Nutan Dhanpal Shah*, Vishal Vilas Shah, Jyoti Waghmare
Appasaheb Birnale College of Pharmacy, Sangli-416 416, Maharashtra, India.

Corresponding Author:
nutanu56@gmail.com

ABSTRACT

Pulmonary drug delivery by DPIs, because of its propellant free nature, high patient compliance, high dose carrying capacity, drug stability and patent protection, has recently become subject of active research to realize full potential of lungs for local and systemic treatment of diseases such as asthma and COPD. Dry powder inhalers (DPIs) are devices through which a dry powder formulation of an active drug is delivered for local or systemic effect via the pulmonary route. In last decade, performance of DPIs has improved significantly through the use of engineered drug particles and modified excipients systems. The controlled release of drugs for pulmonary delivery is a research field which has been so far rather unexploited but is currently becoming increasingly attractive. The development of controlled release formulations for inhalable drugs has been widely investigated since several years. Current research approaches include the use of liposomes, micro- and nanosuspensions dry powder formulations.

Available on www.ijrrpas.com
INTRODUCTION:

The respiratory tract is established as an attractive route for drug delivery. The potential advantages of delivering a drug to the lung by inhalation have been well known to scientists, physicians and drug abusers for many years. For drugs that exert their biological effect in the lung, these include rapid onset of action, reduced dose and minimized side effects compared to the same drug delivered by mouth (Dalby R et al, 2003).

A wide variety of agents has been administered to the lung via oral inhalation, for the treatment of diverse disease states. The most frequent use of inhalation therapy is for the treatment of obstructive airway diseases using drugs such as short and long-acting β sympathomimetics, corticosteroids, and anticholinergic agents. However, the respiratory route has been receiving increased attention since the early 1990s as an alternative to parenteral drug delivery, most notably for the delivery of inhaled insulin (Hickey A et al, 2004) and also for peptide and protein therapeutics.

1. DRY POWDER FOR INHALATION (DPI):

Three main delivery systems have been devised, namely, pressurized metered-dose inhaler (MDI), nebulizer and dry powder inhaler (DPI). Treatment of asthma has improved considerably in recent years owing to the discovery of potent compounds which prevent or alleviate some of the symptoms. However, the efficiency of inhalation therapy is not high since only about 10% of the inhaled dose of the drug reaches the alveoli. To a certain extent, it may be possible to increase the fraction of dose deposited in the lungs by training the patient in ‘correct’ inhalation techniques. However, the therapeutic efficacy of the inhaled drug is governed by the aerosol characteristics (which are a function of a combination of the formulation and device), inter-patient variability and the technique by which the patient uses the inhaler.

The MDI is still the most commonly prescribed inhalation system. However, it has several disadvantages:

- Droplets leaving the actuator orifice can be too large and have an extremely high velocity resulting in extensive oropharyngeal deposition.
- The output of the MDI is delivered in the course of vital capacity manoeuvre rather than tidal breathing and hence it is important to synchronize the aerosol discharge with inspiration. In recent studies it was found that 50% or more adult patients have difficulty in using conventional MDIs efficiently even after a careful training. In an attempt to solve this problem a spacer devices and breathe actuated MDIs have been developed.
- Dysrhythmias and paradoxical bronchoconstriction with MDIs have given rise to some controversy about the safety of propellants or surfactants.
- The use of chlorofluorocarbon (CFC) propellants is to be restricted in future due to their implication in the ozone depletion.
As a result of these problems it might be expected that the future of the MDIs is limited. There are two possibilities for future development which are currently being actively explored. First, alternative ‘ozone friendly’ propellants and second, the design and the use of alternative inhalers that do not use propellants at all. Nebulizer generated ‘wet’ aerosols do not contain propellants but the nebulizers are generated bulky, cumbersome and costly. The ease of operation (precise synchronization of aerosol discharge with inspiration is not required) and relatively low cost of DPI may new systems over the coming decade, providing future benefits to many patients3 (Martin G et al, 1994).

Pulmonary drug delivery by DPIs, because of its propellant free nature, high patient compliance, high dose carrying capacity, drug stability and patent protection, has recently become subject of active research to realize full potential of lungs for local and systemic treatment of diseases such as asthma and COPD. Dry powder inhalers (DPIs) are devices through which a dry powder formulation of an active drug is delivered for local or systemic effect via the pulmonary route. Although DPIs are complex in nature and their performance relies on many aspects including the design of inhaler, the powder formulation and the airflow generated by the patient. In last decade, performance of DPIs has improved significantly through the use of engineered drug particles and modified excipients systems4 (Misra A et al, 2007).

Advantages and disadvantages of DPIs are mentioned as follows,

**Advantages:**
- No propellants
- Provides local action within the respiratory tract and are non-invasive
- Avoids hepatic first-pass metabolism
- Allows for a reduction in systemic side-effects
- Provides rapid drug action
- Optimal particle size of drug for deep lung delivery
- High drug dose carrying capacities, reproducibility (Monodisperse)
- Breath actuated hence no hand-mouth co-ordination required
- Minimal extra-pulmonary loss of drug due to low oropharyngeal deposition, low device retention and low exhaled loss
- Reduces extracellular enzyme levels compared to GI tract due to the large alveolar surface area

Available on www.ijrrpas.com
• Better patient compliance, simple to use and convenient to carry and do not require spacers

Disadvantages:
• Respirable dose dependent on inspiratory flow rate
• Humidity may cause powders to aggregate and capsules to soften
• Dose lost if patient inadvertently exhales into the DPI

Drug delivery to the lung can be improved not only by using better devices but also through more rationalized formulation. DPI consists of drug and carrier particles either mixed or co-precipitated together into dry powder form. Dry powders for inhalation are formulated either as loose agglomerates of micronized drug particles with aerodynamic particle sizes of less than 5 μm or as carrier-based interactive mixtures with micronized drug particles adhered onto the surface of large lactose carriers. The commonly used coarse carrier is inhalation grade lactose.

Size of drug/dry powder is important and should be near spherical in shape and monodispersed with aerodynamic diameter range of 0.5 to 5 μm (Misra A et al, 2007). A particle size of 2–5 μm yields optimal benefit, whereas for systemic effects particle size of less than 2 μm is needed for drug deposition in the small peripheral airways. Particles greater than 5 μm may also result in systemic effects due to impaction in the throat (i.e. oropharyngeal delivery) and oral absorption. The dry powder formulation is aerosolized through a DPI device, where the drug particles are separated from the carrier (from drug–carrier mixtures) or deagglomerates drug particles, and the dose is delivered into the patient’s deep lungs. The large carrier particles normally impinge in the buccal cavity or in the oropharynx, whereas liberated micronized drug particles that overcome the forces of adhesion to the carrier particles deposit further down the respiratory tract. In these systems, particle size and flow property, formulation, drug–carrier adhesion, respiratory flow rate and design of DPI devices extensively influence the performance (Islam N et al, 2008).

However powders in this size range (1-5 μm) exhibit strong inter-particulate cohesion, leading to poor powder flow properties (Steckel H et al, 2004). Furthermore, factors known to influence the aerosolization properties of dry powders (e.g. particle morphology, density and surface composition (Prime D et al;1997) cannot be controlled effectively during the micronization process. Researchers in the field have investigated a number of approaches to improve powder aerosolization, such as mixing the micronized drug with inert carrier particles or modification of particle morphology (Larhib H et al, 2003), particle surface roughness (Giovagnoli S et al, 2007), particle porosity or powder density (Seville P et al, 2008).

Spray drying offers an alternative approach to the generation of dry, potentially respirable powders for local pulmonary drug delivery. Whereas micronization is a destructive technique, spray drying is a one-step constructive process that provides greater control over particle size, particle

Available on www.ijrrpas.com
morphology and powder density\textsuperscript{11} (Seville P \textit{et al}, 2005). Indeed, dry powders generated by spray drying have been investigated by a number of researchers for suitability as dry powder inhaler (DPI) formulations\textsuperscript{12, 13} (Weers J \textit{et al}, 2002, Najafabadi A \textit{et al}, 2004).

2.1 Powder production methods for DPI:
Conventionally DPIs are produced by crystallizing the powder followed by milling to micronize the drug particles for pulmonary delivery. However, these methods have various limitations such as poor control over powder crystallinity, shape, size, and size distribution. Dry milling produces partially amorphous materials with high surface charge causing particle agglomeration. These problems can be resolved by specialized milling methods. In order to reduce the amorphous content in the material produced by milling, the milling can be carried out at elevated humidity (30-70\%) to facilitate in situ crystallization. A conventional ball mill can be used for the process, and the materials selected for the grinding media (e.g. glass, zirconium oxide) were reported to be not crucial. However, the size of the grinding media are preferably 1 mm or less in order to be effective in attrition and imparting less wear to the mill. Since the particles are produced in water, any amorphous regions in the particles would undergo recrystallization. Thus the wet milled powder is anticipated to be crystalline and more stable to moisture than powders produced by dry milling.

Spray drying was explored in the 1980s as an alternative means of making fine particles with desirable flow and dispersion characteristics without need of using coarse carriers. Spray drying has been employed as a method for preparing micron-sized powders for pulmonary administration and has better control on particle formation and hence can be easily translated to large scale production. Previously, DPIs were prepared by spray drying process either by single and/or multiple emulsion technique or co-solvent systems, primarily consisting of an aqueous / organic solvent or combination of aqueous and organic solvents. In spray drying, a drug solution is atomized to fine droplets which are evaporated in a warm air current to form dry particles. Although the drying air temperature can be relatively high (>100\°C), the actual temperature of the evaporating droplets is significantly lower due to cooling by the latent heat of vaporization. Thus, thermal degradation of the active ingredient is not so much a concern as it first appears. In addition to drug production, spray drying has been used to produce carrier particles. Spray drying is not limited to aqueous solutions. Spray drying of ethanolic solutions containing antiasthmatic drugs has been reported. Nonaqueous systems have also been used to prepare porous particles suitable for aerosol delivery. The properties of the spray dried powders are controlled by both the process (atomizing nozzle type, powder collection technique and droplet drying time and rate) and formulation parameters (effects of the active ingredient).

The other techniques for formulation of stable micron sized DPI products includes milling, simple mixing of carrier with the drug, co-precipitation of drug and carrier by lyophilization and milling, specialized spray-drying, spray freeze drying, ultrasound assisted crystallization, flash crystallization,
controlled precipitation, and supercritical fluid technologies. These methods have the advantages of higher product yield, lower operating temperature, and higher powder crystallinity. However, all the techniques suffer from the disadvantage of high operating cost and impurity (Misra A et al, 2007).

2.2 Uptake of inhaled drug after inhalation therapy:
There are several advantages in delivering drugs, to the lungs including a non invasive method of delivery; the surface area of the lung is between 80 m² and 140 m², which is about half the area of a tennis court. In addition, in most pulmonary regions, the thickness of the alveolar epithelium is only between 0.1 μm and 0.2 μm. The total distance between epithelial surface and blood in the alveolar area is between 0.5 μm and 1.0 μm which are much less than in the bronchial system (distance between mucus surface and blood: 30 μm–40 μm). Thus, it appears that pharmaceuticals after deep inhalation and deposition in the peripheral (i.e. alveolar) region of the lung can be rapidly absorbed. Pulmonary delivery therefore has the advantage, compared to nasal delivery, that it is possible to obtain a sufficiently high absorption without the need of enhancers (WO/2003/086516). Another advantage is that these drugs are not subject of a hepatic first pass effect after their absorption as shown in figure 1.

On the other hand, the human lung has different defense mechanisms to prevent aerosol particles penetrating into the deep lung. Primarily, the oropharyngeal region and the bronchial tree are excellent filters to eliminate aerosol particles from the inhaled air and particles deposited on ciliated epithelium are subject to mucociliary transport to the gastrointestinal tract. Therefore, to deliver a drug into the deep lung, one has to surmount these filters. However, even after deposition in the alveolar region of the lung, a number of mechanisms inhibit the absorption of inhaled pharmaceuticals. There are a number of absorption barriers (i.e. mucus layer, alveolar lining fluid layer, macrophages and other cells, alveolar epithelium and basement membrane) which act to varying extents by inhibiting drug permeation into the circulation, there exists competing cellular uptake pathways (e.g. particle phagocytosis by macrophages), and of course proteolytic degradation can limit the amount of intact drug available for absorption. The function of these barriers can be impaired by very different substances and consequently the absorption of drugs can be increased, for example, by the use of absorbance enhancers (e.g. cyclodextrins, detergents and bile acids). Furthermore, proteolytic degradation can be inhibited by protease inhibitors (e.g. nafamostat mesilate and aprotinin) and phagocytosis by macrophages reduced by packaging of substances into porous particles. In principle, absorption kinetics of inhaled substances depend on their molecular weight (small molecules are more rapidly absorbed than larger ones), pH-value, electrical charge, solubility and stability of the inhaled substance.
The other target regions within the lung for inhalable drugs are the large and small bronchial airways. Different pulmonary diseases are located in these parts of the respiratory tract. The most relevant are: asthma, chronic obstructive pulmonary disease (COPD) and bronchial tumors. To treat these diseases locally, one has to deliver the drugs specifically to this region. However, a minor proportion of drugs can also be absorbed into systemic circulation after such a tracheobronchial deposition. In contrast to the inhalation of drugs for systemic treatment, the inhalative therapy of asthma and COPD by means of nebulizers and metered dose inhalers (MDI) has been clinically established for many years and the treatments involve generally low molecular weight molecules in formulations free of stabilizers and absorption enhancers\(^4\) (Scheuch G et al, 2006).

### 2.3 Parameters determining particle deposition in deep lung:

Different biophysical parameters determine regional drug deposition in the human lungs:

- Aerodynamic particle behaviour (e.g. size, density, hygroscopicity, shape, electrical charge)
- Breathing pattern of the patients (e.g. flow rate, ventilation volume, end-inspiratory breath holding)
- Time of aerosol pulse injection into the breathing cycle
- Anatomy of the respiratory tract

Of these factors, aerosol particle size and size distribution are the most influential on aerosol deposition. The aerodynamic particle diameter (AD) is the diameter of a sphere with a density of 1 g/cm\(^3\) that has the same aerodynamic behaviour as the particle which shall be characterized. In that way, aerosol particles with different density and shape can be characterized depending on their aerodynamic properties (Scheuch G et al, 2006).

#### Aerodynamic particle behavior:

The size of the particles is a critical factor affecting the site of their deposition, since it determines operating mechanisms and extent of penetration into the lungs. Aerosol size is often expressed in terms of aerodynamic diameter (AD). The aerodynamic diameter is defined as the equivalent diameter of a spherical particle of unit density having the same settling velocity from an air stream as the particle in question. Thus, particles that have higher than unit density will have actual diameters smaller than their AD. Conversely, particles with smaller than unit density will have geometric diameters larger than their AD. Aerosol size distributions may be characterized as practically monodisperse (uniform sizes) or polydisperse (non-uniform sizes).

The upper airways (nose, mouth, larynx, and pharynx) and the branching anatomy of the tracheobronchial tree act as a series of filters for inhaled particles. Thus, aerosol particles bigger than 100 μm generally do not enter the respiratory tract and are trapped in the nas/o/oropharynx. The particles must be very fine, for example having a aerodynamic diameter of less than 10 μm. Particles having aerodynamic diameters greater than 10 μm are likely to impact the walls of the throat and generally do not reach the lung. Particles having aerodynamic diameters in the range of 5 μm to 0.5 μm will
generally be deposited in the respiratory bronchioles whereas smaller particles having aerodynamic diameters in the range of 2 to 0.05 μm are likely to be deposited in the alveoli (Manca M, 2009).

Particles in the ambient air are transported by different physical mechanisms. The relevant mechanisms for therapeutic aerosols are diffusion by Brownian motion (particles in the size range of <0.5 μm), sedimentation by the gravitational force (particles in the size range of >0.5 μm) and impaction (size range >3 μm).

2.4 Mechanism of drug deposition:
The mechanisms by which particles deposit in the respiratory tract includes impaction (inertial deposition), sedimentation (gravitational deposition), Brownian diffusion, interception, and electrostatic precipitation. The relative contribution of each depends on the characteristics of the inhaled particles, as well as on breathing patterns and respiratory tract anatomy. All mechanisms act simultaneously, but the first two mechanisms are most important for large-particle deposition within the airways (1 mm, AD, 10 mm). Diffusion, however, is the main determinant of deposition of smaller particles in peripheral regions of the lung. Impaction occurs when a particle’s momentum prevents it from changing course in an area where there is a change in the direction of bulk air flow. It is the main deposition mechanism in the upper airways, and at or near bronchial branching points. The probability of impaction increases with increasing air velocity, breathing frequency, and particle size.

Sedimentation results when the gravitational force acting on a particle overcomes the total force of the air resistance. Inspired particles will then fall out of the air stream at a constant rate. This is an important mechanism in small airways having low air velocity. The probability of sedimentation is proportional to residence time in the airway and to particle size, and decreases with increasing breathing rate.

Diffusion occurs when the collision of gas molecules with small aerosol particles exerts discrete non-uniform pressures at the particles’ surfaces, resulting in random Brownian motion. The effectiveness of Brownian motion in depositing particles is inversely proportional to particle diameters of those particles, 0.5 μm, and is important in bronchioles, alveoli, and at bronchial airway bifurcations. Molecule-size particles may deposit by diffusion in the upper respiratory tract, trachea, and larger bronchi (Manca M, 2009).

2.5 Respiratory patterns:
The pattern of respiration during aerosol exposure influences regional deposition, since breathing volume and frequency determine the mean flow rates in each region of the respiratory tract, which, in turn, influence the effectiveness of each deposition mechanism. Turbulence tends to enhance particle deposition, the degree of potentiating depending on the particle size. Rapid breathing is often associated with increased deposition of larger particles in the upper respiratory tract, while slow, steady inhalation increases the number of particles that penetrate to the peripheral parts of the lungs slow breathing, with or without breath-holding, showed a broad maximum deposition in the ciliated airways (tracheobronchial region).
pulmonary maximum occurred between 1.5 μm and 2.5 μm with breath-holding and between 2.5 μm and 4μm without breath-holding. Rapid inhalation showed similar trends: the tracheo-bronchial region maximum falls and shifts to between 3 μm and 6 μm. Pulmonary deposition sharpens and occurs between 1.5 μm and 2 μm with breath-holding, and between 2 μm and 3 μm without breath-holding. When the above considerations are taken into account, the ideal scenario for aerosol would be (Manca M, 2009):

- Aerosol AD smaller than 5 μm, to minimize oropharyngeal deposition
- Slow, steady inhalation and
- A period of breath-holding on completion of inhalation.

2.6 Pulmonary clearance:
The primary function of the pulmonary defensive response to inhaled particles is to keep the respiratory surfaces of the alveoli clean and available for respiration. The elimination of particles deposited in the lower respiratory tract serves an important defense mechanism to prevent potentially adverse interactions of aerosols with lung cells. Insoluble particulates are cleared by several pathways, which are only partially understood. These pathways are known to be impaired in certain diseases and are thought to depend on the nature of the administered material. Swallowing, expectoration, and coughing constitute the first sequence of clearance mechanisms operating in the naso/oropharynx and tracheobronchial tree.

A major clearance mechanism for inhaled particulate matter deposited in the conducting airways is the mucociliary escalator, whereas uptake by alveolar macrophage predominates in the alveolar region. In addition to these pathways, soluble particles can also be cleared by dissolution with subsequent absorption from the lower airways. The rate of particle clearance from these regions differs significantly and its prolongation can have serious consequences, causing lung diseases from the toxic effects of inhaled compounds. It is now well recognized that the lungs are a site for the uptake, accumulation, and/or metabolism of numerous endogenous or exogenous compounds. All metabolizing enzymes found in the liver are also found in the lung, although in smaller amounts. The rate at which a drug is cleared and absorbed from the respiratory tract depends on the dynamic interaction of several factors, predominantly (Manca M, 2009):

- The mucociliary clearance rate
- Site of deposition along the airways
- Biopharmaceutical factors (particulates vs. drug in solution)
- Drug release rate
- The physicochemical properties of the drug, such as molecular weight, partition coefficient, and charge.

Available on www.ijrrpas.com
2.7 Mucociliary clearance:
Mucociliary clearance is a physiologic function of the respiratory tract to clear locally produced debris, excessive secretions, or unwanted inhaled particles. It consists of ciliated epithelial cells reaching from the naso/oropharynx and the upper tracheobronchial region down to the most peripheral terminal bronchioles. Beating of the cilia, together with mucus secreted by the goblet cells, contributes to an efficient clearance mechanism. For normal mucociliary clearance to occur it is necessary that the epithelial cells are intact, the ciliary activity and the rheology of mucus are normal, and that the depth and chemical composition of the periciliary fluid layer is optimal. Thus, the mucociliary escalator can be impaired by altering the volume of mucus secretion, the mucus viscosity and elasticity, or the ciliary beat frequency. Mucociliary clearance is known to be impaired in smokers, in patients with chronic bronchitis, and in acute asthmatics. Certain diseases have the opposite effect that of enhancing clearance rates (Manca M, 2009).

2.8 DPI as controlled release delivery systems:
Development of dry powder inhalers involves powder recrystallization, formulation, dispersion, delivery, and deposition of the therapeutic agent in different regions of the airways in prophylaxis/treatment/diagnosis of pulmonary and systemic disorders. Conventional powder production by crystallization and milling has many limitations resulting into development of alternative techniques to overcome the problems. In the last decade many patents have been filed claiming improvement in aerosol performance of dry powder inhalers through the use of,
(i) Incorporation of fines of carrier particles to occupy active sites on the surface and use of hydrophobic carriers to facilitate deaggregation through reduced surface energy and particle interaction
(ii) Reducing aerodynamic diameters through particle engineering and incorporating drug into porous or low particle density, and/or
(iii) Preparing less cohesive and adhesive particles through corrugated surfaces, low bulk density, reduced surface energy and particle interaction and hydrophobic additives. Moisture within dry powder inhaler (DPI) products has also been shown to influence aerosol performance via capillary force and electrostatic interaction. Better understanding of particle forces and surface energy has been achieved by the use of sophisticated analytical techniques. Understanding the intricacies of particle shape and surface properties influencing specific lung deposition has been further facilitated by the availability of newer and advanced software (Misra et al, 2007).

Drug delivery systems (DDS) that can precisely control the release rates or target drugs to a specific body site have had an enormous impact on the healthcare system. Carrier technology offers an intelligent approach for drug delivery by coupling the drug to a carrier particle such as microparticles, microspheres, nanoparticles, liposomes, etc. which modulates the release and absorption characteristics of the drug. Conventional drug administration does not usually provide rate-controlled release or target specificity. In many cases, conventional drug delivery provides sharp increases of drug concentration at potentially toxic levels. Following a relatively short period at the therapeutic level, drug concentration eventually drops off until re-
administration. Today new methods of drug delivery are possible: desired drug release can be provided by rate-controlling membranes or by implanted biodegradable polymers containing dispersed medication (Manca M, 2009).

The controlled release of drugs for pulmonary delivery is a research field which has been so far rather unexploited but is currently becoming increasingly attractive. The development of controlled release formulations for inhalable drugs has been widely investigated since several years. However, up to now, sustained release formulations for pulmonary delivery have not been marketed yet in spite of the increasing interest in this research (Jaspart S et al, 2007). There are many advantages to developing sustained release formulations for pulmonary drug delivery, including reduced dosing frequency, improved patient compliance and reduction in side effects (Seville P et al, 2008). 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, long acting β2-adrenergic receptor agonists with glucocorticoids used for the relief of asthma- and COPD-related bronchospasm have a plasma half life that constrain the patient to an administration of the drug every 5.5 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. In this purpose the liposomes have been the most extensively investigated carriers. They can be prepared with lung endogenous phospholipids as surfactants, with a wide range of size and are able to incorporate both hydro and lipophilic drugs. Liposomes proved to be able to impart a sustained release profile to the incorporated substances but they also present some disadvantages, i.e., a high production cost, a relative instability during storage and nebulisation that can lead to their disruption and to the premature loss of entrapped substances. Therefore liposomal dry powder formulations are currently getting more attractive. Polymeric microspheres have also been successfully tested in vitro as well as in vivo as sustained release drug delivery system. They are more physicochemical stable than liposomes, both in vitro and in vivo, allowing thus a slower release of encapsulated drugs. Their main disadvantage is that their safety still remains uncertain. It was showed that pulmonary administration of PLA microspheres to rabbits led to histological damages assessed in terms of pulmonary haemorrhage, eosinophilia and neutrophil infiltration. Inflammation can, however, be avoided using large porous particles. 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. These include lipids, proteins, sugars or synthetic polymers such as poly (vinyl alcohol) or polyesters. In particular, PLGA has been widely used, as it is considered biodegradable and weakly toxic (Jaspart S et al, 2007). Spray-drying technology also offers the potential to incorporate a range of
excipients into the formulation. In addition, spray-dried powders that exhibit sustained drug release properties may be generated through the inclusion of drug release modifiers such as hydroxypropyl methylcellulose (HPMC), glyceryl behenate and polylactic acid, chitosan, etc. Leucine-HPMC is the promising excipient combination that can be employed in a wide range of applications, including sustained release preparations. Indeed, this combination has received considerable attention for the formulation of spray-dried powders for pulmonary drug delivery (Seville P et al, 2008).

2. CONCLUSION:
As DPI, because of its propellant free nature, high patient compliance, high dose carrying capacity, drug stability and patent protection, has become subject of active research to realize full potential of lungs for local and systemic treatment of diseases such as asthma and COPD. The controlled release of drugs for pulmonary delivery through DPI is a research field of increasing attraction. Sustained release formulations for pulmonary delivery have not been marketed yet in spite of the increasing interest in this research. The main advantage of sustained release is reduced dosing frequency, improved patient compliance and reduction in side effects. The reduction of the dosing frequency will be of great concern for a number of pulmonary disorders including asthma and chronic obstructive pulmonary disease (COPD). Further, long acting β2-adrenergic receptor agonists with glucocorticoids used for the relief of asthma- and COPD-related bronchospasm have a plasma half life that constrain the patient to an administration of the drug every 5.5 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, which would be the stepping stone towards the pulmonary drug delivery.

1 Figure 1: Uptake of inhaled drug after peripheral/ alveolar deposition

Available on www.ijrrpas.com
Figure 2: Particle size and sites of their deposition

Figure 3: Principle of dry powder inhaler design\textsuperscript{16} (M. Alagusundaram et al, 2010)
REFERENCES

6 Islam N, Gladkib E., Dry powder inhalers (DPIs)—A review of device reliability and innovation, Int. J. Pharm., 2008; 238-244.

Available on www.ijrrpas.com
16 Manca M., Chitosan and PLGA microspheres as drug delivery system against pulmonary Mycobacteria infections (dissertation), Department of pharmacochemico technology, University of Cagliari, 2009; 16-24.