CHAPTER 2

REVIEW OF LITERATURES

2.1 The pulmonary system

The pulmonary system has an important function to exchange CO_2 and O_2 between bloods with the environmental atmosphere. The average pair of human lungs can hold about 6 liters of air. The respiratory tract can be divided into the upper (conducting zone) and lower (respiratory zone) respiratory airways. The conducting airways start from nasal or mouth cavity and the inhalation air stream bending about 90 degrees in the nasopharynx to enter larynx and trachea directly and then separate in two lobes with bronchus to the respiratory zone with bronchiole and alveoli (Figure 2.1). Oxygen transfers through alveolar walls to capillaries and carbon dioxide passes in the opposite direction. The 0.2 mm diameter of the alveolar wall produce more efficient at transferring oxygen and carbon dioxide while inspiration. In healthy human, there are estimated to be as many as 400 million alveolar sacs and the total surface area of the lung is about 75 m^2 (Taylor, 2002).

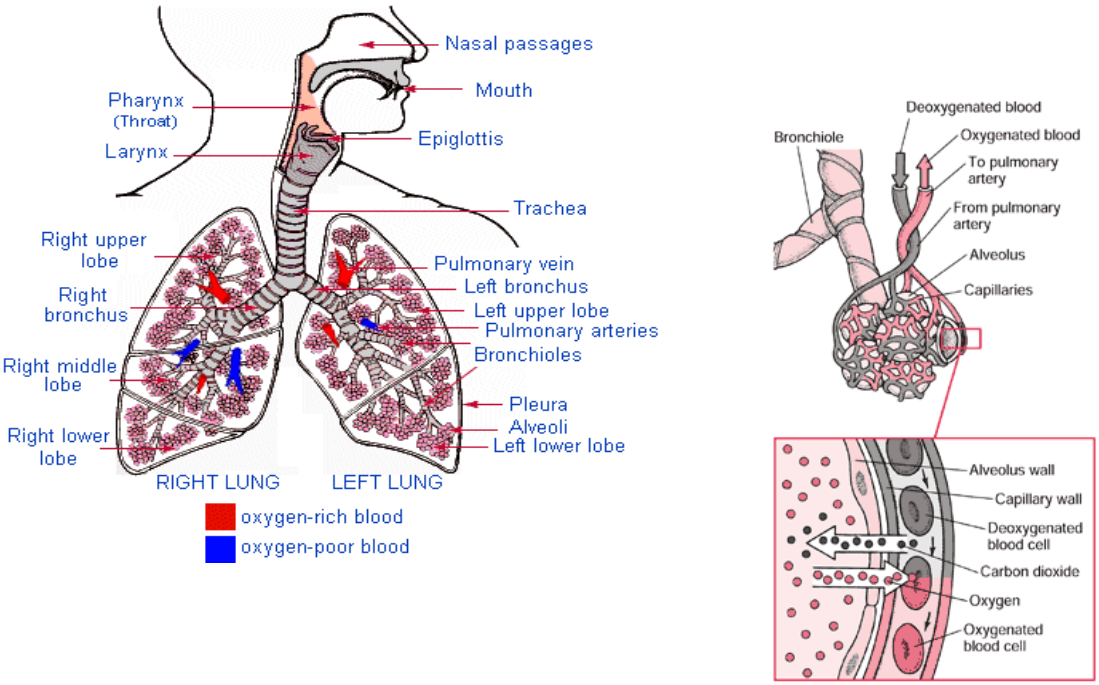
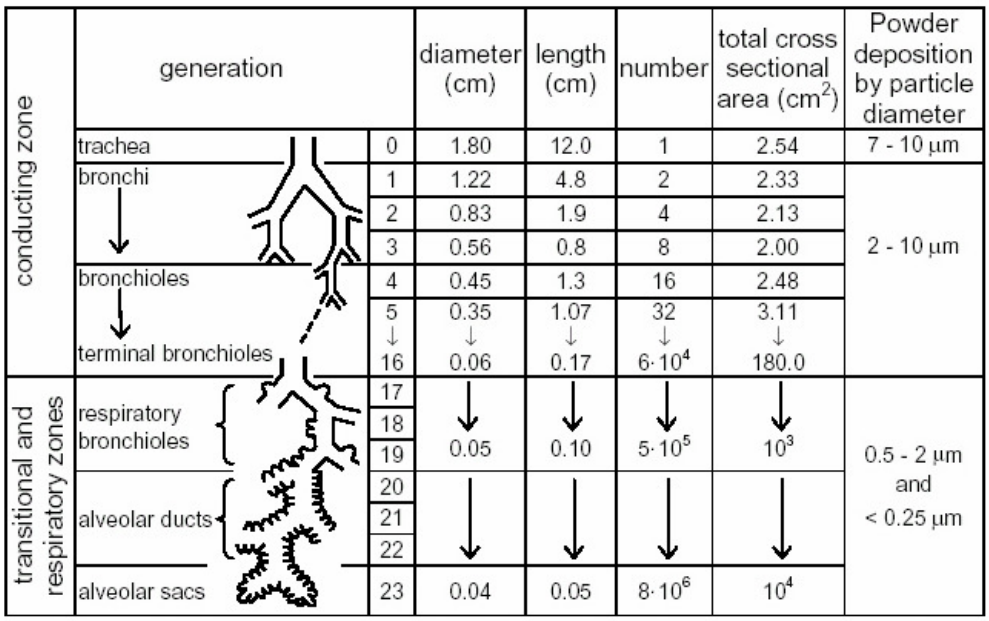


Figure 2.1 Respiratory and the Alveolar system

Physiological of the airway duct (Figure 2.2) shows reduction in diameter from conducting area to respiratory zone, related with reducing from the largest internal diameter that is about 1.8 cm in trachea to smallest diameter about 40 μm in alveolar sacs. Larger than 2 μm of the respired particles will retain at the upper respiratory tract and only below 2 μm particles can diffuse to the lower respiratory tract or into the deep lung. However, it is not possible to characterize fully aerosol deposition within the respiratory system by consider in only diameter dimension because in the lung there are more other factors affect to deposition performance like particle impaction, particle sedimentation, interception and electrostatic deposition (Hinds, 1982). Then, the deposition evaluation apparatus should have design closely to the mechanism that happened in the lung.



	generation		diameter (cm)	length (cm)	number	total cross sectional area (cm^2)	Powder deposition by particle diameter
conducting zone	trachea	0	1.80	12.0	1	2.54	7 - 10 μm
	bronchi	1	1.22	4.8	2	2.33	
		2	0.83	1.9	4	2.13	
		3	0.56	0.8	8	2.00	2 - 10 μm
	bronchioles	4	0.45	1.3	16	2.48	
	terminal bronchioles	5 ↓ 16	0.35 ↓ 0.06	1.07 ↓ 0.17	32 ↓ $6 \cdot 10^4$	3.11 ↓ 180.0	
transitional and respiratory zones	respiratory bronchioles	17	↓	↓	↓	↓	0.5 - 2 μm and < 0.25 μm
		18					
		19	0.05	0.10	$5 \cdot 10^5$	10^3	
	alveolar ducts	20	↓	↓	↓	↓	
		21					
		22					
	alveolar sacs	23	0.04	0.05	$8 \cdot 10^6$	10^4	

Figure 2.2 Physiology of the airways (Hickey and Thompson, 1992)

2.2 Inhalation therapy

Therapeutic aerosols are the most common delivery systems used for the treatment of respiratory diseases involving bronchospasm and airway inflammation from asthma or chronic obstructive pulmonary disease (COPD) (Chapman, 1996). Objective of this delivery pathway is to deliver bronchodilator such as β_2 agonist, sodium cromoglycate or corticosteroid to relieve bronchospasm and attenuate airway inflammation at target site (Howarth, 1997). Aerosol technology also currently uses to deliver high concentration antibiotics to the airway with low systemic bioavailability, thus reducing toxicity. With the development of devices that can target aerosol to the deep lung, the opportunity to deliver medications systemically by the aerosol route has become a reality. Insulin, recently approved in the US as aerosol therapy, and other peptides are systemically absorbed from the distal airways and alveoli (Pang *et*

al., 2005; Rubin, 2006). The advantages of this delivery pathway are such as not an invasion method, no pain, able to deliver large molecule like peptide or gene package. There is no first pass metabolism in gut lumen resulting that the aerosol technology is a prominent for systemic drug delivery system in a future.

2.3 Dry powder inhaler technology

The concept of dry powder inhaler (DPI) technology is a transportation of drug to pulmonary system by use of self breathing of patients aimed to provide: accelerated release of drug from the container and fine particle of dry powder drug to the deep lung. This method was founded in 1967 to transport sodium cromoglycate powder for treatment asthma (Smith and Parry, 2002).

The advantages of this technique are; small amount of active compound, less in systemic side effect compared to oral route, increase in efficacy by avoiding first pass metabolism in the liver, simple to operate when compared with pMDI and no need of propellant (Freon compound). Today this administration technique is admired in major target drug delivery system for treatment the pulmonary disease and plays a role as novel pathway of drug delivery to the systemic system.

Commonly, the degree of drug deposition performance depends upon the forces of interaction within the powder formulation and the mechanical forces of dispersion from the device and patient's inspiration effort (Louey *et al*., 2003).

2.4 Factors affecting DPI performance

2.4.1 Formulation factors

From physiology of the pulmonary system, drug deposition will be related to pulmonary physiology. In general, appropriate particle size should be in range of 0.5-5 μm. While using fine particle of drug, it will produce more surface free energy. Drug aerosol particles will attach firmly to surface they contact and form agglomerates by the cohesive force (Hinds, 1982). This is called drug-drug aggregates formulation.

While the drug-drug agglomerates formulation is difficult to generate the aerosol particles release. Filled with appropriate size of coarser carrier particle about 35 μm will form weak adhesive force (Figure 2.3), resulted in improve percentage of fine drug particle by reducing the force needed to deagglomerate drug particle and improve uniformity of the dosage form (Broadhead *et al*., 1995). This is called drug-carrier aggregates formulation (Figure 2.4).

Sometimes fine particles of the ternary component (eg. leucine, lecithin or magnesium stearate) are used to adjust the interfacial properties of the carrier particles. It decreases forming drug-carrier adhesion force leading to produce more % fine particle fraction of drug (Begat *et al*., 2005).

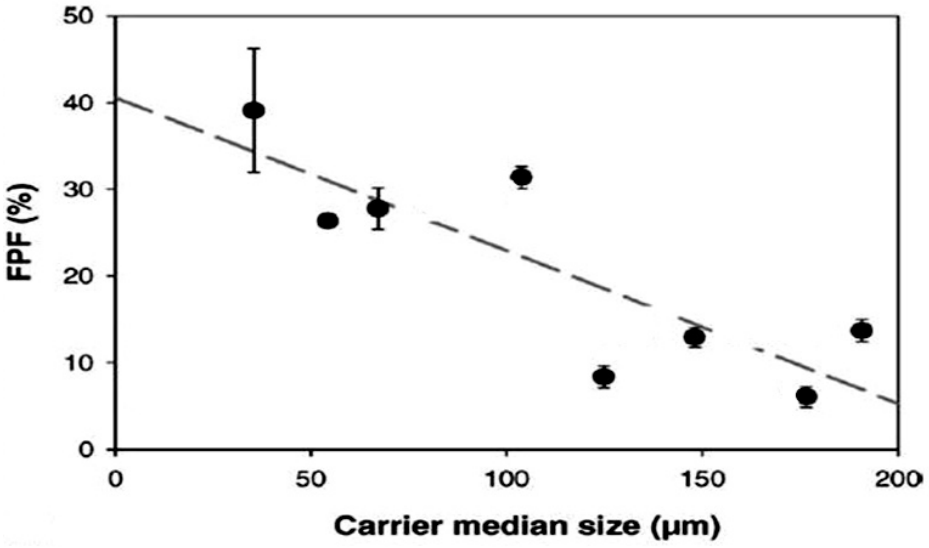
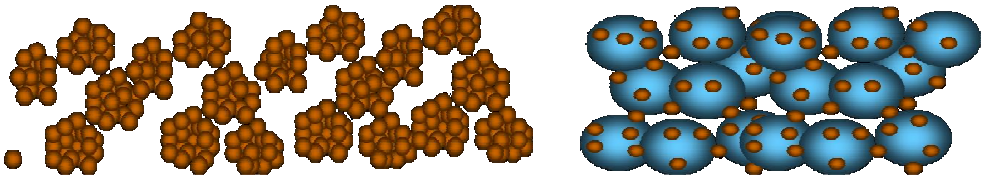
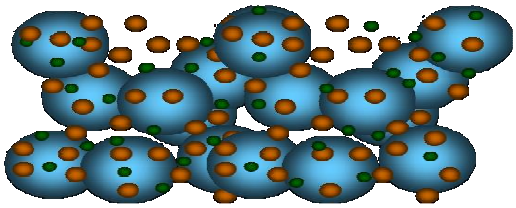


Figure 2.3 Relationship between the %FPF (mean ± S.D., n = 5) and the carrier median diameter (adapted from Louey *et al*., 2003)



(a) (b)



(c)

Figure 2.4 Interaction between particles drug-drug aggregates (a), drug-carrier aggregates (b), drug-carrier aggregates with “ternary component” that shown in small dark particles (c).

To conclude, the important factors in the formulation are cohesive and adhesive forces. To improve deposition to deep lung, fine drug particles must be generated by reducing cohesive force and forming a weak adhesive force as shown in Figure 2.5. The small drug particles have high of

surface cohesive force and form self aggregates result to larger particle and hard to deagglomerate. The method to decrease cohesive force is to produce weak adhesive force between drug-carrier particles by filled with coarser carrier particles, bind on surface of the coarse lactose particle by adhered with micronized carrier particle (Louey *et al*., 2003), reduce carrier roughness by surface treatment of the carrier particle (Flament *et al*., 2004) and/or filled with other exipients.

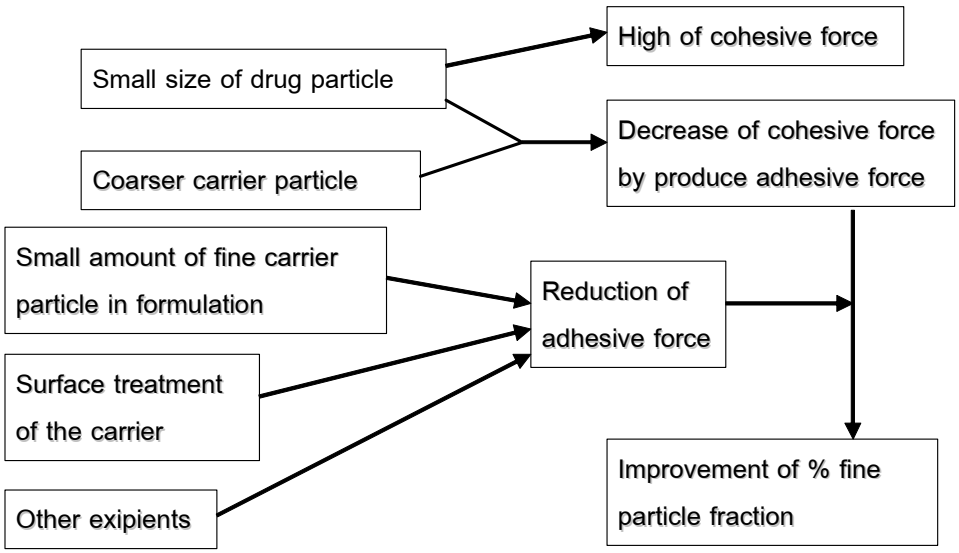


Figure 2.5 Methodology in reducing cohesive force and forming a weak adhesive force

2.4.2 Device factors

All DPIs have four basic features to release drug particles from the device: (1) a dose-metering mechanism, (2) an aerosolization mechanism, (3) a deaggregation mechanism, and (4) an adaptor to direct the aerosol into a patient's mouth. Drug particles are theoretically stripped from the surface of the lactose particles, to which they are loosely attached, during the generation process. This process is illustrated schematically in Figure 2.6. Thus, the drug particles are dispersed and can traverse the upper respiratory tract while the

excipient particles do not pass beyond the mouth-piece of the device or the mouth and throat of the patient (Dalby and Tiano, 1996).

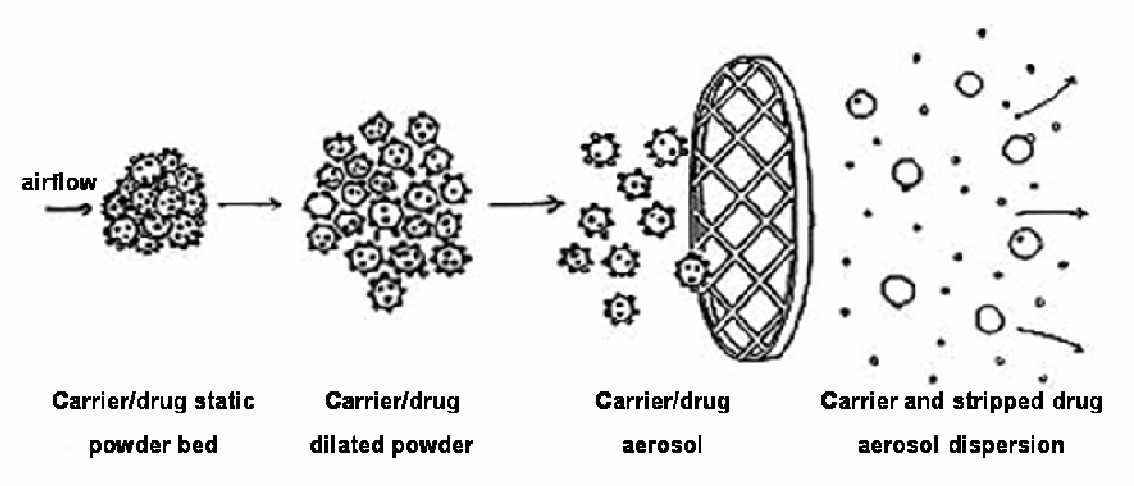


Figure 2.6 Mechanism of drug release from dry powder inhaler (Dalby and Tiano, 1996)

Device design is a crucial factor for DPI delivery performance. In common, device must be able to generate force that de-agglomerates particles to generate fine drug particles (deaggregation mechanism). The concepts on how the powder interacts with the device during dispersion are generally scoped into 3 types of impaction. Air turbulence and mechanical impaction (particle–particle, particle–device surface) are generally accepted as mechanisms controlling powder dispersion in the device (Figure 2.7). As a result, fine drug particles are generated and delivered to the deep lung.

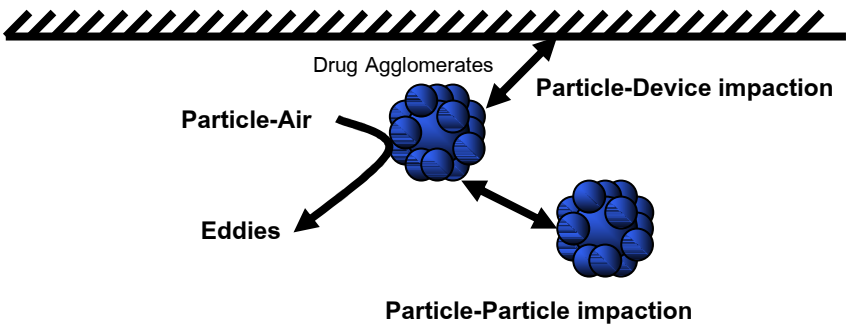


Figure 2.7 Mechanisms for dispersion of powder as aerosol inside an inhaler

Interesting impacting resulted from device design is the device resistance (Figure 2.8). Device resistance is related with breathing force. High device resistance requires high patient's effort which is directly affected patient's operating flow-rate. However, high device resistance provide high degree of turbulence air-flow inside the device, which can increase device performance. In conclusion, the device should balance between optimal resistance and optimal turbulence air-flow (Srichana, et al., 1998).

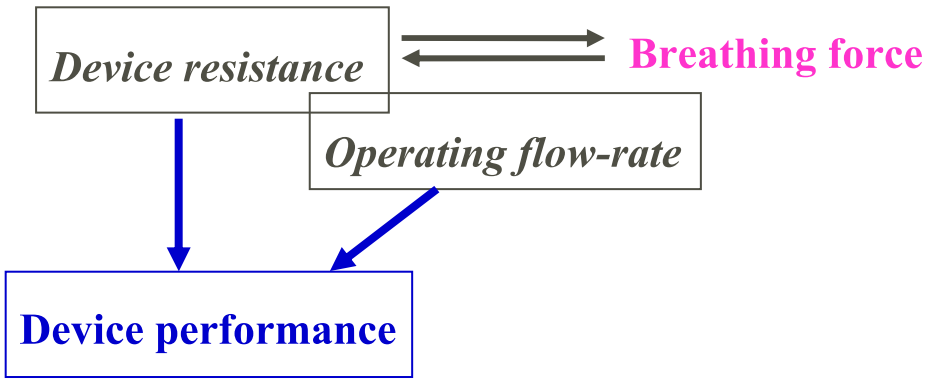


Figure 2.8 Relationship between device resistance, breathing force and device

For present competition dry powder inhaler in the market today, every company must improve their product design to gain customer satisfaction

in addition to drug delivery performance. There are list of possible requirements for an ideal DPI as summarized in Table 2.1.

Table 2.1 Characteristics required from an ideal dry powder inhaler (Ashurst, *et al*., 2000)

Effective dosing	**Efficient device**	**Easy to use**
● Uniform dose through life	● Good environmental protection	● Simple operation
● Targeted and optimized delivery	● In-process controls for quality	● Dose counter
- Controlled respirable fraction	● Compact, portable, cheap and/or reusable	● Dose-ready indicator
- Inhalation of dose-independent aerosol generation	● Clear comparative data for compliance	● Patient feedback of dose administration
- Bolus of aerosol available at the beginning of an inhalation		
● Operable at low inhalation flow rates		

2.5 Commercial DPI device design at present

Dry powder inhaler devices can be classified into 3 types from drug dosing as shown in Table 2.2. The single unit dose and multiple unit dose devices are factory metered dose whereas the multidose is immediately metered after use. The advantages are each unit dose have environmental protection by in-process control during factory dispensing and all of single unit dose or some multiple unit dose device can be reusable. The disadvantage of the unit dose is patient either needs to carry separated reservoir or that device is importable

device. The multidose devices provide the ease of operation and portable compare with unit dose system but the devices cannot be cleaned and reusable.

Table 2.2 Breath-driven dry powder inhalers that are currently marketed

Single unit Dose	**Multiple unit dose**	**Multidose patient/device-metered**
Cyclohaler/ Aerolizer	Diskhaler	Clickhaler
Flowcaps	Diskus/Accuhaler	Easyhaler
Inhalator/ Aerohaler		Pulvinal
Rotahaler		Turbohaler
Spinhaler		Ultrahaler

Because commercial DPI devices at present have different structures and delivery mechanisms. The main objective of device design is to optimize device resistance that patients can inspire while produce good turbulence air-flow inside device. Some mechanisms produce turbulence air-flow in present commercial devices are shown as following.

1. Mechanism of drug release is started by a separation of body from a cap of the capsule. The release of drug from a spinning capsule will raise particle impaction and pass through crucial grating after patient inhale through the Rotahaler device by GlaxoSmithKline, UK as shown in Figure 2.9.

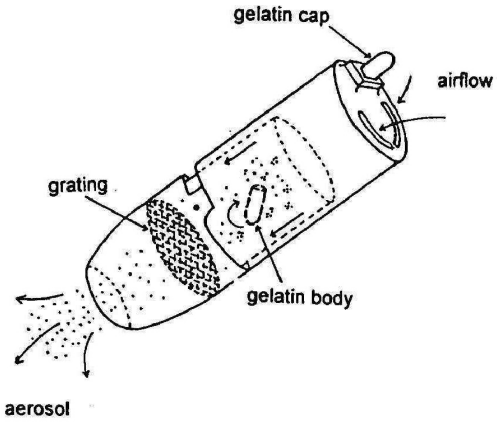


Figure 2.9 Rotahaler (Dalby *et al*, 1996)

2. Crucifix grating is used to trap and breakup particles inside the device. Turbulance air flow was generated as shown in Figure 2.10. This concept is used solely or apply with other techniques for improving drug delivery performance. These devices are Rotahaler, Diskhaler, Diskus (Accuhaler) by GlaxoSmithKline, UK and Inhalator by Boehringer Ingelheim (Figure 2.10).

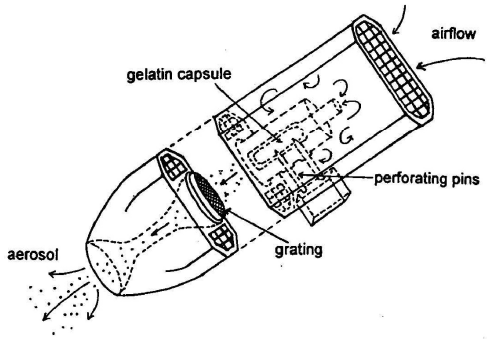


Figure 2.10 Inhalator Ingelheim (Dalby *et al*, 1996)

3. The Spinhaler by Aventis, France. The capsule containing drug is fixed with impeller axis will be bored with small pins. When patient inhales, the impeller with capsule will rotate to produce fine particle from agglomerate particle and release content from the capsule as shown in Figure 2.11.

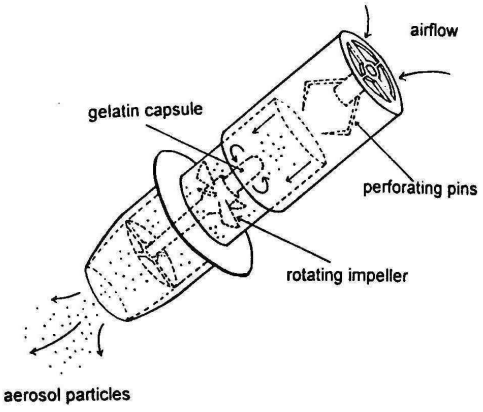


Figure 2.11 Spinhaler (Dalby *et al*, 1996)

4. Tubuhaler is a cylindrical, multi-dose dry powder inhaler device. The dosing is achieved by twisting the turning grip back and forth followed by deep inhalation. It contains 200 metered doses and is equipped with a dosage indicator window. The interesting is the numbered of spiral chancels in device that can produce good fine particle of drug even in drug-drug aggregate formulation as shown in Figure 2.12.

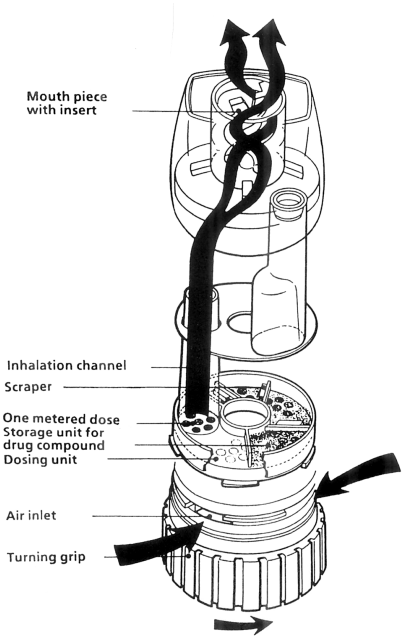


Figure 2.12 Turbuhaler (Hannemann, *et al*., 1999)

5. Recently, Directhalor uses the concept of curved shape and more fold tube to produce more turbulence air flow as shown in Figure 2.13.

Figure 2.13 Directhaler (Keldmann, 2004)

2.6 Drug deposition evaluation

Because there are 4 basic mechanisms of drug release from the inhaler device. Then, differences in device design is an important factor affecting to dry powder inhaler performance and must be evaluated.

2.6.1 The in vivo assessment technique

The in vivo assessment technique commonly measures in human volunteers. There are 2 common techniques include pharmacokinetic-pharmacodynamic measurement and gamma scintigraphy.

Pharmacokinetic data (plasma and urine levels) and pharmacodynamic data (eg. Pharmacological response heart rate or blood pressure) are sometimes used to infer the delivery of asthma medications to the lungs (Kempsford *et al*., 2005). The fact is only classical bioequivalence testing based upon equal rates and extents of drug absorption, therefore is inappropriate for showing equivalence of products containing inhaled asthma drugs, which act directly on the airway surface (Fuller *et al*., 1995; Ball *et al*., 2002). Further, this technique needs to be validated and is probably applicable only to a limited range of pharmaceuticals.

Another in vivo assessment method is the non-invasive imaging technique such as gamma scintigraphy. A method of wide application to radiolabelling dry powders is by adsorbing the radiolabel on the active particles in a suitable liquid. This is achieved by wetting the drug particles with a nonsolvent containing the radiolabel, followed by the evaporation of the solvent, leaving the radiolabel on the surface of the drug particles. This method gives a measure of local bioavailability at the site of action in the lungs, and lung deposition data are strongly correlated with clinical response to inhaled asthma drugs. For assessing the equivalence of inhaled asthma medications, gamma

scintigraphy determines in vivo drug delivery more precisely than in vitro testing, and is more incisive than clinical response studies (Newman and Wilding, 1998). However, all of the in vivo assessment techniques are not easy to monitor in product development processes which need much comparing repeated samples. Therefore the in vitro assessment is still necessary.

2.6.2 The in vitro assessment technique

To evaluate dry powder inhaler deposition performance in vitro, there are 2 common techniques namely; Andersen Cascade Impactor (ACI) which was approved by BP and the USP. Another technique uses Twin Stage Impinger (TSI) which is official in the BP (Figure 2.14).

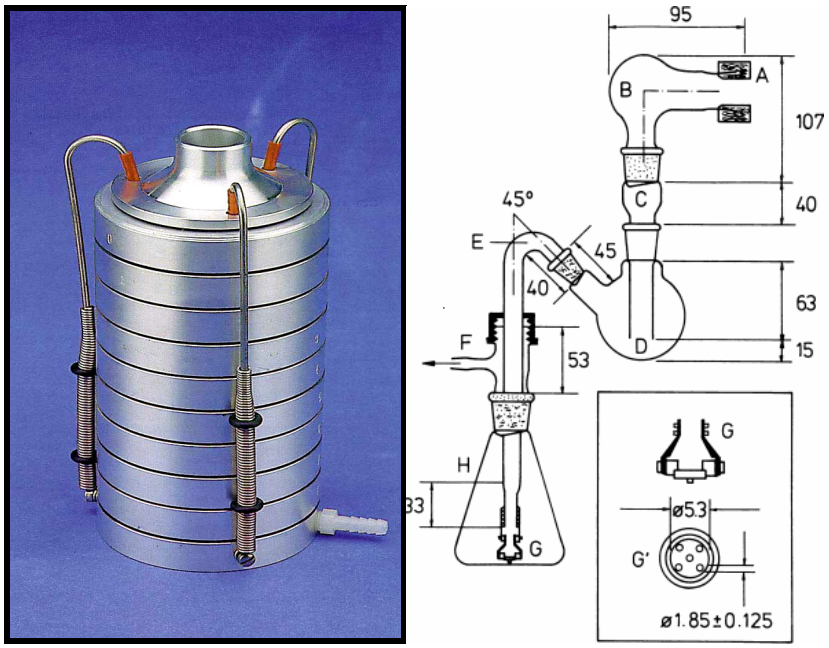


Figure 2.14 Andersen Cascade Impactor (left) and Twin Stage Impinger (right) Dimensions in mm

The TSI is a two stage impinger that uses liquid at first stage and lower stage to capture aerosol material while air drawn through the instrument. Even TSI method is ease of operation than ACI method but limitations arise the fact that the TSI divides the total spray just into only two compartments. Hence, this method cannot discriminate between distributions with specific combinations of size range and cannot precisely predictable when operating out of designed flow rate (Broadhead *et al*, 1995; Geun *et al*., 1997). The data derived from the TSI are intended to differentiate only good or bad formulations as determined by FPF (particle size < 6.4 μm). This device is suitable for quality control of aerosol products (Snell and Ganderton, 1998).

The ACI is a multistage and multi-orifice cascade impactor. The concept of the ACI was evolved on the basis that the human respiratory tract represents an aerodynamic classifying system for airborne particulates. The ACI is comprised of eight aluminium stages which are held together by three spring clamps with o-ring seals. Each impactor stage contains multiple precision orifices that when air is drawn through the sampler, any airborne particles with high momentum were bring toward to impact with the collection plate for each stage and those with low momentum adjust to a new direction of flow and pass around the obstruction as shown in Figure 2.15 (Hickey *et al*., 1996).

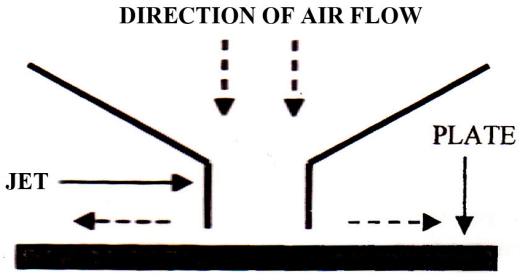


Figure 2.15 General principle of inertial sampling through a jet onto a collection plate

Table 2.3 presents the orifices are progressively smaller from top to bottom stages, ranging from 0.1004 inch diameter diameter on stage 0 to 0.0100 inch diameter on stage 7. When operated at 28.3 L min^{-1}, the jet velocity was used to calculate the jet Reynolds number. The range of particle sizes collected on each stage depends on the jet velocity of that stage and the cut-off diameter of previous stage. Finally, the collected particles on each stage that related with aerodynamic dimension should be used to predict human lung airborne particles deposition (USP 2002).

Table 2.3 The jet dimensions for each stage and ACI (Mark II) parameters operating at 28.3 L min^{-1} (Adapted from Andersen Sampler, 1985 and Vaughan, 1989)

Stage	**Orifice diameter (inches)**	**Number of orifices**	**Jet velocity (cm/s)**	**Re_j**
0	0.1004	96	96.3	163.7
1	0.0743	96	175.8	221.2
2	0.0360	400	179.8	109.6
3	0.0280	400	297.2	140.9
4	0.0210	400	528.9	187.9
5	0.0135	400	1277.0	292.0
6	0.0100	400	2328.8	394.3
7	0.0100	201	4618.1	782.0
F	0.1100	Filter		

Every in vitro assessment techniques must be validated. The performance of inhaler device was reported as % Fine Particle Fraction (%FPF) and Median Mass Aerodynamic Diameter (MMAD).

2.7 Balance of device resistances and degree of turbulence

Amongst inhalers, dry powder inhalers (DPIs) play a major role in aerosol delivery to humans. However, due to the complexity of peripheral airways, lungs and physical mechanisms governing aerosol delivery, the development of this kind of devices and associated powder formulations remains mainly empirical.

A measure of aerosol delivery efficiency is often produced in laboratory (in vitro) testing employing apparatus especially designed for the aerodynamic assessment of fine particles by inertial impaction (e.g., the TSI or the ACI). In addition, it is assumed that the delivery efficiency is significantly determined by the fine particle fraction in the aerosol (Prime *et al*., 1997). This fraction shows the highest probability of depositing in the lower airways, a process which depends on numerous variables including the characteristics of the powder formulation and the specific features of the inhaler device (de Boer *et al*., 1996; van der Palen, 2003).

The inhaler device produces a pressure drop as the air passes through it. The pressure drop is defined as the difference between the values of static pressure measured at two points in a system. A higher flow resistance leads to a larger pressure drop and ultimately produces a lower flow rate, for the same inhalation effort. However, a higher pressure drop in the device, resulting from narrow passage areas for the air flow, may also present a beneficial effect on the generation of fine particles (Srichana, *et al*., 1998) due to larger shear

stresses acting on the particles and/or higher local turbulence, which, in turn, leads to a better de-agglomeration of the powders. As a consequence, the inhalation of smaller-size individual particles, which is ready to reach the lungs, is promoted. The contradictory was observed that the decrease in inlet mouthpiece resulted in increase particles velocity release from device. This caused a drug loss via inertial impaction as shown in Figure 2.16 (DeHaan and Finlay, 2004).

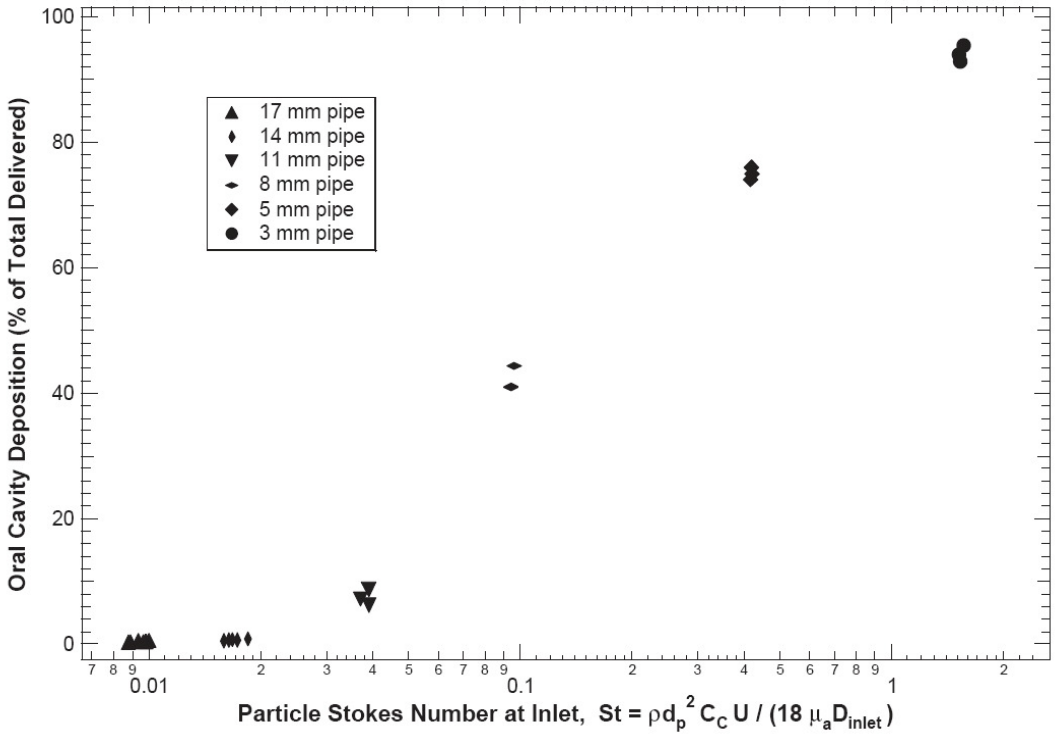


Figure 2.16 Oral cavity deposition for a 5 μm diameter aerosol at 32 L min^{-1} entering through various diameter straight tube inlets (DeHaan and Finlay, 2004)

Thus, decreasing device inlet mouthpiece diameter may be useful to produce high turbulence air-flow through device. However, it should be aware that it may cause a drug loss in oral cavity via inertial impaction.