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APPROACHES TO PULMONARY DRUG DELIVERY SYSTEMS

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ABSTRACT

Pulmonary route have been used to treat various respiratory diseases for centuries. Ancient inhalation therapies included the use of leaves from plants, vapors from aromatic plants, balsams, and myrrh. The pulmonary route has gained increasing importance in the recent times due to its unique properties such as a large absorptive area of up to 100m^2; extremely thin 0.1 µm – 0.2 µm absorptive mucosal membrane and good blood supply. New dispersible formulations and drug aerosol delivery devices for inhalable peptides, proteins and various small molecules have, in the past decade, become of increasing interest for the treatment of systemic and respiratory diseases. This review enlightens the concept of pulmonary drug delivery and the recent advances in the field.

INTRODUCTION: The pulmonary route has gained increasing importance in the recent times due to its unique properties such as a large absorptive area of up to 100m^2; extremely thin 0.1 µm - 0.2 µm absorptive mucosal membrane and good blood supply. Devices used to deliver drug by pulmonary route area based on one of three platforms pressurized metered dose inhaler, nebulizer and dry powder. Pulmonary route possesses many advantages over other routes of administration for the treatment of specific disease states, particularly lung associated large protein molecules which degrade in the gastrointestinal conditions and are eliminated by the first pass metabolism in the liver can be delivered via the pulmonary route if deposited in the respiratory zone of the lungs [1, 2].

Pulmonary route have been used to treat various respiratory diseases for centuries. Ancient inhalation therapies included the use of leaves from plants, vapors from aromatic plants, balsams, and myrrh. In the 1920 s adrenaline was introduced as a nebulizer solution, in 1925 nebulizer porcine insulin was used in experimental studies in diabetes, and in 1945 pulmonary delivery of the recently discovered penicillin was investigated [2, 3]. Steroids had been introduced in the mid 1950s for the treatment of asthma and nebulizers were enjoying widespread use. In 1956 the pressured metered dose inhaler (pMDI) was introduced, over the past 5 decades, helped by the advances in molecule design and drug discovery the pMDI has risen to become the main stay of asthma treatment.

Over the decade certain drugs have been sold in compositions suitable for forming drug dispersion for pulmonary delivery to treat various conditions in humans. Such pulmonary drug delivery compositions are designed to be delivered by inhalation by the patient of drug dispersion so that the active drug within the dispersion can reach the lung. It has been found that certain drugs given by pulmonary route are readily absorbed through the alveolar region directly into blood circulation. Pulmonary route possesses

many advantages over other routes of administration for the treatment of specific disease states, particularly lung associated large protein molecules which degrade in the gastrointestinal conditions and are eliminated by the first pass metabolism in the liver can be delivered via the pulmonary route if deposited in the respiratory zone of the lungs. By facilitating the systemic delivery of large and small molecule drugs through inhalation deep into the lung, this advanced pulmonary technology provides a unique and innovative delivery alternative for therapies that must currently be administered by injection (i.v., i.m., s.c.) or by oral delivery that causes adverse effects or is poorly absorbed.

New dispersible formulations and drug aerosol delivery devices for inhalable peptides, proteins and various small molecules have, in the past decade, become of increasing interest for the treatment of systemic and respiratory diseases [1, 3]. These include, but also extend well beyond, the traditional and long available (although still underutilized) therapies for asthma and chronic obstructive pulmonary disease (COPD). Advances in the use of the lungs as portals for delivery of medication to the blood stream have greatly expanded the potential applications of pulmonary delivery. This advanced technology was initially applied to the systemic delivery of large molecules, such as insulin, interferon-*b*, or *a*1 proteinase inhibitor [4].

Advantages of drug delivery via the pulmonary route: Pulmonary delivery is expanding a category of drugs called ‘‘inhalables,’’ defined as respiratory and systemic therapies administered simply by inhaling. Inhalables offer several advantages over injectables, transdermal or oral methods of delivery [4].

- Provide a non-invasive method of delivering drugs into the bloodstream for those molecules that currently can only be delivered by injection. These include peptides and proteins, such as insulin for diabetes or interferon beta for multiple sclerosis and most of the drugs developed in recent years by biotechnology companies.
- Enable effective drug targeting to the lungs for relatively common respiratory tract diseases such as asthma, emphysema, bronchiectasis and chronic bronchitis.
- Provide for very rapid onset of action similar to the i.v. Route and quicker than can be achieved with either oral delivery or subcutaneous injections.
- Inhaling helps avoid gastrointestinal tract problems such as poor solubility, low bioavailability, gut irritability, unwanted metabolites, food effects and dosing variability.
- Reduction of dosage i.e. Drug content of one 4 mg tablet of salbutamol equals to 40 doses of meter doses.

Pulmonary delivery the best route of Drug Delivery [5, 6]: While injection has served as the primary means of delivering macromolecules produced by biotechnology, many non-invasive routes have been explored as alternatives. Oral delivery remains the most common method of delivery for most small molecule drugs. However, oral delivery most often does not work for macromolecules because proteins are digested before they have an opportunity to reach the bloodstream. The skin offers an even less naturally permeable boundary to macromolecules than the gastrointestinal tract.

Thus, passive transdermal delivery of proteins and peptides using technology has not succeeded. Peptides and proteins can be shot through the skin into the body using high-pressure ‘‘needle-less’’ injection devices. The devices, which inject proteins like insulin, have been available for years, however they have failed to impress doctors or patients due to the associated discomfort. Nasal delivery is inefficient in terms of the amount of drug actually delivered to the body and to increase its efficiency, penetration enhancers must be added that may cause local irritation. In contrast, research has shown that many molecules are absorbed through the deep lung into the bloodstream naturally with relatively high bioavailability and without the need for enhancers used by other non-invasive routes.

Respiratory system and the pulmonary epithelium: The human respiratory system is a complicated organ system of very close structure-function relationships. The system consisted of two regions: the conducting airway and the respiratory region. The airway is further divided into many folds: nasal cavity and the associated sinuses, and the nasopharynx, oropharynx, larynx, trachea, bronchi, and bronchioles. The respiratory region consists of respiratory bronchioles, alveolar ducts, and alveolar sacs.

The lung provides an enormous surface area through which molecules can be absorbed into the bloodstream. When a breath of air is inhaled, it travels down the trachea and the conducting airways to reach the alveolar epithelium. The conducting airways branch 12–23 times and their surface area measures approximately 0.8m2 in adults [5]. The epitheliums of the branching airways of the lungs are lined by a relatively thick, ciliated, pseudostratified columnar epithelial layer covered with low viscosity periciliary fluid. Floating above the periciliary fluid are large ''rafts'' of thicker gel-like mucus which are propelled towards the pharynx by the rapidly beating cilia.

Once a drug aerosol has made its way through the conducting airways to deposit in the deep lung, the major barriers to entering the body are the 0.15 *m*m layer of type I alveolar cells that are covered by a very thin layer of epithelial lining fluid consisting mainly of surfactant and the relatively permeable endothelium of the alveolar capillaries [1-3]. Alveolar cells have so called ''tight'' junctions that act as a relative barrier to the absorption of large molecules such as proteins and peptides and prevent the development of pulmonary edema.

The alveolar epithelium measures approximately 100m2 in adults. It is made up of approximately 500,000,000 tiny air sacs, 300 *m*m in diameter, called alveoli. These are enveloped by an equally large capillary network and it is across this enormously large and extremely thin (0.1–0.2 *m*m) membrane that gas exchange and the transcytosis of large and small molecules occurs [6]. The alveolar epithelium is composed of a thin, non-ciliated, nonmucus- covered cell layer consisting mainly of type I and type II fixed alveolar cells.

A thin epithelial lining fluid, mainly surfactant, covers the type I. Macrophages are the immune system's first line of defense against inhaled organisms. The key to preventing macrophages from engulfing inhaled drug particles is solubility. Ideally, drugs are rapidly dissolved in the epithelial lining fluid on the surface of the epithelium thus assisting their ingestion by macrophages. This process can be accelerated by means of small, drug-containing, lipid particles.

Absorption through the pulmonary epithelium[7, 8]: The body absorbs peptides and proteins into the bloodstream by a natural process known as transcytosis which occurs deep in the lung. Transcytosis is the process by which large molecules move across an impermeable cell membrane without creating holes in the cells and destroying the barrier. It is performed by tiny membrane bubbles, or transcytotic vesicles, which form invaginations of the cell membrane on one side of the cell and dissolve back into the membrane on the other side of the cell.

Small molecules and peptides are also thought to be absorbed through the lung surface by an analogous process called paracellular transport. This is achieved through the tight junctions which connects cells to each other. The result is that small volumes of alveolar fluid, including dissolved proteins, are carried from one side of a cell to the other of the bloodstream with relatively high bioavailability and without the use of penetration enhancers.

Approaches to Pulmonary Drug Delivery: The drugs can be administered by pulmonary route utilizing two techniques [7];

- Aerosol inhalation
- Intratracheal instillation

By applying aerosol technique, we could achieve more uniform distribution with greater extent of penetration into the peripheral or the alveolar region of the lung, but this costs more and also faced with difficulty in measuring the exact dose inside the lungs. In contrary to this, instillation process is much simple, not expensive and has non-uniform distribution of drugs.

Challenges in Pulmonary Drug Delivery:

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

Following types of inhalation devices are present:

- Inhalation drug delivery system by- metered dose inhalers
- Inhalation drug delivery system by- dry powder inhalers
- Inhalation drug delivery system by- nebulizer

A) Inhalation drug delivery system by metered dose inhalers: A metered-dose inhaler (MDI) is a complex system designed to provide a fine mist of medicament, generally with an aerodynamic particle size of less than 5 microns, for inhalation directly to the airways for the treatment of respiratory diseases such as asthma and COPD.[8-11]

Trends in MDI technology:

- There has been much interest in the differences in effects of Enantiomer of many medications, and beta agonist adrenergic bronchodilators have received much attention. Recently levo salbutamol active enantiomer of salbutamol is present in market which is free from termers and palpitation that seen in salbutamol.
- Use of Spacers to improve patient coordination with MDI.
- The Autohaler TM is the first breath actuated or activated pressurized metered dose inhaler. Autohaler solve the key problem of the pressurized metered dose inhaler (pMDI), does not rely on the patient's inspiratory effort to aerosolize the dose of medication unlike dry powder inhalers.

B) Inhalation drug delivery device by dry powder inhalers: Dry powder aerosols are frequently highly soluble and quickly dissolve in the fluid layer lining the surface of the deep lung before passing through the thin cytoplasm of the type I alveolar cells the interstial space and capillary endothelium. The main advantages of dry powder systems include product and formulation stability, the potential for delivering a low or high mass of drug per puff, low susceptibility to microbial growth, and applicability to both soluble and insoluble drugs. Current challenges facing the development of these systems for macromolecules include moisture control, efficient powder manufacturing, reproducible powder filling, unit dose packaging and development of efficient reliable aerosol dispersion and delivery devices.[8-12]

Currently there are two types;

- Unit-Dose: Devices Single-dose powder inhalers are devices in which a powder contained capsule is placed in a holder. The capsule is opened within the device and the powder is inhaled.
- Multi-dose Devices: Multi-dose device uses a circular disk that contains either four or eight powder doses on a single disk. The doses are maintained in separate aluminum blister reservoirs until just before inspiration.

Trends in dry powder inhalation technology:

- Changes in the performance of the DPI can be achieved either through changes in the design of the device through changes in the powder formulation, the forces governing the particle-particle interactions in the agglomerates and the forces playing a role in the de-agglomeration process [9, 10].
- Supercritical fluid technology is applied to improve the surface properties of the drug substance. Large porous particles have reduced inter-particulate forces because of their low density, the irregular surface structure and/or reduced surface free energy. Moreover, these particles are claimed to have improved aerodynamic behavior in the airways, whereas

phagocytosis of the deposited particles in the alveoli is reduced. In another approach, smaller porous particles (3-5 mm) have been used to improve de-agglomeration and lung deposition [11, 12].

- Changes in device technologies are few new developments really aim at an increase of the de-agglomeration forces generated during the inhalation.

- Air classifier Technology has been recently used in the devices to prevent agglomeration in devices [12].

- Modified form of Air classifier technology is multiple air-classifier technology. In this technology multiple classifier chambers are placed in a parallel arrangement, which further increases the dose that can be aerosolized. [10-12]

C) Inhalation drug delivery devices by nebulizer: Mainly there are two general types of nebulizer systems, the ultrasonic and the air jet. In ultrasonic nebulizers, ultrasound waves are formed in an ultrasonic nebulizer chamber by a ceramic piezoelectric crystal that vibrates when electrically excited. These set up high energy waves in the solution, within the device chamber, of a precise frequency that generates an aerosol cloud at the solution surface. The aerosol produced by an air jet nebulizer is generated when compressed air is forced through an orifice; an area of low pressure is formed where the air jet exists. Nebulizers are particularly useful for the treatment of hospitalized or non-ambulatory patients [13-15].

Trends in nebulizer technology:

- Recent developments in liquid aerosol technology combine the advantages of mDIS and nebulizers are called metered dose liquid inhalers. The major advantage that all these systems aim for is a reduced velocity of the aerosol. Liquid inhalers applying the concept of a low velocity aerosol are often referred to as 'soft mist inhalers'.

- Wet nebulization aims at the generation of monodisperse aerosols, the absence of propellants in the formulation by applying aqueous drug formulations, a reduction in the residual volume after nebulization and an improved portability compared with nebulizers.

Recent advances in Pulmonary Drug Delivery: A formulation that is retained in the lungs for the desired length of time and avoids the clearance mechanisms of the lung is necessary. Various techniques are used to improve the current formulation techniques such as; [15-18]

- Micronization via jet milling,

- Precipitation,

- Spray drying using various excipients, such as lipids and polymers,

- Carrier systems like lactose.

- Liposomes

Liposomes: Liposomes, as a pulmonary drug delivery vehicle, have been studied for years and used as a means of delivering phospholipids to the alveolar surface for treatment of neonatal respiratory distress syndrome. More recently, they have been investigated as a vehicle for sustained-release therapy in the treatment of lung disease, gene therapy and as a method of delivering therapeutic agents to the alveolar surface for the treatment of systemic diseases.

Large Porous Particles: Pulmospheres are the new type of aerosol formulation is the large porous hollow particles,. They have low particle densities, excellent dispersibility and can be used in both MDI and DPI delivery systems. These particles can be prepared using polymeric or nonpolymeric excipients, by solvent evaporation and spray-drying techniques. Pulmospheres are made of phosphatidylcholine, the primary component of human lung surfactant. The large size of Pulmospheres allows them to remain in the alveolar region longer than their nonporous counterparts by avoiding phagocytic clearance.

Biodegradable polymers: Biodegradable polymer microspheres are currently being studied as sustained release pulmonary drug Carriers. Polymers such as polylactic acid are used in medical. Applications such as sutures orthopedic implants and medical Dressings, and poly glycolic acid have been investigated.

Propellants used in pulmonary drug delivery devices: Recently HFA propellants are a new alternative for CFC propellants in pulmonary drug delivery devices.

Recent Formulations of Pulmonary Drug Delivery [18-20]:

- Insulin by Aerosol
- Nicotine Aerosol for Smoking Cessation
- Aerosols for Angina.
- Alpha 1 Antitrypsin
- Gene Therapy via Aerosol
- In Cancer chemotherapy
- Pentamidine Aerosol
- Gentamycin aerosol
- Ribavirin Aerosol
- Pulmonary delivery of lower molecular weight Heparin.
- Controlled delivery of drugs to lungs
- Pulmonary delivery of drugs for bone disorders

Future Scope: Despites the many challenges faced by pulmonary drug delivery system, several peptide and protein drugs are currently investigated for potential systemic absorption through pulmonary system, and that includes insulin, calcitonin, luteinizing-hormone-releasing hormone (LHRH) analogs, granulocyte colony-stimulating factor (rhG-CSF), and human growth hormone (hGH). Despite considerable clinical experience with aerosolized macromolecules, there have been no serious safety issues to date, nor have there been significant problems with throat irritation or cough.

CONCLUSION: Given the advances in pulmonary delivery technology, the issues for drug companies and patients concerning pulmonary delivery revolve around economic evaluations, approvals, administration and managed health care. As these issues are resolved, pulmonary delivery will doubtless become regarded as one of the leading drug delivery alternatives.

REFERENCES:

1. Akwete, A.L., Gupta, P.K., Eds.; Niven, delivery of biotherapeutics by inhalation aerosol. In Inhalation Delivery of Therapeutic Peptides and Proteins; Marcel Dekker, Inc., New York, 1997: 151–231.
2. Patton, J.S. Mechanisms of macromolecule absorption by the lungs: Adv. Drug Delivery Rev. 1996; 3–36.
3. O'Riordan, T.G.; Palmer, L.B.; Smaldone, G.C.: Aerosol deposition in mechanically ventilated patients: optimizing nebulizer delivery. Amer. J. Resp. Crit. Care Med. 1994; 149: 214–219.
4. Hindle, M.; Byron, P.R. Dose emissions from marketed dry powdered inhalers. Int. J. Pharm 1999; 116–169.
5. Akwete, A.L., Gupta, P.K., Eds.; Delivery of biotherapeutics by inhalation aerosol. In Inhalation Delivers of Therapeutic Peptidos and Proteins; Marcel Dakker, Inc.: New York, 1993: 151–231.
6. Everard, M.L.; Devadason, S.G.; Summers, Q.A.; Le Souef, P.N. Factors affecting total and 'respirable' dose delivered by a salbumatol metered dose inhaler. Thorax 1995; 746–749.
7. Patton, J.S.; Platz, R.M. Aerosol insulin—a brief review. Respiratory Drug Delivery IV 1994; 65–74.
8. Ogden, Jill, Dr.; Rogerson, C.; Smith, I. Issues in pulmonary delivery. In Scrip Magazine; June 1996; 56–60.
9. Kohler, D. Aerosolized heparin. Journal of Aerosol Medicine. 1994; 7 (4): 307–314.
10. Kinnula, V.; Cantell, K.; Mattson, K. Effect of inhaled natural interferon-alpha on diffuse bronchioalveolar carcinoma. European Journal of Cancer. 1990; 26: 740–741.
11. Martin, R.J.; Boguniewicz, M.; Henson, J.E. The effects of inhaled interferon gamma in normal human airways. Amer. Rev. of Respiratory Disease. 1993; 148: 1677–1682.
12. Adjei, A.L. Regulatory issues concerning systemic delivery via the respiratory tract: leuprolide as a demonstration model. Journal of Aerosol Medicine, 1995; 8: 131.
13. McElvaney, N.G.; Hubbard, R.C.; Birrer, P. Aerosol *a*-1 antitrypsin treatment for cystic fibrosis. Lancet. 1991; 337: 392–394.
14. Hall, C.B. Aerosolized treatment of acute pulmonary infections. Journal of Aerosol Medicine 1989; 2.
15. Michael T. Newhouse, Encyclopedia of Pharmaceutical Technology, second edition, Dekker, New York Informa Healthcare USA, 2000;19:1279-1285.
16. Albert H. L. Chow, Henry H. Y. Tong, Pratibhash Chattopadhyay, and Boris Y. Shekunov, "Particle Engineering for Pulmonary Drug Delivery," Pharmaceutical Research, 2007; 24(3):411-433.
17. David A. Edwards, Abdelaziz Ben-Jebria, and Robert Lange "Recent advances in pulmonary drug delivery using large, porous inhaled particles," J Appl Physiology .1998; 85(2): 379-385.

18. Rohan Bhavane, Efstathios Karathanasis, Ananth V. Annapragada, "Agglomerated vesicle technology": a new class of particles for controlled and modulated pulmonary drug delivery, Journal of Controlled Release 2003; 15– 28.
19. P.P.H. Le Brun, A.H. de Boer, H.G.M. Heinemann and H.W. frijlink "A review of the technical aspects of drug nebulization", Pharm World Sci. 2000; 22(3): 75-81.
20. N R Labiris and M B Dolovich, Pulmonary drug delivery. "Part II: The role of inhalant delivery devices and drug formulations in therapeutic effectiveness of aerosolized medications", Br J Clin Pharmacol. 2003; 56(6): 600–612.

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