The articles in this series are independently researched and compiled by PSA commissioned authors and peer reviewed.

Pulmonary drug delivery

By Dr Christopher McConville

Continuing Professional Development

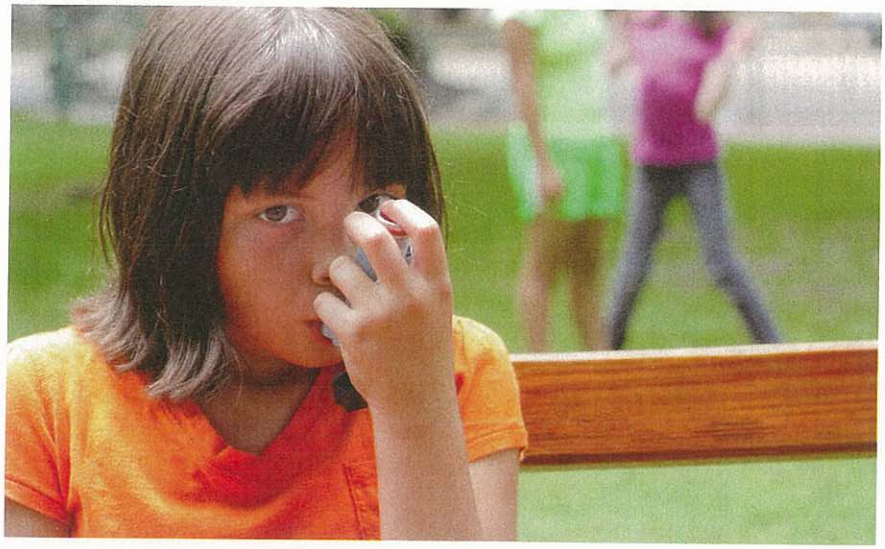
Learning objectives

After reading this article you should be able to:

- Describe the effect of formulation parameters, particularly particle size
- Discuss the effect of delivery device on the effectiveness and deposition of drugs delivered by the pulmonary route
- Discuss the advantages and disadvantages of pulmonary drug delivery compared to other routes of administration.

Competency standards (2010) addressed: 7.1.2

Accreditation number: CAP110303g



The respiratory system

The respiratory system is divided into two main regions – the upper and lower respiratory tract. The upper respiratory tract includes the mouth, nose and nasal cavity, pharynx and larynx. The lower respiratory tract includes the trachea, bronchi, bronchioles and alveoli (Figure 1).

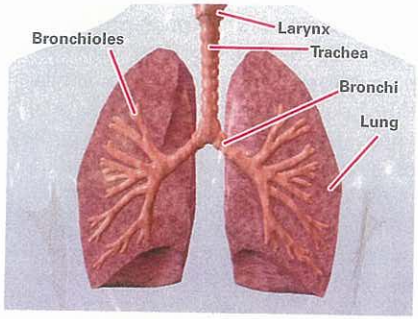
The breathing process occurs when the diaphragm moves down, drawing air in through the mouth and nose where it is heated, filtered and moistened. The air then passes the pharynx and larynx and enters into the trachea, where tiny hairs called cilia catch any dust particles in the air. These dust particles are then removed from the body through the process of coughing. The trachea then divides into two tubes called bronchi, with one entering the left lung and the other entering the right lung. Inside the lung the bronchi split into several tertiary bronchi, which further divide into the bronchioles (very narrow tubes of less than 1 mm in diameter that lead to the alveoli). The alveoli are contained within the alveolar sacs. The alveoli have very thin membranes which allow for the oxygen to be removed from the air and transferred to the blood stream where it is transported around the body, and for carbon dioxide (produced in the body) to be removed from the blood back up through the respiratory system and out the mouth and nose. This process is known as the exchange of gases.

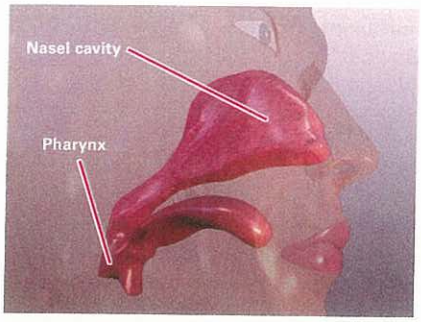
Pulmonary drug delivery

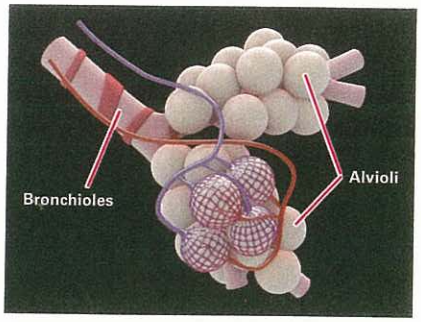
The history of drug inhalation dates back as far as the Egyptians, who inhaled substances for ritual or healing purposes. Pulmonary drug delivery has been used for many years in the treatment of lung diseases, such as asthma and chronic obstructive pulmonary diseases, and is regarded as the optimal route of administration for drugs used to treat such diseases. Pulmonary drug delivery has also been investigated as a possible route of administration for drugs that act

Dr Christopher McConville *is Senior Lecturer in Pharmaceutics, School of Pharmacy, Curtin University.*

Figure 1. Schematic diagram of the respiratory tract







systemically, rather than locally in the lungs. The driving force behind this was the observation that peptides and proteins could be absorbed systemically when delivered via the lungs. This has led to the development of new ways of delivering drugs such as morphine, sildenafil and triptans.[1,2] The development of inhalation devices that allow for the delivery of larger doses (milligrams compared to micrograms) while improving the deposition efficiency to the lungs have also helped to enhance research into systemic drug delivery via pulmonary administration.[3]

In order for drugs which are to be delivered to the lungs or use the lungs as a route of systemic administration to be therapeutically effective, the appropriate amount of drug must be delivered past the oropharynx, which lies just behind the oral cavity. Furthermore, the site of deposition and the distribution of the inhaled drug will also have considerable influence on its therapeutic effectiveness. The particle size of the aerosol has a major influence on the location of drug deposition and the mechanisms of deposition.[4,5] Therefore the formulation should retain a defined aerosol particle size when delivered to the lungs, which is achieved by the nature of the various delivery devices available.[6–10]

Drug deposition and particle size

Deposition can occur by impaction, gravitational sedimentation or diffusion (Brownian motion) depending on the size of the particle. Deposition by impaction tends to occur in the upper respiratory tract where the air velocity is high and the airflow is turbulent.[11] Particles with an aerodynamic diameter greater than 10 µm tend to be deposited by impaction in the upper respiratory tract, especially if the device used for delivery requires a high inhalation flow rate (such as dry powder inhalers) or the device has a high forward velocity (such as metered dose inhalers).[12,13] These larger particles are subsequently swallowed but have limited contribution to the therapeutic effect of the dose. Deposition by impaction will also occur with smaller particles in the trachea due to the bends where it divides into the bronchi. Particles with an aerodynamic diameter less than 10 µm tend to deposit in the lower respiratory tract by gravitational sedimentation due the lower air velocity.[11] Particles with an aerodynamic diameter less than 1 µm tend to reach the alveoli where the air velocity is negligible, thus deposition by impaction does not occur. Particles in the alveoli tend to have a longer residence time, with deposition occurring by gravitational sedimentation and diffusion. Gravitational sedimentation tends to occur with particles above 0.5 mm, while diffusion occurs with particles below 0.5 mm. Due to the low inertia of these small particles, any that have not been deposited upon inhalation tend to be exhaled, sometimes as much as 80%.[14,15] Deposition by impaction and gravitational sedimentation can be effected by the breath pattern used. For example slow inhalation and holding your breath can improve deposition into deeper airways.[4]

Targeting of the drug to a particular area of the lung can be achieved by varying the particle size of the aerosol and also the inhalation flow rate. However, this second option may be difficult to control since breathing patterns differ among patients. Aerosols containing particles with an aerodynamic diameter between 5 and 10 µm tend to be deposited in the upper respiratory tract while those that contain particles with an aerodynamic diameter between 1 and 5 µm tend to be deposited in the lower respiratory tract. Where systemic absorption is required, particles with a small aerodynamic diameter would be best to ensure the drug is carried to the alveoli where it can diffuse into the blood stream.[16]

The effect of delivery device on pulmonary drug delivery

Inhalation devices for pulmonary drug delivery can be divided into three main categories:

1. nebulisers;
2. metered dose inhalers; and
3. dry powder inhalers.

Nebulisers

Nebulisers have been around for many years and can be further divided into two groups: jet nebulisers and ultrasonic nebulisers. Jet nebulisers work using the Bernoulli principle, where compressed air (or oxygen) carries a liquid medicine through a narrow hole at high velocity turning it into an aerosol which is subsequently inhaled by the patient. The ultrasonic nebuliser works when an electronic oscillator generates an ultrasonic wave which vibrates a piezoelectric element at high frequency. The piezoelectric element is in contact with a liquid medication and its high frequency vibrating converts the liquid into a vapour mist. The higher the frequency of vibration, the smaller the vapour droplets.

The majority of nebulisers can aerosolise most drug solutions and allow for the delivery of large doses,

The articles in this series are independently researched and compiled by PSA commissioned authors and peer reviewed.

with limited skill or training required by the patient. However, nebulisers are expensive, time consuming and inefficient with a lot of drug wastage. The majority of the drug never reaches the lungs, with most of it either retained within the nebuliser (dead volume) or released into the environment.[17] Approximately 10% of the dose from a nebuliser actually reaches the lungs.[17] Furthermore, the physical properties of the liquid formulations, such as surface tension, viscosity, osmolarity, pH and ionic strength, can affect the efficiency of the nebuliser. For example a hyper or hypo osmolar liquid formulation or a low pH liquid formulation can irritate the respiratory tract resulting in coughing, which would remove some of the drug from the lungs.[18,19] The development of vibrating mesh technology (VMT), where a mesh with thousands of laser drilled holes is placed on top of the liquid formulation resulting in very fine droplets being formed, has improved the efficiency of nebulisers and resulted in shorter treatment times.

Metered dose inhalers

Metered dose inhalers (MDIs) use a propellant gas such as hydrofluroalkanes (HFA) to drive a liquid formulation through a narrow nozzle at high velocity. MDIs are portable, compact, inexpensive and can facilitate multiple and reproducible dosing, while providing a sealed environment which improves drug stability upon storage. However, MDIs are only capable of delivering approximately 10 to 20% of the medicated dose into the lungs.[20] 50 to 80% of the dose is deposited in the upper respiratory tract due to the high velocity and large aerodynamic diameter of the particles.[21] Furthermore, a patient's breathing and hand-to-mouth coordination can significantly affect the efficiency of MDIs. The development of spacer tubes, valved holding chambers and various mouth extensions have improved the efficiency of MDIs by eliminating coordination requirements and reducing the amount of drug deposited in the upper respiratory tract, through reducing both the velocity and size of the particles.[22,23]

Dry powder inhalers

Dry powder inhalers (DPIs) deliver the medication in the form of a dry powder, and were developed to overcome the coordination issues associated with MDIs. Air is forced through a powder containing the drug, a carrier powder (e.g. lactose) and other stabilising excipients. Turbulent air created inside the powder container breaks down (deaggregates) the large particles into smaller particles capable of penetrating into the lungs, while removing the drug from the carrier powder.[24] There are currently a wide range of DPIs available, from single dose devices (e.g. *Aerolizer* and *Rotahaler*) where the patient loads the dose into the inhaler, to multidose devices where multiple doses are sealed in blisters on a blister strip which moves through the inhaler each time a dose is delivered (e.g. *Diskhaler*). There are also reservoir, bulk powder DPIs available (e.g. *Turbuhaler*). The deposition of drug in the lung varies significantly depending on the type of DPI used. Between 12% and 40% of the dose is deposited in the lungs with 20% to 25% being retained in the DPI,[25–27] caused by poor deaggregation of the smaller drug particles from the larger carrier lactose particles. The efficiency of drug delivery to the lungs by DPIs is significantly affected by changes in storage conditions such as humidity and temperature.[28,29] DPIs rely on sufficient patient inhalation flow rates to break up the powder aggregates; therefore a low inhalation flow rate could result in poor powder deaggregation leading to reduced dose delivery and ultimately poor device performance. Attempts have been made to improve the efficiency of DPIs and remove the issue of a patient's inhalation flow rate by adding a battery-driven propeller to help disperse the powder (e.g. *Spiros inhaler*) or by developing DPIs that have a minimum inhalation flow rate requirement before they release the dose. Despite these issues, DPIs have the advantage of being compact, portable and easy to use as well as having no reliance on good hand-to-mouth coordination.

Why use pulmonary drug delivery?

For the local treatment of various lung diseases such as asthma, cystic fibrosis and bronchitis, pulmonary drug delivery allows the administration of high concentrations of drugs directly to the site of action, thus minimising the side effects of systemic administration while providing a rapid effect. Furthermore, it improves therapeutic efficacy by by-passing the hepatic first pass metabolism of the liver as well as the poor absorption of the intestines that is associated with oral drug delivery, thus allowing for similar therapeutic effect from a smaller dose. For systemic administration, pulmonary drug delivery offers a non-invasive method of delivery with low enzyme activity and no hepatic first pass effect suitable for small and macromolecular drugs.[30–32] Macromolecules delivered by other non-invasive routes are rarely absorbed into the systemic circulatory system;[9,32–34] those delivered via the lungs are readily absorbed. The bioavailability of macromolecules delivered via the lungs is relatively low; the large surface area of the lungs and access to the arterial blood supply may compensate for this. As pulmonary drug delivery avoids the gastrointestinal tract reproducible absorption kinetics are achieved due to the lack of interference from the variation in an individual patient's diet and metabolism.[31]

References

1. Krajnik M, Podolec Z, Siekierka M, et al. Morphine inhalation by cancer patients: a comparison of different nebulization techniques using pharmacokinetic, spirometric, and gasometric parameters. J Pain Sympt Manage. 2009; 38:747–57.
2. Watts AB, McConville JT, et al. Current therapies and technological advances in aqueous aerosol drug delivery. Drug Develop Indust Pharm. 2008; 34:913–22.
3. Dolovich M. New propellant-free technologies under investigation. J Aerosol Med. 1999; 12:9–17.
4. Courrier H, Butz N, Vandamen TF. Pulmonary drug delivery systems: recent developments and prospects. Crit Rev Ther Drug Carrier Syst. 2002; 19:425–98.
5. Yang W, Peters IJ, Williams III RO. Inhaled nanoparticles – A current review. Int J Pharm. 2008; 356:239–47.
6. Mason RJ. Biology of alveolar type II cells. Respirology. 2006; 11:12–5.
7. Bailey MM, Berkland CJ. Nanoparticle formulations in pulmonary drug delivery. Med Res Rev. 2009; 29:196–212.
8. Boehm GM. Air pollution and lung cancer. Cancer Detect Prev. 1982; 5:371–4.
9. Scheuch G, Siekmeier R. Novel approaches to enhance pulmonary delivery of proteins and peptides. J Physiol Pharmacol. 2007; 58:615–25.
10. Patton JS, Byron PR. Inhaling medicines: delivering drugs to the body through the lungs. Nat Rev Drug Discov. 2007; 6:67–74.
11. Lourenco RV, Cotromanes E. Clinical aerosols. I. Characterization of aerosols and their diagnositic uses. Arch Intern Med. 1982; 142:2163–72.
12. Heyder J. Particle transport onto human airway surfaces. Eur J Respir Dis. 1982; 63:29–50.
13. Brain JD, Blanchard JD. Mechanisms of aerosol deposition and clearance. In: Moren F, Newhouse MT, Dolovich MB, eds. Aerosols in Medicine. Principles, diagnosis and therapy. 2nd edn. New York: Elsevier Science Publishers (BiomedicalDivision); 1993. p117–56.
14. Byron PR. Prediction of the human respiratory tract following aerosol inhalation. J Pharm Sci. 1986; 75:433–38.

15. Heyder J. Deposition of inhaled particles in the human respiratory tract and consequences for regional targeting in respiratory drug delivery. Proc Am Thorac Soc. 2004; 1:315–20.
16. Effros RM, Mason GR. Measurements of pulmonary epithelial permeability in vivo. Am Rev Resp Dis. 1983; 127:59–66.
17. O'Callaghan C, Barry PW. The science of nebulized drug delivery. Thorax. 1997; 52:31–44.
18. Weber A, Morlin GL, Cohen M, et al. Effect of nebulizer type and antibiotic concentration on device performance. Pediatric Pulmonol. 1997; 23:249–60.
19. Eschenbacher WL, Boushey HA, Sheppard D. Alterations in osmolarity of inhaled aerosols cause bronchoconstriction and cough, but absence of a permeant anion causes cough alone. Am Rev Respir Dis. 1984; 129:211–15.
20. Newman SP, Clarke SW. Inhalation devices and techniques. In: Clark TJH, Godfrey S, Lee TH, eds. Asthma. 3rd edn. London: Chapman & Hall; 1992. p469–505.
21. Newman SP, Pavia D, Moren F, et al. Deposition of pressurized aerosols in the human respiratory tract. Thorax. 1981; 36:52–55.
22. Dolovich MB. Characterization of medical aerosols: physical and clinical requirements for new inhalers. Aerosol Sci Technol. 1995; 22:392–9.
23. Dolovich M, Chambers C, Mazza M, et al. Relative efficiency of four metered dose inhaler (MDI) holding chambers (HC) compared to albuterol MDI. J Aerosol Med. 1992; 5:307.
24. Concessio NM, VanOort MM, Knowles MR, et al. Pharmaceutical dry powder aerosols: correlation of powder properties with dose delivery and implications for pharmacodynamic effect. Pharmaceut Res. 1999; 16:828–34.
25. Pedersen S. Inhalers and nebulizers: which to choose and why. Resp Med. 1996; 90:69–77.
26. Dolovich M. New propellant-free technologies under investigation. J Aerosol Med. 1999; 12: 9–17.
27. Newman SP, Moren F, Trofast E, et al. Deposition and clinical efficacy of terbutaline sulphate from Turbuhaler, a new multi-dose inhaler. Eur Respir J. 1989; 2:247–52.
28. Newhouse MT, Kennedy A. Condensation due to rapid, large temperature (t) changes impairs aerosol dispersion from Turbuhaler (T). Am J Respir Cell Mol Biol. 2000; 161:A35.
29. Newhouse MT, Kennedy A. Inspiryl Turbuhaler (ITH) DPI vs. Ventolin MDI + Aerochamber (AC): aerosol dispersion at high and low flow and relative humidity/temperature (RH/T) in vitro. Am J Respir Crit Care Med. 2000;161:A35.
30. Wolff RK. Safety of inhaled proteins for therapeutic use. J Aerosol Med. 1998; 11:197–219.
31. Byron PR, Patton JS. Drug delivery via the respiratory tract. J Aerosol Med. 1994; 7:49–75.
32. Patton JS. Mechanisms of macromolecule absorption by the lungs. Adv Drug Del Rev. 1996; 19:3–36
33. Beauchesne PR, Chung NS, Wasan KM. Cyclosporine A: a review of current oral and intravenous delivery systems. Drug Dev Ind Pharm. 2007; 33:211–20
34. Degim IT, Celebi N. Controlled delivery of peptides and proteins. Curr Pharm Des. 2007; 13:99–117.

Questions

A score of 3 out of 4 attracts 0.75 CPD credits.

1. What is the major mechanism(s) of drug deposition in the upper respiratory tract?

a) Gravitational sedimentation.
b) Impaction.
c) Diffusion.
d) Impaction and diffusion
e) Gravitational sedimentation and diffusion.

2. What is the major mechanism(s) of deposition for particles with an aerodynamic diameter of 1 µm or below?

a) Gravitational sedimentation.
b) Impaction.
c) Diffusion.
d) Impaction and diffusion.
e) Gravitational sedimentation and diffusion.

3. Approximately how much of the dose reaches the lungs when using a nebuliser as the delivery device?

a) 10%.
b) 20%.
c) 40%.
d) 60%.
e) 80%.

4. Which **one** of the following is an advantage of pulmonary drug delivery?

a) It is associated with high enzymatic activity.
b) It involves the hepatic first pass effect of the liver.
c) It is non invasive.
d) It is affected by the patient's diet.
e) The lungs have a small surface area.

March 2011

Note: The CPD questions are now at the end of each article.

PSA members can answer online at www.psa.org.au and receive automatic feedback.

- You will need to login to submit your answers online. If you do not have member access details, you can request them via a link from the login page.
- Select Pharmacist Members from the blue, left hand side menu.
- Select Submit Answers.
- Select Australian Pharmacist CPD.

Australian Pharmacist Continuing Professional Development (CPD) is a central element of PSA's CPD&PI program. It is also part of the New Zealand College of Pharmacists (NZCP) education program for NZ pharmacists.

The CPD section is recognised under the PSA CPD&PI program as a Group 2 activity. Members can choose which articles they want to answer questions on and get CPD credits based on the questions they answer. The credits allocated to each section and the pass mark are shown with the questions.

CPD credits are allocated as follows: a minimum of 6 out of 8 questions correct attracts 1.5 credits, a minimum of 4 out of 5 questions correct attracts 1 credit, and a minimum of 3 out of 4 questions correct attracts three quarters of a credit.

If not submitting online, write the correct answers in the spaces provided on the answer panel on the back of the address sheet, fill in your name, member number and address details, then either mail or fax the answer page to the relevant address and fax number for marking.

Submit your answers before 1 May 2011 online at www.psa.org.au and receive automatic feedback or fax/mail to:

Pharmaceutical Society of Australia

PSA Fax: (03) 9389 4044
PSA Mail address: PSA CPD answers
PSA Victorian Branch
Level 1, 381 Royal Parade
PARKVILLE VIC 3052

NZCP Fax: (04) 381 4786
NZCP Mail address: NZCP CPD answers
PO Box 11 640
Wellington