sources, vol. 196, no. 20, 2011, pp. 8500–8508.

[21] Huang, Tzu-Hsuan, et al. “Ultra-Low Pt Loading for Proton Exchange Membrane Fuel Cells by Catalyst Coating Technique with Ultrasonic Spray Coating Machine.(Report).” International Journal of Hydrogen Energy, vol. 37, no. 18, 2012, pp. 13872–13879.

[22] “PARI Granted Orphan Drug Designation for Inhaled Cyclosporine - Potential New Therapy for Lung Transplant Patients.” PR Newswire, 2004, p. 1.

[23] “Active Aerosol Delivery, The I-neb and Vibrating Mesh Technology”. Archived from the original on 2010-08-04. Retrieved 2010-04-09.

[24] “Product details of IH50 nebulizer, with a vibrating membrane”. Retrieved 2015-04-21.

[25] “Micropump nebulizers, Aeroneb, Vibrating Mesh Technology”. Archived from the original on 2010-02-03. Retrieved 2010-04-09.

[26] CJ, Cates, et al. “Cochrane Review: Holding Chambers (Spacers) versus Nebulisers for Beta-Agonist Treatment of Acute Asthma.” Evidence-Based Child Health: A Cochrane Review Journal, vol. 1, no. 4, 2006, pp. 948–1017.

[27] Colombo, Paolo, et al. Inhalation Drug Delivery: Techniques and Products. Wiley-Blackwell, 2013.

[28] Setter, et al. “Inhaled Dry Powder Insulin for the Treatment of Diabetes Mellitus.” Clinical Therapeutics, vol. 29, no. 5, 2007, pp. 795–813.

[29] The Mechanics of Inhaled Pharmaceutical Aerosols: An Introduction. Elsevier Science, 2001.

[30] Recent advances in controlled pulmonary drug delivery Zhenglin Liang, Rui Ni, Jieyu Zhou and Shirui Mao

[31] Smyth, Hugh D. C, and Hickey, Anthony J. Controlled Pulmonary Drug Delivery. Springer, 2011.

[32] Oberdörster, G. “Lung Clearance of Inhaled Insoluble and Soluble Particles.” Journal of Aerosol Medicine: Deposition, Clearance, and Effects in the Lung, vol. 1, no. 4, 1988, pp. 289–330.

[33] Takeuchi, et al. “Mucoadhesive Nanoparticulate Systems for Peptide Drug Delivery.” Advanced Drug Delivery Reviews, vol. 47, no. 1, 2001, pp. 39–54.

[34] Yamamoto, et al. “Surface-Modified PLGA Nanosphere with Chitosan Improved Pulmonary Delivery of Calcitonin by Mucoadhesion and Opening of the Intercellular Tight Junctions.” Journal of Controlled Release, vol. 102, no. 2, 2005, pp. 373–381.

[35] Murata, et al. “Pulmonary Delivery of Elcatonin Using Surface-Modified Liposomes to Improve Systemic Absorption: Polyvinyl Alcohol with a Hydrophobic Anchor and Chitosan Oligosaccharide as Effective Surface Modifiers.” European Journal of Pharmaceutics and Biopharmaceutics, vol. 80, no. 2, 2011, pp. 340–346.

[36] Rouse, et al. “Controlled Drug Delivery to the Lung: Influence of Hyaluronic Acid Solution Conformation on Its Adsorption to Hydrophobic Drug Particles.” International Journal of Pharmaceutics, vol. 330, no. 1, 2007, pp. 175–182.

[37] Surendrakumar, et al. “Sustained Release of Insulin from Sodium Hyaluronate Based Dry Powder Formulations after Pulmonary Delivery to Beagle Dogs.” Journal of Controlled Release, vol. 91, no. 3, 2003, pp. 385–394.

[38] Wischke, and Schwendeman. “Principles of Encapsulating Hydrophobic Drugs in PLA/PLGA Microparticles.” International Journal of Pharmaceutics, vol. 364, no. 2, 2008, pp. 298–327.

[39] Ungaro, Francesca, et al. “Engineered PLGA Nano- and Micro-Carriers for Pulmonary Delivery: Challenges and Promises.” Journal of Pharmacy and Pharmacology, vol. 64, no. 9, 2012, pp. 1217–1235.

[40] Rytting, Erik, et al. “Biodegradable Polymeric Nanocarriers for Pulmonary Drug Delivery.” Expert Opinion on Drug Delivery, vol. 5, no. 6, 2008, pp. 629–639.

[41] Beck-Broichsitter, Moritz M, et al. “Controlled Pulmonary Drug and Gene Delivery Using Polymeric Nano-Carriers.” Journal of Controlled Release, vol. 161, no. 2, 2012, pp. 214–224.

[42] Dailey, La, et al. “The Role of Branched Polyesters and Their Modifications in the Development of Modern Drug Delivery Vehicles.” Journal of Controlled Release, vol. 101, no. 1-3, 2005, pp. 137–149.

[43] Dailey, Lea Ann A, and Thomas Kissel. “New Poly(Lactic-Co-Glycolic Acid) Derivatives: Modular Polymers with Tailored Properties.” Drug Discovery Today: Technologies, vol. 2, no. 1, 2005, pp. 7–13.