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IJPBS |Volume 2| Issue 3 |JULY-SEPT |2012|286-298

Review Article
Pharmaceutical Sciences

PULMONARY TARGETING EMPLOYING POROUS PARTICULATES

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ABSTRACT

Pulmonary drug delivery has been employed for topical as well systemic therapy. The perfusion through a large surface area (about 100 $m^{2)}$ and ease of passage of substances through alveolar wall into the capillary circulation; makes lung a potential site for systemic drug delivery. Targeting to alveolar region is determined by a number of pharmacokinetic (PK) parameters. Drug deposition to the lungs varies significantly with the type of delivery device and particle size. Particle size range of approximately 3.5–6 µm can penetrate to some extent at slow inspiratory flow rates beyond the central airways into the peripheral region of the lung. Particles can be made in the respirable range, even as their geometric particle size is on the order of 20 µm, show that very light particles (ρ~0.4 g/cm) with d>5 µm can be deposited in the lungs. The microspheres obtained were characterised using particle size and morphology by scanning electron microscopy (SEM), transmission electron microscopy (TEM), other testing includes differential scanning calorimetry (DSC), thermogravimetric analysis (TGA) and Infra red spectroscopy (IR) FTIR spectrophotometer.

KEYWORDS

Pulmonary drug delivery, Drug deposition, Respirable range, Particle size range.

INTRODUCTION TO PULMONARY DELIVERY

For last few decades pulmonary drug delivery has been successfully employed for topical as well systemic therapy, with the goal of achieving pronounced pulmonary effect while reducing side effects. Some drugs that are given by oral have very low bioavailability, and to make them effective noninvasive, pulmonary route is an alternative [1]. The great surface area of the lung about 100 m^2, its perfusion, as well as the ease of passage of many substances through not only the alveolar wall but airway walls into the capillary circulation, make the lung a potential site for systemic drug delivery.

Human beings are exposed to billions of particles every day and these are inhaled with the ambient air. Many of these particles are deposited in the respiratory tract depending on surface properties of the particles and the breathing pattern of the individual. We have been trying to understand the particle behaviour in the human respiratory tract. From the toxicologic point of view, all particles smaller than 10 µm in diameter have the potential of being biologically active in susceptible individuals [2].

The degree of pulmonary targeting is determined by a number of pharmacokinetic (PK) i.e. the lung deposition. Once released from the device, a fraction of the delivered dose (respirable fraction) will be deposited in the lung, while larger particles will be deposited in the oropharynx [3]. Impaction of all inhaled particles on the luminal surface of the airways is governed by physical forces, such as gravity, inertia, and diffusion. Inhaled particles are carried with the tidal air through the respiratory system. However, because of forces acting upon the particles, their trajectories are different from air stream lines. The most important mechanical forces are gravity, inertia, and impulse transfer from collisions with gas

molecules. Particles are therefore displaced off stream lines and transported toward the surfaces of the respiratory tract by sedimentation, impaction, and diffusion. Whenever particles cover more than 30 µm/second by one of these transport mechanisms, particle deposition is influenced by them [3]. Other factors include the aerosol particle properties and breathing pattern [4-6]. Some of the factors are discussed here.

PHARMACOKINETICS

The passage of a drug from the inhaler device to its therapeutic or biological site of action is governed by many factors, which may be grouped empirically into two categories: (1) physical factors, which determine the deposition of drug from the mouth and onto the surface of the airway lumen, and (2) pharmacokinetic factors, which influence the amount of drug passing from the airway lumen to the target cell or tissue, i.e., the site at which the drug acts in producing a therapeutic action.

Physical Factors

In general, the impaction of all inhaled aerosol particles on the luminal surface of the airways is governed by physical forces, such as gravity, inertia, and diffusion. Other factors that may be modified to influence aerosol deposition include the following.

Aerosol Particle Size

The influence of particle size on the deposition pattern of a drug in the lung is summarized as follows [7]:

Selection of an appropriate monodisperse (i.e., uniform particle size) aerosol may permit the administration of a drug to the central or peripheral airways, a process that may be of benefit in targeting drugs for local or systemic actions. In general, however, aerosols used in therapy are polydisperse (i.e., consist of a range of particle sizes) and, therefore, distribute throughout the airways. Nevertheless, it should be recognized that 10% or less of an administered aerosol dose will attain the airways, with the remainder depositing on the mouth or pharynx or being swallowed [6].

Breathing Pattern

The rate of breathing and depth of breathing also influence drug deposition in the airways. Rapid, shallow inspiration promotes central deposition of a drug, whereas slow, deep inspiration leads to peripheral airway deposition [8]. Furthermore, the rate of ventilation and tidal volume (volume of air inspired each breath) determines the residence time of the drug in the lungs, that is, the period in which the airways are exposed to drug [4]. Holding one's breath at the end of inspiration of an aerosol promotes deposition through sedimentation (by gravitation) and diffusion.

Airway Geometry

The caliber and tortuosity of the airway influences the flow of air through the segment and, thereby, affects aerosol particle impaction. Disease states that alter airway caliber, such as obstructive airways disease, influence the pattern of aerosolized drug deposition in the airways by influencing airway geometry.

PARTICLE DEPOSITION IN LUNGS

Drug deposition to the lungs varies significantly with the type of delivery device and particle size. Efficient devices not only increase the amount of drug in the lung but also reduce the amount of drug that is available for absorption from the GI tract. In recent years, improvements in the design of delivery devices have increased pulmonary deposition from 10–20% to up to 40% [9,10].

The important "size" characteristic for deposition is called aerodynamic diameter: it is determined by the actual size of the particle, its shape, and its density. Numerous studies show that a fraction of particles in the aerodynamic size range of approximately 3.5–6 µm can penetrate to some extent at slow inspiratory flow rates beyond the central airways into the

peripheral region of the lung, while particles less than 3.5 µm and greater than approximately 0.5 µm will largely bypass the bronchial airways during inhalation and penetrate almost entirely to the "deep" lung. Larger particles are dominated by their inertial mass and will impact in upper airways due to their inertia. This impaction is exacerbated by higher inhalation flow rates, and even at controlled inhalation flow, oropharyngeal deposition shows very high levels of inter- and intrasubject variability. In contrast, particles smaller than 0.5 µm may not deposit at all, since they move by Brownian motion and settle very slowly. Moreover, they are inefficient, as a 0.5 µm sphere delivers only 0.1% of the mass that a 5µm sphere carries into the lungs[7, 11].

Once in the lungs, particles must release the therapeutic substance at a desired rate and, in some cases, escape the lungs' natural clearance mechanisms until their therapeutic payload has been delivered. In the central airways (trachea to terminal bronchioles), a drug may interact with the mucus layer, can be removed by the mucociliary escalator [12-14]. The mucociliary escalator, coughing, and alveolar clearance are the 3 major physical ways of removing deposited particles. In the conducting airways deposited particles are rapidly cleared by the mucociliary clearance (MCC) into the pharynx. In the terminal airways (alveoli), absorptive or non-absorptive processes remove deposited particles. Both the particle size and surface properties of materials influence their efficiency of macrophagic uptake and clearance. Factors affecting the particle deposition are discussed below.

Particle size:

Since the early 1990s, the notion of producing particles of a specific size, density, and morphology has evolved, and it has the potential to lead to significant advances in pulmonary drug delivery [3]. Typically, particles for use by inhalation would be produced by a milling (micronization) process that would result in a batch of material with a size range between 1.0 and 3.0 microns (necessary for inhalation). Scientists have realized that there may be more elegant techniques available for the production of small particles, including supercritical fluid recrystallization, spray-drying, or controlled precipitation, in which size control could be achieved and other desirable properties (e.g., extended release of the drug) may be realized [15].

Aerodynamic Diameter and Dynamic Shape Factor

Aerodynamic diameter is the most appropriate measure of aerosol particle size, because it relates to particle dynamic behavior and describes the main mechanisms of aerosol deposition; both gravitational settling and inertial impaction depend on aerodynamic diameter. To reach the peripheral airways, where drug is most efficiently absorbed, particles need to be in the 1–5 µm aerodynamic diameter range [16].

The aerodynamic diameter, D_{ae}, is defined by the diameter of an equivalent volume sphere of unit density D_{eq} with the same terminal settling velocity as the actual particle. For particles larger than 1 µm, the following expression describes the relationship between these dimensions.

$$D_{ae} = D_{eq}\sqrt{\left(\frac{\rho_p}{\rho_o X}\right)}$$

Where ρ_p and ρ_o are particle and unit densities, and X is the dynamic shape factor. Pharmaceutical powders are rarely spherical, and shape factors are dimensionless measures of the deviation from sphericity [17].

The aerodynamic diameter can be decreased by decreasing the particle size, decreasing particle density, or increasing the dynamic shape factor. This concept is shown graphically in **Fig. 1**

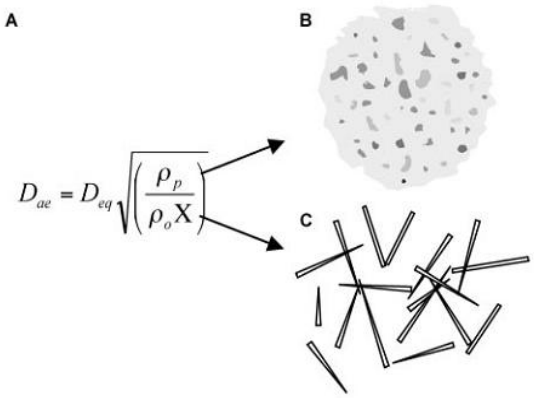

Fig1: Strategies for altering the aerodynamic diameter. A: Aerodynamic diameter equation. B: Large, low-density porous particles. C: Needle-shaped particles. Particles in both B and C are expected to have aerodynamic diameters smaller than their size would suggest. D_{ae} aerodynamic diameter. D_{eq} unit density of equivalent volume sphere. ρ_p particle density. ρ_o unit density. X dynamic shape factor.

Fine-Particle Fraction

"Fine-particle fraction" is the percentage of particles in the fine-particle range (1–5 µm). "Fine-particle mass" is the total mass of the particles that are in the fine-particle range[18]. The fine-particle component of aerosols is usually defined as the percentage of particles that are smaller than 5 µm aerodynamic diameter, or, in the case of certain a cut-off diameter that is close to 5 µm. Quite often this may be in the 6–7 µm range. It gives the definitive measures of equivalency with the effect of particle size on deposition[19].

Aerosol Particle Physics

Dry powders of respirable drug particles (i.e., aerodynamic size 1–5 µm) are traditionally difficult to deliver in a deaggregated state to the lungs since interparticle adhesion forces, such as elecrostatic and van der Waals forces, promote particle–particle aggregation in the initial dry powder. To overcome such forces, inhalers can be designed to deliver sufficient power to overcome these interparticle forces and effectively disperse the particles for inhalation. A major advantage of large porous particles lies in the fact that they disperse far more easily than standard nonporous particles of similar aerodynamic diameter; thus they can be effectively dispersed even from relatively simple inhaler systems.

Losses of inhaled therapeutic can be attributed to a variety of factors; for example, inhaled aerosol particles must possess a very narrow range of ''aerodynamic diameters'' (related to a particle's geometric diameter and mass density) to pass through the filter of the mouth and throat. Even if properly designed and produced, aerosol particles may be propelled with too high a velocity and consequently deposited in the mouth and throat by inertia. Once in the lungs, particles must release the therapeutic substance at a desired rate and, in some cases, escape the lungs' natural clearance mechanisms until their therapeutic payload has been delivered.

To meet these challenges, new inhaler devices have been, and continue to be, developed. These fall in the categories of metered-dose inhalers, dry-powder inhalers, and nebulizers. When combined with optimized aerosol formulations, these new inhalers promise to significantly expand the use of inhalation therapy in humans[13].

ADVANTAGES OF LARGE AND POROUS AEROSOL PARTICLES

A new type of inhalation aerosol has recently been identified that may help to address limitations of the current inhalation therapies. This aerosol is formed by particles possessing low mass density and, consequently, large size, such that the particles'mean aerodynamic diameter fits into the window of 1–3 µm. The advantage of large size and low mass density is twofold: first, increased particle size results in decreased tendency to aggregate; hence, in combination with low mass density, this leads to more efficient aerosolization in a given air field; second, since phagocytosis of particles by macrophages diminishes with increasing particle size beyond ,2–3 µm, very large particles deposited in the pulmonary region may escape clearance by alveolar macrophages and, therefore, permit drug release for longer periods of time and more efficiently.

To clarify the potential for large and porous aerosols to increase systemic bioavailability as well as to provide sustained-release capability in the lungs, Edwards et al. [13] encapsulated insulin into a biodegradable copolymer commonly used in biodegradable sutures and in controlled-release, implantable or injectable depot systems [20]. Porous or hollow particles exhibit very different equivalent volume diameters from their aerodynamic diameters, in terms of density, as described by the Stokes equation. Particles can be made in the respirable aerodynamic diameter range, even as their geometric particle size is on the order of 20 µm [21]. We show that very light particles (ρ~0.4 g/cm) with d>5 µm can be deposited in the lungs. This offers some important advantages in the dispersion of these particles, due to the reduced van der Waals forces, which reduces their tendency to aggregate and makes them more responsive to shear in an airflow path. However, there is a limit to how much such an approach can be used, because the peripheral airways of the lungs are very small. Consequently, beyond a particular geometric size, penetration to the periphery would not be possible. In addition, low-density particles carry little mass in a unit volume. Therefore, the limits on dose delivery must be considered carefully. With these caveats, for potent, low-dose drugs these particles can be excellent delivery systems.

Large porous particles can be useful vehicles for the sustained delivery of drugs to the lungs. They can also be useful for delivery of drugs rapidly into the lungs or bloodstream, potentially at relatively high drug doses, for reasons described in the following section. Prepared in dry powder form, they can finally be designed to provide room-temperature stability. This breadth of potential carries with it formulation challenges that demand flexibility, particularly in terms of porous particle composition [16].

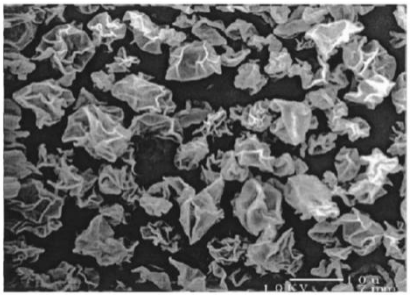

Fig 2: Scanning electron micrograph of large porous particles.

Large porous particles aerosolize more easily than small nonporous particles, in the absence of large pharmaceutically inert "carrier particles" and for the same drug loading per particle, consider the case of particles adhered by van der Waals attractive forces (similar arguments can be made for electrostatic interactions).

For two identical spherical particles of envelope or geometric diameter Dg and surface material density ρs, this attractive force is given by

$$F_a = \alpha \rho_s^2 D_g$$

Where

$$\alpha = \pi^2 C / 24 z^2 M_w^2,$$

With z the separation distance between the two particles and Mw the molecular weight of the atoms comprising the particles. That is, the force holding any two particles together increases proportionally with their diameter. In dry powder inhalers, the dispersive force (F_d) required to overcome F_a is provided by a linear air shear field, and grows proportionally with the square of distance between particle centers. For two powders of identical mass and identical density, dispersion of the powders will increase in ease with the inverse fourth power of the geometric diameter. Alternatively, for two powders of identical mass and identical aerodynamic diameter (but different geometric diameter), dispersion of the powders will increase in ease with the inverse square power of the geometric diameter.

PREPARATION LARGE POROUS PARTICLE

Large porous microspheres are usually prepared by double emulsion technique and spray drying.

- **Emulsion technology**: Here the polymer is dissolved together with the dissolved or suspended drug in a volatile organic solvent. The solution is then emulsified with an aqueous solution forming an oil-in-water (o/w) emulsion. Upon evaporation the volatile solvent is removed resulting in an aqueous suspension of microspheres. For a water-soluble drug the entrapment efficiency may be low due to the partitioning of drug to the continuous external aqueous phase during the evaporation process. Furthermore, the bioactivity of peptides and proteins is often reduced upon contact with organic solvents. The use of the double emulsion method results in a more favorable process for the entrapment of water soluble substances into microspheres. Briefly, the drug is initially dissolved in a small aqueous aliquot, which is subsequently emulsified with the organic PLGA solution forming a water-in-oil (w/o) emulsion. This emulsion is added to an aqueous solution followed by a second emulsification resulting in a w/o/w double-emulsion.

Using the double emulsion method for the entrapment of drugs into microspheres various process parameters will influence the properties of the prepared microspheres.

- **Spray drying technique**: The polymer is first dissolved in a suitable volatile organic solvent such as dichloromethane, Acetone, etc. The drug in the solid form is then dispersed in the polymer solution under high-speed homogenization. This dispersion is then atomized in a stream of hot air. The atomization leads to the formation of the small droplets or the fine mist from which the solvent evaporate instantaneously leading the formation of the microspheres in a suitable size range. Micro particles are separated from the hot air by means of the cyclone separator while the trace of solvent is removed by vacuum drying. One of the major advantages of process is feasibility of operation under aseptic conditions. This process is rapid and leads to the formation of porous micro particles [21].

CHARACTERIZATION

1) Particle size and size distribution

Particle size analyzers range from the historical sieve to modern automated light scattering instruments. The most appropriate selection for a particular application depends on a number of factors including the size range of interest, nature of the sample, the information required from the analysis, sample throughput, and price.[22] The particle size distribution is measured using laser diffraction particle size analyzer. The prepared microparticles are placed in a sample holding cell with stirrer so that the sample, diluted with distilled water (refractive index 1.33), were stirred to keep the sample in suspension while particle size is being measured. The polydispersity of the particles was expressed in terms of the SPAN index according to the following equation [23]:

$$\text{SPAN index} = \frac{D[v, 90] - D[v, 10]}{D[v, 50]}$$

2) Morphology and Surface topography

For morphology and surface topography, various techniques have been used like photon correlation spectroscopy (PCS), Scanning electron microscopy (SEM), transmission electron microscopy (TEM) etc. SEM is used widely, for which microparticles are coated with gold–palladium; platinum etc. under an argon atmosphere at room temperature and then the surface morphology is studied with the help of scanning beam of electrons [24, 25].

3) Particle flow properties

Powder densities are estimated by tapped density measurements. A known weight (150 mg) of microparticle are transferred to a graduated 1 ml syringe, and the initial volume is recorded. The syringe is tapped up to a volume plateau. Tapped density of the particles is calculated as the ratio between the sample weight (g) and the final volume (ml) occupied after tappings. The theoretical mass mean aerodynamic diameter ($MMAD_{th}$) of the particles was calculated using the equation:

$$MMAD_{th} = d\,(\rho/\rho_{\circ}X)^{1/2}$$

Where, d is the geometric mean diameter obtained from particle size analysis, ρ is the tapped density, $\rho_{\circ}$ is the reference density of 1 g/cm^3, and X is the shape factor, which equals to 1 for a sphere.

Furthermore, to obtain information about the microparticles' compressibility and flowability properties, the compressibility index (Carr's index) is estimated by calculating the relative percent difference between bulk and tapped density as stated by the US Pharmacopoeia:

$$\text{Carr's index} = \frac{(1-\rho_i)}{\rho} \times 100$$

where ρ and ρ_i are tapped and bulk densities of the powder, respectively. Based on reported values for Carr's index, powder flowability is defined as follows: 5–12% excellent; 12–18% good; 18–21% fair; 21–25% poor, fluid; 25–32% poor, cohesive; 32–38%, very poor; >40% extremely poor [26,27].

4) *In vitro* aerosolization study

Aerodynamic particles sizes of a particular size range (i.e., typically < 5 µm is usually referred to as the respirable dose). A variety of methods are available to characterize the particle size of the drug. They can be broadly categorized into two areas: Optical methods and inertial methods. A brief list of the optical methods includes: microscopy, Time-of-Flight, Laser Diffraction and Laser Doppler/Phase Doppler Anenometry . In general, the major weaknesses of these techniques are that they are not drug specific (is., unable to discriminate between drug particles and carrier particles if present) and in some cases, it is very difficult to characterize the delivered (ex-device) particle size in a simulated patient use testing regime. The majority of particle sizing methods acceptable to regulatory agencies are based on

inertial impaction and the most common systems are listed below:

1. Twin impinger (TI)

It operates on the principle of liquid impingement to divide the dose emitted from the inhaler into respirable and non-respirable portions. The non-respirable dose impacts on the oropharynx and is subsequently swallowed. This is considered as the back of the glass throat and the upper impingement chamber (collectively described as Stage 1). The remaining respirable dose penetrating the lungs is collected in the lower impingement chamber (Stage 2). The Glass Twin Impinger has been retained as Apparatus A in the European Pharmacopoeia, because of its value as a simple and inexpensive quality control tool.

Fig. 3: Twin Stage Impinger

2. Multi-Stage Liquid Impinger (MSLI)

The Multi-Stage Liquid Impinger (MSLI) is the apparatus 4 of USP. Whilst the 5-Stage MSLI does not offer the number of stages of the ACI or NGI, it does, by definition, have no inter-stage losses and is suitable throughout the range 30-100 L/min. Unlike the ACI and NGI, the collection stages of the MSLI are kept moist which eliminates the problem of particle bounce associated with conventional impactors.

Fig.4: Multistage liquid impinger

3. Cascade impactor

The human respiratory tract is an aerodynamic classifying system for airborne particles. Cascade impactors measure aerodynamic particle size which is a function of density and viscosity as well as the physical dimensions and shape of the particles concerned. This is important since it helps to explain how particles behave in a moving air stream (as exemplified by the respiratory tract) as opposed to simple "geometric" size.

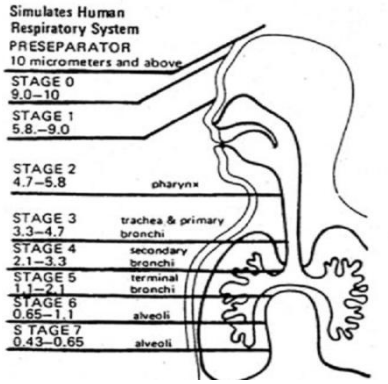

Fig.5 :Impactor sampler simulating Human Respiratory system

Cascade impactors differ from impingers in that the collection substrate is a solid surface, whereas, impingers use a liquid to collect the particles. One of the most common inertial methods used in the pharmaceutical industry is the Andersen cascade impactor. A representative Figure of cascade impactor is given below in **Fig. 6**

Fig. 6: Andersen Cascade Impactor(ACI) with Induction Port

Its popularity is based in part on the fact that it has 8 impaction stages with Effective Cut-Off Diameters (ECDs) between 10 and 0.7 µm, thus providing quantitation and resolution in the respirable aerodynamic particle size range.

Both the TI and MI do not provide any size distribution data and only give information on the mass of drug less than a particular aerodynamic particle size. For the TI, it is the mass of particles with ECDs less than 6.4 µm and for the MI it is the mass of particles with ECDs less than 9.8 µm[28].

	28.3 L/min	60 L/min	90 L/min
Stage -2	---	---	9.0
Stage -1	---	9.0	5.8
Stage -0	---	5.8	4.7
Stage 0	9.0	---	---
Stage 1	5.8	4.7	3.3
Stage 2	4.7	3.3	2.1
Stage 3	3.3	2.1	1.1
Stage 4	2.1	1.1	0.7
Stage 5	1.1	0.7	0.4
Stage 6	0.7	0.4	---
Stage 7	0.4	---	---

Table 1: Stage cut off diameter for each stage in Andersen Cascade Impactor (ACI) [29]

4. Next Generation Impactor

Next Generation Impactor (NGI), are recently launched in 2000. Both design and subsequent archival calibration are documented to pharmaceutical standards. The NGI is a high performance, precision, particle classifying cascade impactor having seven stages plus a micro-orifice collector (MOC).

Fig.7: Next Generation Impactor (NGI)

In practice, its flexibility of use and high productivity are making the NGI the new "workhorse" within many inhaler research

laboratories. This trend will no doubt continue as reproducibility and productivity are improved with the addition of new accessories designed to automate the particle sizing process. Correlation studies between ACI and NGI show good agreement between particle size distributions.

Flow rate (L/min)									
Stage	15	30	40	50	60	70	80	90	100
1	14.10	11.72	10.03	8.89	8.06	7.42	6.90	6.48	6.12
2	8.61	6.4	5.51	4.90	4.46	4.12	3.84	3.61	3.42
3	5.39	3.99	3.45	3.09	2.82	2.61	2.44	2.30	2.18
4	3.30	2.30	2.01	1.81	1.66	1.54	1.45	1,37	1.31
5	2.08	1.36	1.17	1.04	0.94	0.87	0.81	0.76	0.72
6	1.36	0.83	0.7	0.61	0.55	0.5	0.46	0.43	0.40
7	0.98	0.54	0.45	0.38	0.34	0.31	0.28	0.26	0.24

Table 2: Stage cut off diameter for Next generation Impactor (NGI) [30]

5) Measurement of the true density

The true density of the microspheres can be calculated through gas displacement using helium pycnometer. A weighted amount of microparticle is taken into the sample holder after calibration of the pycnometer using standard stainless steel spheres supplied by the manufacturer, and the volume of the helium gas displaced by the powder was measured giving the true (skeletal) density [31].

6) *In vitro* drug release studies: a reasonable approach for *in vitro* release study involves selecting a dissolution method in w hich the acceptable and unacceptable drug i nformation is distinguished by having different Dissolution rates. This study can be performed either by Franz diffusion cell (Maha Nasr et al.) [23] or simply in test tube using shaker (N. Celebi et al).

- Franz diffusion cell fitted with a cellulose acetate membrane to monitor the in vitro drug release. (Maha Nasr et al.). The receptor compartment contained 7.5 ml phosphate buffered saline pH 7.4 maintained at 37 °C by a circulating water jacket and constantly stirred at 150 rpm with a small magnetic bar. The quantity of RS released was determined using UV spectrophotometry.
- The microparticles are suspended in a test tube containing 10 ml of isotonic phosphate buffer solution, pH 7.4. The tubes are shaken in a shaker bath at 37°C. Samples were withdrawn at predetermined intervals. The drug content of each sample was assayed by UV spectroscopy. The release data can be evaluated kinetically using a computer program [32].

Regulatory and Market status

Many of the tests suggested by the regulators for ensuring the safety, quality and efficacy of orally inhaled drug products are common to all pharmaceutical dosage forms. The tests that specifically relate to these are- delivered dose uniformity (DDU) and aerodynamic particle size distribution (APSD) are universally accepted as key parameters in assessing performance. In vitro APSD data can give a broad indication of the likely in vivo deposition behaviour of the drug, with a size of 5µm or below being widely recognized as an approximate cut-off diameter for penetration into the lung. Regulatory

guidance recommends aerodynamic particle size measurement, using cascade impaction, for all orally inhaled drug products. These fractions are easily recovered from collection surfaces within the impactor for chemical analysis, allowing an APSD to be established specific to the API. A cascade impactor is not designed to simulate the lung; the deposition properties of which are extremely complex and difficult to replicate in vitro. The principal aim of cascade impaction is to obtain a relative measure of APSD for the emitted dose, rather than an absolute measure. Measurements ensure that the marketed product is similar to the product that was tested in the clinic, for which regulatory approval was obtained [33].

The ultimate responsibility for the safety, quality and efficacy of medicines and medical devices lies with the various national regulatory bodies designated to safeguard public health. In Europe and the US, this function is performed by the EMEA and FDA, respectively. The principal guidelines relating to orally inhaled drug products have been laid down by the EMEA [34-35] and FDA [36-40].

CONCLUSION

Whereas considerable work remains to clarify the potential of large porous aerosol formulations in humans with bioavailability. But the results to date suggest that such particle proves to provide efficiency gains and may play a major role in the development and optimization of new inhalation therapies in the future.

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