

RECENT ASPECTS OF PULMONARY DRUG DELIVERY SYSTEM- AN OVERVIEW

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ABSTRACT

Pulmonary delivery of drugs has become an attractive target in the health care industry as the lung is capable of absorbing pharmaceuticals either for local deposition or for systemic delivery. Half of all pharmaceuticals are not soluble in water, but are soluble in lipid. As the lung is able to absorb both water and oil into the tissue, this is not a limitation of pulmonary delivery. However, existing jet nebulizers cannot aerosolize viscous liquids and ultrasound nebulizers destroy drug emulsions, thereby greatly limiting the potential use of pulmonary drug delivery. Current nebulizers also cannot effectively deliver peptide or protein based biotechnology drugs. Targeted drug delivery to the lungs has evolved to be one of the most widely investigated systemic or local drug delivery approaches. The use of drug delivery systems (DDS) for the treatment of pulmonary diseases is increasing because of their potential for localized topical therapy in the lungs. This route also makes it possible to deposit drugs more site-specific at high concentrations within the diseased lung thereby reducing the overall amount of drug given to patients (10–20 % of the peroral quantity), as well as increasing local drug activity while reducing systemic side effects and first-pass metabolism.

INTRODUCTION

Pulmonary drug delivery systems have been used for decades to deliver drugs for treatment of respiratory disorders. The lungs provide a huge surface area of alveoli with rich capillary network which acts as an excellent absorbing surface for administration of drugs. Throughout the past several years, rapid onset of action and higher efficiency has been responsible for the success of pulmonary delivery system for symptomatic relief in treatment of asthma and chronic obstructive pulmonary disease (COPD). Research in the area of pulmonary drug delivery has gathered momentum in the last several years, with increased interest in using the lung as a means of delivering drugs systemically. Advances in device technology have led to the development of more efficient delivery systems capable of delivering larger doses and finer particles into the lung. As more efficient pulmonary delivery devices and sophisticated formulations become available, physicians and health professionals will have a choice of a wide variety of device and formulation combinations that will target specific cells or regions of the lung, avoid the lung's clearance mechanisms and be retained within the lung for longer periods. It is now recognized that it is not enough just to have inhalation therapy available for prescribing; physicians and other healthcare providers need a basic understanding of aerosol science, inhaled formulations, delivery devices, and bioequivalence of products to prescribe these therapies optimally. The recent approval of inhaled insulin stands as a major advancement not only in the field of diabetes treatment, but also for pulmonary delivery of macromolecules and systemically acting drugs.¹ Although perhaps not readily apparent, the significance and impact of this accomplishment is far reaching, as many of the technical and perceived barriers obstructing the development of pulmonary drug delivery of systemically acting drugs have been dismantled by this achievement. Among the frequently cited advantages of pulmonary drug delivery are targeted delivery for improved efficacy and reduced incidence of unwanted systemic side effects, a large surface area for absorption, a relatively thin alveolar epithelium permitting rapid absorption, absence of first-pass metabolism, rapid onset of action, and enhanced bioavailability. For these reasons, systemically acting small and large molecules are attractive candidates for pulmonary delivery when more traditional routes are either impractical or unacceptable. As follows, many commercial and academic groups have sought to develop inhalation aerosols that demonstrate these advantages for clinically relevant disease states. Numerous carriers and particulate systems for pulmonary delivery have been designed to directly address these delivery issues. Until recently, these systems may have been seen as high risk investments with many assumed barriers to achieving commercial success. Indeed, many such technologies are distant from the regulatory approval stage, but there is now renewed confidence that they will find eventual clinical application for respiratory drug delivery. This article highlights some classes of carrier systems currently under investigation for specifically overcoming the hurdles facing the next generation of pulmonary drug delivery technologies. The development of controlled release formulations for inhalable drugs has been widely investigated since several years. Nonetheless, no controlled release product for pulmonary application is currently on the market. The reduction of the dosing frequency is of great concern for a number of pulmonary disorders including asthma and chronic obstructive pulmonary disease (COPD). In particular, short-acting β 2-adrenergic receptor agonists used for the relief of asthma- and

COPD-related bronchospasms have a relatively short plasma half life that constrain the patient to an administration of the drug every 4-6 hours. A controlled release formulation leading to a prolonged duration of action of more than 8 hours would prevent nocturnal exacerbation in bronchial asthma. Controlled release formulations are widely used in oral or parenteral formulations but have not been established for pulmonary applications. Current research approaches include the use of liposomes, micro- and nanosuspensions and dry powder formulations. Liposomes have been widely investigated but suffer from a poor physical stability during the nebulization process. To date, the commercial use of such products is thus difficult. For similar reasons it is also difficult to aerosolize a particle suspension in a way to ensure a constant delivered dose to the lung. Therefore, dry powder formulations have attracted attention. The formulation typically contains structural components of the particle as well as agents allowing the release of the drug over an extended period of time.

ADVANTAGES:

1. The ability to nebulize viscous drug formulations for pulmonary delivery, thereby overcoming drug solubility issues with the ability to use lipid, water or lipid/water emulsions as drug carriers.
2. Ability to nebulize viscous liquids into droplets in the 2-5 μ m range regardless of the carrier composition solubility which would allow for a wide range of drug formulation options.
3. Increased drug delivery efficacy due to size-stable aerosol droplets with reduced hygroscopic growth and evaporative shrinkage.
4. Liposomal drug formulations remain stable when nebulized.
5. Ability to nebulize protein-containing solutions.
6. For hand held inhaler applications, drug does not need to be emulsified in liquefied nebulizing gas to achieve aerosolization.

APPLICATIONS:

Effective pulmonary delivery of any drug, be it water or lipid soluble, for the treatment of pulmonary disorders or for a systemic delivery.

LIMITATIONS

Limitations of pulmonary drug delivery systems including:

- ❖ stability of drug in vivo;
- ❖ transport;
- ❖ targeting specificity;
- ❖ drug irritation and toxicity;
- ❖ immunogenicity of proteins; and
- ❖ drug retention and clearance.

PULMONARY DELIVERY FOR LOCAL LUNG DISORDERS

The past 30 years of biotechnology discoveries unleashed a wave of therapeutic proteins, also known as biomolecules, macromolecules, biotherapeutics, and biologicals. Most are administered via injection or intravenous methods to avoid degradation in the gastrointestinal tract. Patients, however, fear and avoid injections and IV treatments, which are painful, inconvenient, and expensive. Pulmonary delivery offers a patient-friendly, non-invasive alternative to injections and can also be a more efficient and effective way to deliver a drug and achieve patient compliance.

Pulmonary delivery utilizes the natural permeability of the lung to transfer molecules to the bloodstream. The systemic delivery of biomolecules via the lungs is an under-exploited route today. About 85 protein and peptide therapeutics are currently marketed, and about 350 more are undergoing clinical evaluation. In 2002, drug companies sold \$ 33 billion in protein therapeutics, and sales of \$ 71 billion are projected by 2008 (Market for Bioengineered Protein, 2004). This same report predicts that the market for protein drugs will grow at an annual rate of 12.2 % from 2003 to 2008, faster than the industry's overall annual growth rate of 8 %. Sales of drugs using pulmonary delivery systems also are predicted to grow from \$ 8 billion in 2001 to \$ 15 billion by 2006 (Minter 2003). Although today, most of these drugs include those that treat local lung disease such as asthma and chronic obstructive pulmonary disease (COPD). With the approval of Pfizer's Exubera® (human insulin [rDNA origin]) Inhalation Powder, the promise of pulmonary delivery has finally been delivered and this advance opens up a myriad of possible candidates for pulmonary delivery. Many of these biologics are already under development and being tested in clinical trials. Pulmonary drug delivery refers to treatments inhaled through the mouth rather than the nose. Some nasal formulations reach the lung, but it has been shown to be an ineffective delivery route, as most formulations are absorbed through the nasal

membranes and as a result have low bioavailability unless they are enhanced. The nasal mucosa cannot transport doses of large biomolecules, and enhancers to increase bioavailability can cause irritation with repeated use. Nasal formulations may represent forerunners of more efficient inhaled drugs, and some nasal drugs will be described when appropriate.

Growth hormone	Nesiritide
Calcitonin	Alpha-1 proteinase inhibitor
Parathyroid hormone	Colony-stimulating factor
Interferons	Somatostatin
Interleukins and antagonists	Luteinizing hormone releasing hormone
Erythropoietins	Follicle stimulating hormone
Vaccines	Nerve growth factors
Monoclonal antibodies	Adenosine deaminase
Heparins	Gene vectors
Coagulation Factors	Chorionic gonadotropin
Tissue plasminogen activator	Granulocyte colony stimulating factor
Streptokinase	
Urokinase	Human deoxyribonuclease I

ASTHMA AND COPD

Humans have inhaled a wide range of substances since ancient times. Until recently, pulmonary delivery of drugs focused on medications to treat asthma and other lung diseases. Aerosol systems that deliver bronchodilators to relax airways and corticosteroids to control inflammation in asthma and COPD are widely used today and carry a proven track record. Today's inhaled drug delivery market is dominated by this class of treatments. More than 300 million people worldwide suffer from asthma, and annual sales of asthma products in the U. S. and Europe in 2003 reached \$ 11.8 billion, up from \$ 9.7 billion in 2002. The current market for COPD therapies is estimated at \$ 4 billion yearly, with a predicted growth to \$ 10 billion by 2010 (Asthma and COPD Market Outlook, 2004).

The three main drug classes (bronchodilators, corticosteroids, and anti-cholinergics) contain agents with similar efficacy and side effects. Products from GlaxoSmithKline (GSK) and AstraZeneca lead the market in sales. Slight advantages over competitors are explored and marketed using new delivery devices or combination formulations to deliver a more effective payload of medicine. For example, Vogelmeier *et al.* (2005) demonstrated that AstraZeneca's combination product Symbicort (containing the corticosteroid budesonide and long-acting bronchodilator formoterol) reduces the risk of severe asthma attacks by 24 %, compared to GSK's Seretide (fluticasone / salmeterol), in a one-year,

head-to-head trial of 2 143 patients. Symbicort is also approved for COPD, and its worldwide sales in 2004 totaled \$ 797 million. Patients find it more convenient to use one inhaler, and combination products simplify treatment. Sales of combination treatments showed an impressive growth of 47 % in 2003, according to the Asthma and COPD Market Outlook (2004).

As a first-in-class asthma therapy, Genentech / Novartis introduced the monoclonal antibody Xolair (omalizumab) in 2003 to treat asthma. Xolair blocks IgE, preventing a cascade of asthmatic symptoms. Although Xolair offers a novel approach, it requires subcutaneous injections every 2 to 4 weeks, and so is not widely used. The yet unexplored pulmonary delivery of monoclonal antibodies could allow for wider use and appeal of antibody treatments. COPD, a chronic disease linked to smoking, comprises chronic bronchitis and emphysema and causes one million deaths annually. Short-acting bronchodilators form the traditional therapy for COPD, but the newer anti-cholinergic agent tiotropium proves more convenient and effective, according to Cooper and Tashkin (2005). Boehringer Ingelheim launched the dry powder inhaler Spiriva (tiotropium) in 2001 as a first-line therapy for COPD management. Novartis developed Foradil (formoterol fumarate powder) for asthma and COPD, which acts within 5min and lasts 12 h. Foradil is approved in several European countries. In addition, Novartis teamed with SkyePharma (London, U. K.) to develop a dry powder form of the drug marketed as the Foradil Certihaler. An inhaled drug known as VR496, which is made by Vectura (Wiltshire, U. K.), and currently under development, breaks down mucus in the lungs and may help COPD and cystic fibrosis (CF) patients. The active ingredient is an undisclosed, off-patent drug never developed as an anti-mucolytic agent. It appears that the future of asthma / COPD therapy lies in combination products or novel single agents

OTHER LUNG DISORDERS

Anti-infectives

Considering the rapid, local action of asthma and COPD drugs, inhaled medicines and vaccines seem a practical consideration for nearly every lung disease. Inhaled anti-infectives already provide local control of respiratory infections, such as pneumonia and cystic fibrosis (CF). The first inhaled protein ever approved, Genentech's Pulmozyme (dornase alfa), was marketed in 1993 to treat CF. This aerosol treatment reduces the incidence of respiratory infections requiring intravenous antibiotics and improves overall lung function. U. S. sales of Pulmozyme have grown from \$ 22 million in 1994 to \$ 44 million in 2004.

Nektar Therapeutics (San Carlos, CA, U. S. A.) and Chiron, a Novartis company (Emeryville, CA, U. S. A.) are collaborating on a next-generation, dry powder tobramycin to treat lung infections in cystic fibrosis patients. This product which is currently in Phase III trials is called Tobramycin inhalation powder or TIP. Chiron introduced TOBI in 1998 as the first inhaled antibiotic given by nebulizer to CF patients. Nektar's dry powder formulation represents a next generation therapy that allows patients to receive higher doses for improved efficacy without the lengthy administration time of TOBI. A 12-person trial showed that 3.5times more inhaled TOBI reaches the lung using a dry powder

formulation than with a nebulized liquid solution, report Newhouse *et al.* (2003). As Chiron's second highest selling drug, TOBI's sales reached over \$ 220 million in 2004. Nektar is also collaborating with Bayer HealthCare AG to develop an inhaled, dry powder formulation of ciprofloxacin to treat CF and other chronic lung infections with convenient dosing. Inhaled gentamicin is an established treatment for chronic *Pseudomonas aeruginosa* (PA) infections in CF. Heinzl (2002) demonstrated that daily inhalations of gentamicin delays the acquisition of chronic PA infections and decreases disease progression in children with CF.

Relenza (zanamivir), made by GSK, was the first inhaled anti-viral medication approved by the FDA in 1999. The dry powder is inhaled twice daily for five days to reduce the duration and severity of flu symptoms. Relenza inhibits neuraminidases, which are essential for the release of influenza virus from infected cells. By concentrating on the surface of the respiratory tract, Relenza prevents the influenza virus from replicating (Hayden *et al.* 1997) directly at the site where it promotes infections.

Pentamidine, an inhaled treatment for pneumocystis carinii pneumonia (PCP), sells generically or under the brand names Nebupent or Pentam. Intravenous pentamidine causes serious side effects of anemia, low blood sugar, arrhythmias, and kidney problems. In contrast, inhaled pentamidine produces milder side effects like chills, headache, and cough.

Nektar is also evaluating an inhaled antifungal product to prevent pulmonary aspergillosis in immunosuppressed patients. ABIP (amphotericin B inhalation powder) is designed to target the site of infection directly with a novel formulation of amphotericin B, a broad spectrum, "gold-standard" antifungal drug. Pulmonary delivery directly at the site of infection could potentially eliminate systemic, dose-limiting toxicities found with current formulations of amphotericin B that are delivered intravenously. Aspergillosis has a high mortality rate of over 50 %, and in some immunosuppressed patient groups the mortality rate may be as high as 100 % (Lin *et al.* 2001).

PULMONARY ARTERIAL HYPERTENSION

In 2004, the FDA approved Ventavis (iloprost), an inhaled treatment for pulmonary arterial hypertension, made by CoTherix (South San Francisco, CA, U. S. A.). In pulmonary arterial hypertension, severe restriction of blood vessels results in early death. Iloprost naturally dilates blood vessels.

CANCER CHEMOTHERAPY

Lung cancer is the leading cause of cancer deaths globally, and inhaled chemotherapy seems a logical approach to treat lung tumors. Despite new chemotherapeutic agents for lung cancer, the 5-year survival rate of 15 % has not changed in 50 years, according to Placke *et al.* (2002). Pulmonary delivery increases the cytotoxic dose of drugs that can reach tumors to improve responses, while minimizing systemic toxicity.

A multi-center Phase I clinical trial is evaluating Resmycin™ (doxorubicin HCl inhalation solution) in lung cancer patients (Otterson *et al.* 2005). Made by Zivena, Inc., a subsidiary of BatellePharma (Columbus, OH, U. S. A.), Resmycin delivers more doxorubicin to lung tumors than can be achieved intravenously. In earlier studies in dogs, Resmycin following surgical removal of primary lung tumors extended survival time to 199 days, compared to 63 days for dogs receiving surgery alone (Placke *et al.* 2002). As

many as 400 000 lung cancer patients could benefit from inhaled chemotherapy, which could capture a large share of the \$ 3 to \$ 5 billion inhaled oncolytics market.

team led by Koshkina (2004) gave aerosolized paclitaxel solution to mice with lung tumors. The treatment significantly reduced lung tumors and prolonged survival. Aerosol delivery of the anti-cancer agents difluoromethylornithine and 5-fluorouracil reduced lung tumors in mice 50 % and 60 %, respectively, according to Wattenberg *et al.* (2004). Interleukin-2 (IL-2) stimulates immune function in cancer patients, but injections cause fever, malaise, and local swelling. In a Phase I study of patients with lung metastases who inhaled IL-2, Skubitz and Anderson (2000) report no significant toxicity; efficacy was not evaluated.

People who inhale carcinogens in cigarette smoke account for half of lung cancer deaths in the U. S. Mulshine and Hirsch (2003) propose that inhaled chemopreventative drugs may block early epithelial damage in smokers. They showed in rodents that aerosolized retinoids significantly reduce lung tumor nodules caused by tobacco carcinogens, whereas oral retinoids do not bring protection.

VACCINES

Nearly 100 vaccines are approved in the U. S. (Fig. 1). About half of these prevent respiratory infections, yet all are currently injected. Inhaled vaccines are an untapped market opportunity. Not only would they address needle fears, especially in children, but they could also generate more potent local immune responses than when they are injected into muscles.

As a proof-of-concept, an inhaled measles vaccine given by nebulizer (created by vaccine pioneer Albert Sabin) brings superior immunogenicity at lower doses than an injected counterpart, as demonstrated by trials in Mexico (Bennett *et al.* 2002). The Measles Aerosol Project of the World Health Organization is coordinating the development of better delivery devices and a dry powder formulation. Measles infects 30 to 40 million children in underdeveloped nations.

As far back as the 1960s, influenza experts tested aerosol flu vaccines. Waldman *et al.* (1969) found that volunteers receiving aerosolized flu vaccine had 79 % fewer cases of influenza. This is compared to injected volunteers who only had 27 % fewer illnesses against controls receiving no vaccine. The aerosol vaccine also shortened the duration of infections and caused as few side effects as a placebo.

- *Chlamydia pneumonia* – 10 % of all pneumonias
- Group A Streptococci – 25 million cases per year in U. S.
- Group B Streptococci – Leading cause of death in newborns
- Nontypeable *Haemophilus influenza* – most common ear infection, 25 million office visits per year
- *Moraxella catarrhalis* – a major cause of lower respiratory infections in adults (COPD), 3rd most common ear infection
- *Mycoplasma pneumonia* – 15 million cases per year
- *Pseudomonas aeruginosa* – common in CF and HIV patients
- Tuberculosis – 2 billion infections worldwide

APPROACHES IN PULMONARY DELIVERY

Pulmonary delivered drugs are rapidly absorbed except large macromolecules drugs, which may yield low bioavailability due to enzymatic degradation and/or low mucosal permeability. Pulmonary bioavailability of drugs could be improved by including various permeation enhancers such as surfactants, fatty acids, and saccharides, chelating agents and enzyme inhibitors such as protease inhibitors. Some reports suggest that pulmonary absorption of insulin was significantly enhanced in the presence of several adjuvants such as glycocholate, surfactin, span 85, and nafamostat. Calcitonin was delivered with various fatty acids, surfactants, and protease inhibitors and effect of these were studied for enhancement of absorption in the lungs to evaluate the pharmacological response and plasma calcium reduction. Researchers at various academic institutions are working on a novel concept to deliver drugs to diseased lungs by using perfluorocarbon liquid. They are hoping to dispel the edematous fluid by drug dissolved perfluorocarbon liquid and eventually spread evenly throughout the airspace of lungs. This would result in distribution of drug throughout the lung and will provide higher local tissue concentrations than with aerosol-borne drug particles. Various therapeutic agents (adenosine, adenosine triphosphate, and nitric oxide) are currently under investigation to be delivered by this technique. Another technique is under development to use a respiratory spray to treat lesions appeared in the mucous membranes of smoker's lungs. Retinoids are effective against lung cancer but in pill form retinoids produce harsh side effects so. A novel dosage form is sought to administer retinoids locally than in the pill that acts throughout the body. It is hoped that it may be more effective since it allows up to 100 times more active substance to be delivered to the diseased lungs.

The routine pulmonary administration of drugs including peptide and protein faces many challenges. First, the delivery issue must be addressed, several devices as mentioned above being tested and marketed worldwide. The most important issue is the protein stability in the formulation: the dry powder formulation may need buffers to maintain the pH, and surfactants such as Tween to reduce any chance of protein aggregation. The stabilizers, such as sucrose) are also added in the formulation to prevent denaturation during prolonged storage.

Pulmonary bioavailability largely depends on the physical properties of the delivered protein and it is not the same for all peptide and protein drugs.

Insulin liposomes are one of the recent approaches in the controlled release aerosol preparation. Intratracheal delivery of insulin liposomes (dipalmitoylphosphatidyl choline:cholesterol ,7:2) have significantly enhanced the desired hypoglycemic effect. The coating of disodium fluorescein by hydrophobic lauric acid is also an effective way to prolong the pulmonary residence time by increasing the dissolution half time. In another method, pulmonary absorption properties were modified for protein/peptide drug (rhG-CSF) in conjugation with polyethylene glycol (PEGylation) to enhance the absorption of the protein drug by using intratracheal instillation delivery in rat.

LATEST DEVELOPMENTS

Aradigm has developed AERx pulmonary technology, which would help in delivering morphine and insulin into the lungs. On the other hand, Alkermes has designed an inhalation technology (AIR), which would enable us to deliver efficient dry powder of small molecule, peptide and protein drug particles to the deep lungs. Nektar Therapeutic in conjunction with Pfizer began dosing first diabetic patients for the phase III clinical trial for inhaleable insulin Exubera[®]. They are also developing several other active drug molecules to be delivered by using its proprietary delivery technology.

Despite 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).

RESPIRATORY SYSTEM

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

FORMULATIONS

The drugs can be administered by pulmonary route utilizing two techniques: aerosol inhalation (also used in intranasal applications) and 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.

AEROSOLS

Aerosol preparations are stable dispersions or suspensions of solid material and liquid droplets in a gaseous medium. The drugs, delivery by aerosols is deposited in the airways by: gravitational sedimentation, inertial impaction, and diffusion. Mostly larger drug particles are deposited by first two mechanisms in the airways, while the smaller particles get their way into the peripheral region of the lungs by following diffusion.

Although there is similarity in drug absorption from the lungs and the other mucosal surfaces, but due to the complexity in aerosol-particle disposition, the aerosol administration further complicated by the hygroscopic properties of most therapeutic aerosols that allow the particle size to change drastically during the drug transport in the highly humid atmosphere of the respiratory tract. Other factors, which directly influence the aerosol deposition by above three mechanisms, are aerodynamic size distribution of the aerosol particles, and the density of the aerosol particles.

There are three commonly used clinical aerosols: jet or ultrasonic nebulizers, metered-dose inhaler (MDI), and dry-powder inhaler (DPI). The metered-dose inhalers are most frequently used aerosol delivery system. The dry-powder-inhalers are designed to deliver drug/excipients powder to the lungs.

Recently, a number of add-a-device or also called as spacers are added to use with MDIs, in order to remove some non-respirable particles by impaction on their walls and valves. 3M Drug Delivery Systems has recently introduced actuators that will make pulmonary and nasal MDIs more effective and efficient by increasing the respirable fraction of the drug delivered. This will also reduce the side effects

Almost all aerosols were using a CFC (chlorofluorocarbon) propellant but in mid-nineties efforts were made to consider an alternative to ozone depleting CFC by other classes of environmental friendly propellants such as hydrofluoroalkanes (HFAs: HFA -134a and HFA-227). These HFA compounds contain no chlorine, which in fact causing the ozone depletion effect (2). The safety and efficacy of these new introduced propellants were investigated to meet the requirements of American and European regulatory agencies. In most cases, these two propellants met the safety conditions and found that they have safety compliance as of their predecessor CFC propellant (3). In recent years, many MDIs and DPIs containing CFC Aerosol is a pressure package or pressurized package. It can be defined as a “system that depends on the power of a compressed or liquefied gas to expel the contents from the container”.

Certain gases under pressure liquefy while some gases are not capable of being liquefied. Both these types of gases serve as medium in which the drug is uniformly dispersed to form the product. The product is packaged under high pressure in a container. The aerosol product container has provision of being opened and closed easily. When it is opened, it releases the product into the atmosphere, where the liquefied or compressed gas goes back into the gaseous phase dispersing the product into fine particles, the size of which is determined by the type and concentration of the gas used in the product.

Aerosols have been used for both topical as well as oral inhalation aerosols for pulmonary delivery of drugs such as bronchodilators and steroids. Topical products are used for treatment of burns, minor cuts, bruises and infections.

Some of the products in India are;

1. Beclate Inhaler by CIPLA containing 50 µg Beclomethasone dipropionate as the active ingredient.
2. Beclate Rotocaps by CIPLA contains 100 µg Beclomethasone dipropionate.
3. Asthalin Inhaler by CIPLA contains 100 µg Salbutamol
4. Aerocort Inhaler CIPLA- Salbutamol 100 µg & Beclomethasone dipropionate 50 µg
5. Budecort 200 Inhaler CIPLA- Budesonide 200 µg suspended in Prop HFA 134 a
6. Bricaryl Inhaler Astra- Terbutaline sulphate 250 µg

Advantages of an Aerosol

Aerosol has a number of advantages which include:

1. A dose can be removed without contamination of remaining material. Stability is enhanced for those substances adversely affected by oxygen and / or moisture. When sterility is an important factor, it can be maintained while a dose is being dispensed. 2. The medication can be delivered directly to the affected area in a desired form such as spray, stream, quick breaking foam or stable foam. 3. Irritation produced by the mechanical application of topical medication is reduced or eliminated. Other advantages are ease and convenience of application and application of medication in a thin layer.

PULMONARY DRUG DELIVERY SYSTEMS

The Micro-channel Nebulizing Nozzle is small enough to be placed directly into the ventilator tubing close to the patient. Viscose bound water or oil formulations resist droplet size changes increasing the lung deposition efficiency.

Emulsion Nebulization: Emulsion formulations for pulmonary delivery remain intact with micro-channel nebulization. A 15% water (stained with Evans Blue) in fatty acid oil mini-emulsion provides a water-in-oil emulsion. Water-in-oil droplets are produced when this emulsion was nebulized with the micro-channel nebulizer. The blue water core is evident as seen in two-phase 2-5µm droplets impacted onto a counting slide.

Ventilator Pulse Nebulizer Adaptation: Atomizing air and drug flow is synchronized with the inspiration cycle of the ventilator. Atomized droplets are injected into the inspired air flow while aerosol generation is stopped during exhale. The micro-channel nebulizer uses about 50cc of air for nebulization per one second inhaled breath cycle.

Inhaler Applications benefit from less complicated formulations as the propellant gas is not part of the formulation itself. Completely insoluble and environmentally safe propellants can now be used for inhalers. represents an attractive, rapid and patient-friendly route for the delivery of systemically acting drugs, as well as for drugs that redesigned to act locally on the lungs themselves. This concept is especially exciting now that the concept of an inhaled systemic macromolecule, in the form of Exubera insulin, has been approved in Europe and the US. Vectura has specialized in developing innovative formulation and

device technologies for delivering drugs to the lungs in a predictable and reproducible manner. In particular, Vectura has pioneered the development of small-molecule drugs for systemic delivery, creating the concept ROSAT: rapid onset systemic aerosol therapies. One of the key factors for success in this area is the ability to control the combined powder and device properties. This is essential for the development of dry-powder inhaler (DPI) products, yet remains a major technical hurdle to those wishing to succeed with this route and exploit the product opportunities arising from the numerous market drivers: • Rapid onset of action, Improving patient acceptance and compliance for a non-invasive systemic route, Reduction of side effects, Differentiation of new product and competitive brand opportunities, Expedition of regulatory approval through improved consistency of delivery and product stability, Product lifecycle enhancement, New forms of inhaled therapeutics often requiring high doses and/or greater efficiency and accuracy. Attractive device form with convenient and easy operation and delivery This has been the motivation behind Vectura's combined study of particle science and device technology.

TECHNICAL CHALLENGES

Developing an efficient and effective portable inhalation system for medicinal use provides greater challenge than most other drug delivery forms, requiring a complex integration of formulation and device technologies. In the case of DPI systems, the art and science required to produce high quality aerosols, repeatedly and reproducibly, arguably reach their zenith. Creating an aerosol cloud that is almost entirely composed of particles smaller than 5 μm (or even less for systemic use), using a conveniently small, simple to-use and reliable device certainly represents significant technical and commercial challenge.

DRY-POWDER INHALERS

Interest in DPIs as an effective, efficient and environmentally friendly way of delivering drugs to the lung has accelerated in recent years. A fundamental difficulty with developing solid state aerosols, or DPIs, is managing both the ubiquitous and the transient forces contained in powder beds. Indeed, managing such particulate forces, for example via particle engineering techniques, is now considered central to successful DPI formulation and production (Begat P, Morton D AV, Staniforth J N and Price R, "The cohesive/adhesive balances in dry-powder inhaler formulations II: influence on fine particle delivery characteristics", *Pharm Res* 2004, Vol 21, No 10, pp 1826-1833). In consequence, much attention is currently focused on producing "smart" formulations, where it may be possible to achieve excellent powder flow and low cohesive forces. However, having an efficient and robust formulation technology in the laboratory is only start on the road to producing a successful DPI product. Pharmaceutical scientists all too frequently meet major obstacles when they engage in the world of DPI product design – not least because of the further complications of this area resulting from the plethora of DPI device designs. There is tremendous variation in the methods used to store and meter powders and to generate the

aerosol cloud. In the case of DPI Aerosol generation, there is a great deal of variation between different types of device, in the fluid dynamic and electrostatic environment that the powder formulation experiences. Too often, it has been claimed that innovators in the field of DPI device or formulation design have produced a new system that will suit all. Our experience shows that there is no such thing as either a device or formulation that can be regarded in isolation as the solution to all DPI aerosol development requirements. Only when DPI device design and formulation design are harnessed as a joint developer really move towards a truly efficient and effective system that is going to progress from the laboratory to manufacturing and on into the hands of the patient in a timely and economical manner. 1. There can be no assumption that a powder that worked well in one device or in one specific test will always perform similarly in another device or environment. 2. Development any new DPI formulation should be conducted in parallel with the identified device as early in the development stage as possible.

SUMMARY

The potential for liposomes as carriers for pulmonary drug delivery is attributed to their putative capacity to address many of the aforementioned delivery issues.² A literature search of Pubmed reveals on the order of 120 citations for liposomal aerosol systems. These systems may have received most attention as carriers due to the apparent ease of preliminary formulation. of inhalation aerosols using nebulizer systems. As a consequence, the literature is populated with empirically-based or nonoptimized reports. However, research of protein and DNA delivery systems that employ liposomes are providing useful insight to the delivery modulation. The past 15 years have been marked by intensive research efforts on pulmonary drug delivery (PDD) not only for local therapy but for systemic therapy as well as diagnostic purposes, primarily due to the several advantages the pulmonary route offers over other routes of drug administration. Drugs that undergo extensive first-pass metabolism or gastrointestinal degradation (such as proteins and peptides) are ideal candidates for pulmonary delivery. Even though the lung is enzymatically active, examples abound where these drugs have shown improved bioavailability after pulmonary administration [1, 2]. Pulmonary administration is less invasive and will lead to increased patient compliance. Lower incidence of side effects, especially for local therapies, is often observed due to localized drug deposition and reduced systemic and generalized exposure. To further exploit the other advantages presented by the lungs, as well as to overcome some challenges encountered, scientists developed interests in particulate DDS for pulmonary administration. These systems can be broadly classified into immediate release [e. g. lactose-drug mixtures for dry powder inhaler (DPI) application] and controlled release systems (such as liposomes, micelles, nano- and microparticles based on polymers). Particulate drug carriers such as liposomes, microparticles and nanoparticles can be / have been used to improve the therapeutic index of new or established drugs by modifying drug absorption, reducing metabolism, prolonging biological half-life or reducing toxicity. Drug distribution is then controlled primarily by properties of the carrier and no longer by physico-chemical characteristics of the drug substance only. A careful design of such DDS, based on a thorough understanding of the clinical requirements for the disease conditions to be treated, lung architecture / physiology, appropriate selection of the carrier materials, production process and device, are key to successful delivery using advanced DDS such as liposomes and microparticles.

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