AEROSOLS: PULMONARY DRUG DELIVERY SYSTEM

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ABSTRACT
Pulmonary drug delivery system is a needle free technique. The origin of inhaled therapies seen in back 4000 years ago to India, where people smoked the leaves of the Atropa belladonna plant to suppress cough. In the 19th and early 20th centuries, asthmatics smoked asthma cigarettes that contained stramonium powder mixed with tobacco to treat the symptoms of their disease. But administration of drugs by the pulmonary route is technically challenging because oral deposition can be high, and variation in inhalation techniques can affect the quantity of a drug delivered to the lungs. Pulmonary drug delivery remains the preferred route for administration of various drugs. It is an important research area which impacts the treatment of illnesses including asthma, chronic obstructive pulmonary disease and various diseases. Due advancement in application nowadays Pulmonary drug delivery is useful to treat Diabetes, angina pectoris, cancer, bone disorders, migraine, tuberculosis, acute lung injury and others. In this article, we summarize the outline of this dosage form.

Keywords: Asthma, pulmonary route, inhalation therapy, propellants.

INTRODUCTION
An inhalation therapy that is effective and safe depends not only on a pharmacologically active molecule, but also on a delivery system and its application. The respiratory tract is exposed to a relatively large number of biological and non biological particulates. These are contained in the 20,000 L of air that must be inhaled daily to accomplish gas exchange. It is a characteristic of the effectiveness of lung defense mechanisms that in healthy people’s lungs are sterile below the larynx. By pulmonary route drug goes gives direct to a target organ. In the treatment of obstructive respiratory diseases, pulmonary delivery can minimize systemic side effects, provide rapid response and minimize the required dose since the pulmonary route is better alternative to other routes because if we compare it with parental route injection is associated with pain. Secondly, chronic injection is an unpleasant prospect with a host of hygiene issues and potential side effects. Drug delivery by Nasal route is inefficient in terms of the amount of drug actually delivered to the body and to improve its efficiency penetration enhancers must be added that may cause local irritation. But in case of pulmonary route 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 noninvasive routes. Intra dermal route offers an even less naturally permeable boundary to macromolecules than the gastrointestinal tract. The devices, which inject proteins like insulin, have been available for years, however they have not very well accepted by doctors as well as patients due to the discomfort and the potential for “splash back” to transmit blood borne diseases associated with it. Thus pulmonary route is better route as compare to other routes.
The dosage forms used for this purpose are known as AEROSOLS. They are the dosage forms containing therapeutically active ingredients that are packaged under pressure in a sealed container and are released as a fine mist of spray upon activation of a suitable valve system.

**Basic components**
1. The container
2. Propellants
3. Product concentrate (containing API)
4. Valve and Actuators.

**Types**
1. Two-phase system. (Gas & liquid)
2. Three-phase system. (Gas, liquid, solid/liquid).

**Propellants**
For pressurized metered dose inhalations propellants perform the essential function of expelling the material from the container by supplying the necessary pressure within the aerosol system. They are liquefied or compounded gases having vapor pressures exceeding employed to obtain the necessary delivery and spray characteristics of the aerosol.

**Table 1: Commonly used propellants in aerosol systems**

<table>
<thead>
<tr>
<th>Propellants</th>
<th>Molecular weight(g/mol)</th>
<th>Vapor pressure(PSI at 25°C)</th>
<th>Boiling point (°C at 1 atm)</th>
<th>Density (g/cm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>011(CCl3F)</td>
<td>137.4</td>
<td>13.4</td>
<td>23.8</td>
<td>1.48</td>
</tr>
<tr>
<td>012(CCl2F2)</td>
<td>120.9</td>
<td>94.5</td>
<td>-29.8</td>
<td>1.31</td>
</tr>
<tr>
<td>114(C2Cl2F4)</td>
<td>170.9</td>
<td>27.6</td>
<td>3.8</td>
<td>1.46</td>
</tr>
<tr>
<td>134(CH2FCF3)</td>
<td>102.0</td>
<td>96.0</td>
<td>-26.5</td>
<td>1.20</td>
</tr>
<tr>
<td>227(CHF2C2F5)</td>
<td>170.0</td>
<td>72.6</td>
<td>17.3</td>
<td>1.92</td>
</tr>
</tbody>
</table>

The commonly used propellants in aerosol systems are hydrocarbons, especially the fluorochloro derivatives of methane and ethane (Table 1), the butanes and pentanes and compressed gases are used.

**Containers**
Aerosol containers are usually made up of glass, plastic, metal or combination of these materials. Glass containers must be precisely engineered to provide maximum in pressure, safety and impact resistance. Plastics must be employed to coat the glass to improve safety characteristics or to coat metal containers to improve corrosion resistance and enhances the stability of formulation. Suitable metals include stainless steel, aluminum and tin-plated steel. Aerosol containers are made of metal (stainless steel, aluminum or tin-plated steel), glass or plastic or a combination of these materials. The containers must be so designed that they provide the maximum in pressure safety and impact resistance.
1) Metered Dose Inhalers (MDIs)
Metered dose inhalers are the most commonly used devices for generation of aerosol (Figure 1). They consist of a micronized form of the drug in a propellant under pressure with surfactants to prevent clumping of drug crystals. Lubricants for the valve mechanism and other solvents are the other constituents. When the device is actuated, the propellant gets exposed to atmospheric pressure, which leads to aerosolisation of the drug. As it travels through the air, the aerosol warms up leading to evaporation of the propellant that reduces the particle size to the desirable range. The fraction of drug to the airways ranges from 5 percent to 15 percent.

Metered dose inhalers have been popular because of ease of usage, small and compact size and the relative cost-effectiveness. On the other hand, the commonest error in the usage of an MDI is the lack of coordination between the actuation of the device and the initiation of inspiration. Many other problems can also be associated with the use of MDI. The physician who prescribes these devices should keep these things in mind and the same should be conveyed to the patient as well.

2) Dry Powder Inhalers (DPIs)
Dry powder inhalers (DPI) consist of pharmacologically active powder as an aggregate of fine micronized particles in an inhalation chamber (Figure 2). These aggregates are converted into an aerosol by inspiratory airflow through the inhaler generated by the patient. This basic fact excludes the problem of coordination between the delivery of the drug and the initiation of inspiration. But the very same fact also makes it unsuitable for patients who are unable to generate high inspiratory flow rates. Lack of requirement of propellant is an advantage of DPIs over MDIs. The fraction of the drug delivered to the site of action by a DPI varies from 9% to 30% and varies among different commercially available products. The DPIs tend to fail in patients who cannot generate moderate to high inspiratory flow rates since unlike the MDI, they are driven by the patient’s own effort. In a DPI, the aerosol needs to be generated from the powder formulation by patient’s own effort5-9.

Valves
The valve regulates the flow of the active ingredient(s) and propellant from the container and determines the spray characteristics of the aerosol. It must be manufactured from materials which are inert to the contents of the aerosol. The
commonly used materials are rubber, plastic, aluminum and stainless steel. Products for oral or nasal inhalation require metered-dose valves which ensure delivery of a uniform quantity of spray and an accurate dose of the active ingredient(s), both within specified tolerances, with each activation of the valve.

**Actuators**

The actuator or adaptor which is fitted to the aerosol valve stem is a device which on depression or any other required movement opens the valve and directs the spray to the desired area. The design of the actuator which incorporates an orifice of varying size and shape and expansion chamber is very important in influencing the physical characteristics of the spray or foam, particularly in the case of inhalation aerosols, where the active ingredient(s) must be delivered in the proper particle size range. A proportion of the active ingredient(s) is usually deposited on the inner surface of the actuator; the amount available is therefore less than the amount released by actuation of the valve.

**Advantages of Pulmonary Drug Delivery**

1. It is needle free pulmonary delivery.
2. It requires low and fraction of oral dose.
3. Pulmonary drug delivery having very negligible side effects since rest of body is not exposed to drug.
4. Onset of action is very quick with pulmonary drug delivery.
5. Degradation of drug by liver is avoided in pulmonary drug delivery.

**Current Applications of Pulmonary Drug Delivery**

1) Application of pulmonary drug delivery in Asthma and COPD. Asthma is a chronic long term lung disease that is characterized by inflammation and narrowing of airways. Asthma causes recurring periods of wheezing, chest tightness, shortness of breath, and coughing. The coughing often occurs at night or early in the morning. Asthma affects people of all ages, but it most often starts in childhood. In the United States, more than 22 million people are known to have asthma. Nearly 6 million of these people are children. 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 the three main classes of drug such as bronchodilators, corticosteroids, and ant cholinergic. Nowadays all above three classes of drugs given by pulmonary route. For management of asthma advances done in drugs such levosalbutamol inhalers which having superior efficacy as compare to salbutamol. COPD means chronic obstructive pulmonary diseases. COPD is linked to smoking, comprises chronic bronchitis and emphysema and causes one million deaths annually. Some of the marketed products are listed in Table 2.

2) Pulmonary delivery in cystic fibrosis. Nowadays cystic fibrosis is very common disease. Pulmonary delivery played an important role in the management of CF for decades. The main aim of aerosol system is to deliver drugs to infants and children. Recently following drugs are given by pulmonary route for cystic fibrosis. Tobramycin-spray dried, Tobramycin powders containing nano particles for pulmonary delivery. Tobramycin is widely used to treat patients with CF. Overall, evidence suggests improved lung function and probably reduced hospitalization when tobramycin is part of maintenance therapy in CF.
Table 2: Some marketed products

<table>
<thead>
<tr>
<th>Name of Product</th>
<th>API of drug</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epaf</td>
<td>Salbutamol</td>
<td>3M Pharmaceuticals</td>
</tr>
<tr>
<td>Ventolin</td>
<td>Albuterol Sulphate</td>
<td>GSK</td>
</tr>
<tr>
<td>Flutotide</td>
<td>Fluticasone Propionate</td>
<td>GSK</td>
</tr>
<tr>
<td>Qvar</td>
<td>Beclomethasone dipropionate</td>
<td>3M Pharmaceuticals</td>
</tr>
<tr>
<td>Asmol</td>
<td>Salbutamol</td>
<td>3M Drug Delivery systems</td>
</tr>
</tbody>
</table>

CONCLUSION
Drug delivery to the respiratory tract has been characterized in the past decade by an increase in knowledge of drug droplets or particle manufacture, behavior aerosol dispersion, lung deposition and clearance. Pulmonary drug delivery is an important research area which impacts the treatment of illnesses including asthma, chronic obstructive pulmonary disease and various diseases. Inhalation gives the most direct access to drug target. In the treatment of obstructive respiratory diseases, pulmonary delivery can minimize systemic side effects, provide rapid response and minimize the required dose since the drug is delivered directly to the conducting zone of the lungs. It is a needle free several techniques have been developed in the recent past, to improve the Quality of pulmonary drug delivery system without affecting their integrity. Because of advancement in applications of pulmonary drug delivery it is useful for multiple diseases. So pulmonary drug delivery is best route of administration as compare to other routes.

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