

chapter 8

Respiratory dosage forms

Overview

In this chapter the following points will be discussed/described:

- an overview/description of respiratory dosage forms and the rationale for their use
- formulation strategies for aerosols and related products that are specifically designed for administration to the respiratory tract
- the advantages and disadvantages of respiratory dosage forms
- considerations for the manufacture of respiratory dosage forms.

Introduction

Drug delivery to the respiratory tract is principally performed for the treatment of local disorders, e.g. asthma and cystic fibrosis. However, due to the excellent blood perfusion of this organ, large surface area of the alveoli and the thin barrier for absorption, this route of administration may be employed to achieve drug absorption into the systemic circulation without direct passage to the liver. These features have been commercially exploited for the systemic delivery of insulin, ergotamine and other drugs for which oral absorption is inappropriate. There are several methods by which therapeutic agents may be successfully delivered to the lungs, including the use of aerosols, dry-powder inhalers (DPIs) and nebulisers. Uniquely, the performance of the respiratory drug delivery system is dependent on both the formulation and the nature/properties of the delivery system (i.e. the inhalation system).

Advantages and disadvantages of respiratory drug delivery**Advantages**

- Respiratory drug delivery ensures that the required dose of drug is delivered to the

KeyPoints

- Administration of dosage forms to the respiratory tract is performed for the treatment of localised disorders, e.g. asthma (β -agonists, corticosteroids), infections (gentamicin, ciprofloxacin). However, due to the extensive blood supply to the alveoli, this route of administration may be used to gain systemic absorption (without first-pass metabolism).
- The size of the inhaled solution/particles is a key determinant of the resulting clinical activity.
- The main types of dosage form that are administered by the respiratory route are solutions (for nebulisation) and particles (the latter either as a drug powder or as an aerosol). The control of particle size of solutions is performed by the nebuliser whereas the control of the particle size for dry powders/aerosols is defined by the size of the particle used in the formulation and the possible aggregation in either the solid or the suspended state.

site of action (where local effect is required). In so doing the incidence of side-effects is minimised.

- Due to the large surface area of the lungs (i.e. the alveoli), the excellent blood supply and the thin nature of the barrier between the lung and the systemic circulation, the lungs act as a portal for systemic drug absorption. Therefore, respiratory drug delivery systems offer a viable alternative to parenteral medications.
- There is a rapid onset of action following respiratory drug delivery. This is particularly beneficial for the treatment of asthma and, more recently, for the lowering of postprandial blood glucose levels.
- The delivery system used in respiratory dosage forms is, in most instances, portable and is therefore convenient for the patient to carry.

Disadvantages

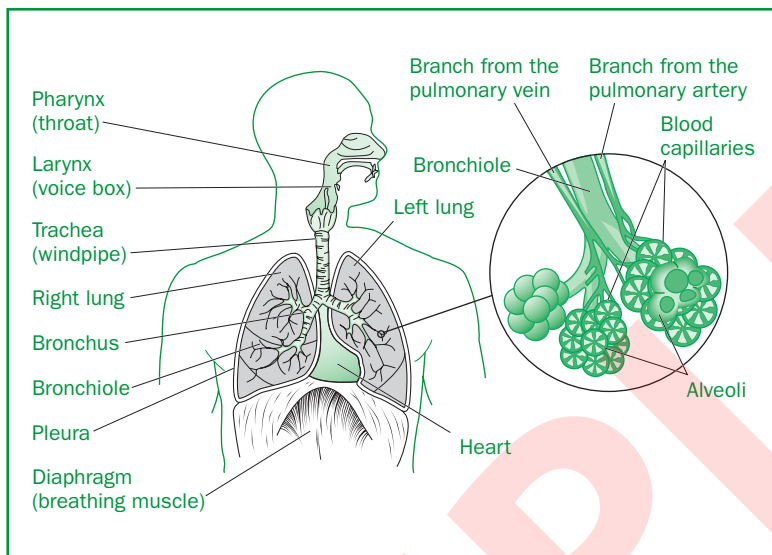
- In some dosage forms (e.g. conventional aerosols) coordination is required between activating the inhaler and inspiration. Failure to do so results in the deposition of the drug in the upper airways. There are respiratory delivery systems that do not require this coordination; however, many of these are bulky and therefore conspicuous in use.
- Deposition of drug to the lower airways may be impeded in the presence of high volumes of mucus (e.g. due to an infection).
- The physical stability of pharmaceutical aerosols may be problematic.

Physiology of the respiratory tract

The key physiological aspects of the respiratory tract that are pertinent to respiratory drug delivery are as follows:

- The physiological role of the respiratory tract is in the transfer of oxygen into the blood from inspired air and the removal of carbon dioxide from the blood into the expired air.
- The respiratory tract (Figure 8.1) may be subdivided into several regions:
 - The upper respiratory tract, comprising:
 - nose
 - throat
 - pharynx
 - larynx.
 - The lower respiratory tract, comprising:
 - trachea, dividing into:
 - bronchi, dividing into:

Figure 8.1 Diagrammatic representation of the respiratory tract.



- bronchioles, dividing into:
 - alveoli.
- The role of the upper respiratory tract and the trachea, bronchi and bronchioles is in the conduction of air to and from the alveoli. The role of the alveoli is in the transfer of respiratory gases.
- The diameters of the conducting airways sequentially decrease towards the alveoli. This has a profound effect on the deposition of particles/droplets within the respiratory tract.
- The bronchioles divide into a series of alveolar sacs (Figure 8.1), each of which contains circa $2-6 \times 10^8$ alveoli. An extensive capillary network is associated with these alveolar sacs and, furthermore, the diffusion barrier between the blood supply and the alveoli is relatively thin, enabling rapid drug diffusion and absorption into the bloodstream. The combined surface area of the alveoli is large ($70-80 \text{ m}^2$), which, in addition to the points raised previously, makes the respiratory tract particularly suitable for the systemic absorption of therapeutic agents.
- The epithelial cells in the conducting airways are ciliated and are responsible for the transport of foreign particles upwards towards the upper respiratory tract for subsequent elimination. Furthermore, goblet cells produce mucus which acts to trap foreign particles (prior to removal by the ciliated epithelia).

Factors affecting the deposition of particles/droplets within the respiratory tract

All respiratory dosage forms deliver the drug to the respiratory tract as either particles or droplets. It is therefore essential that these particles/droplets are deposited to the required site of pharmacological action, e.g. the bronchioles for asthma treatment or the alveoli for systemic absorption. To achieve the optimum pharmacological effect, the pharmaceutical scientist must fully understand and embrace the factors that affect the deposition of the drug within the respiratory tract as these will influence the formulation of respiratory dosage forms. These factors are as follows: (1) the size of the inspired particles/droplets; and (2) the effect of humidity on particle size.

The size of the inspired particles/droplets

The diameters of the various airways leading to the alveoli sequentially decrease and therefore the location of the deposited particle/droplet is dependent on particle size. The distribution of diameters of particles in an aerosol is non-normal and, as a result, these are normally plotted as log-normal distributions. Due to this heterogeneous distribution of particles, conventional parametric statistics may not be used to summarise the central tendency and variance of the distribution. The size of particles designed for pulmonary administration is defined using a parameter that accounts for this limitation and relates the diameter of the particles to the particular application, namely, the *aerodynamic diameter*. This is the diameter of a spherical particle of unit density (1 g/cm^3) that possesses the same gravitational settling velocity as the particle under examination and, in the case of spherical particles, may be expressed as follows:

$$d_s = \sqrt{\left(\frac{\rho}{\rho_o}\right)} \times d$$

where d_s is the aerodynamic diameter; ρ is the density of the particle under examination; ρ_o is the density of the spherical particle (i.e. 1 g/cm^3); and d is the diameter of the particle under examination.

Typically the aerodynamic diameter is proportional to the velocity of settling of the particle within the respiratory tract.

In addition, the aerodynamic diameter may be expressed in terms of the *mass median aerodynamic diameter* (MMAD), i.e. the aerodynamic diameter that divides the distribution equally in two parts in terms of the weight of particles.

The variance (and hence the dispersity) of the log-normal distribution of particles in therapeutic aerosols may be expressed in terms of the *geometric standard deviation* (s_g). The log-normal distribution will be normally distributed and the geometric standard deviation is therefore the standard deviation of the distribution following the log-normal transformation.

Following inhalation, the deposition of the particles within the respiratory tract is dependent on the size of the inhaled particles. Typically particles with a mass median aerodynamic diameter greater than 10 μm will be trapped in the trachea, whereas particles exhibiting MMADs of circa 5 μm and 2 μm will be deposited within the bronchioles and alveoli. Particles that are trapped in the higher regions of the respiratory tract will be removed from the lung by muciliary clearance (entrapment in the mucus and movement towards the mouth by the action of the cilia). Particles with an MMAD diameter of <1 μm are inhaled to the lowest sections of the lung but are then exhaled, thereby providing no pharmacological effect.

The effect of humidity on particle size

Following entry within the respiratory tract, the particle will be exposed to a highly humid environment (circa 99%) and this results in the deposition of a layer of moisture on the surface of the particle. The effect of this deposited layer on particle size is dependent on the hydrophilicity/lipophilicity of the particle:

- *Lipophilic inhaled particles.* The adsorbed layer of moisture is negligible and therefore does not affect the MMAD of the inhaled particle.
- *Hydrophilic inhaled particles.* The adsorbed layer of moisture results in the dissolution of the hydrophilic particle. Due to the differences in the vapour pressures of water (moisture) and the solution of therapeutic agent that has formed on the surface of the hydrophilic particle (the latter being lower), further moisture is adsorbed on to the surface of the particle until the vapour pressures of the two systems are similar. The continuing adsorption of moisture on to the surface of the particle results in further dissolution of drug with the attendant increase in effective particle size and possible deposition within the higher regions of the respiratory tract.

Mechanisms of particle deposition within the respiratory tract

The previous section has outlined the effect of particle size on the deposition of particles within the respiratory tract (and hence on

the clinical efficacy of aerosol products). Particle size additionally affects the mechanisms by which the particles are deposited within the respiratory tract. There are four main mechanisms that operate in aerosol products: (1) inertial impaction; (2) gravitational sedimentation; (3) Brownian diffusion; and (4) electrostatic precipitation.

Inertial impaction

Inertia may be defined as the property of a particle that enables it either to remain at rest or to remain in uniform motion until exposed to an external force. Following inhalation, aerosol particles must (frequently) change direction to ensure deposition at the required site within the respiratory tract. Initially the particles will move horizontally towards the back of the throat; however, the flow of air will change direction both into the trachea and then at the other main tributaries along the respiratory tract until the alveoli are reached. The inertial effect resists the change in direction of flow and, as a result, particles with sufficient momentum (the product of the velocity and the mass) will attempt to maintain their initial path of flow. This resistance results in impaction of the particle with the respiratory tract at sites prior to the bronchioles and alveoli.

The probability of impaction ($Pr_{\text{impaction}}$) may be mathematically defined as:

$$Pr_{\text{impaction}} = \frac{U_t U \sin \theta}{rg}$$

where: U_t refers to the terminal settling velocity (i.e. the velocity of motion whenever the force of the falling particle downwards is equal to the drag force acting in the opposite direction; this results in a net zero force and a constant particle velocity); U refers to the velocity of the air stream following inhalation; θ refers to the angle of the airflow change; g refers to gravity; and r is the radius of the airway.

Accordingly, the probability of the occurrence of inertial impaction increases as the angle and velocity of airflow increase, whereas the probability decreases in airways of larger radius. Inertial impaction is relevant for particles of larger MMAD (>5 μm) within the larger airways, e.g. nose, mouth, pharynx and larynx. As the airflow velocity decreases within the lower sections of the respiratory tract (due to the effects of branching of the airways providing resistance to the flow of air), the contribution of inertial impaction on the deposition of particles within the deeper regions of the respiratory tract is lower.

Gravitational sedimentation

As the term implies, gravitational sedimentation refers to the downward movement of particles under the action of gravity. Gravitational sedimentation is an important mechanism for the deposition of particles of small MMAD (typically 1.0–5.0 μm) within the bronchioles and alveoli. Furthermore, the probability of impaction by gravitational sedimentation within these sites may be enhanced by either a steady rate of breathing or holding the breath. This is particularly relevant for the deposition of particles with an MMAD of circa 1.0 μm .

Brownian diffusion

Brownian motion refers to the random movement of particles within a fluid (liquid or air), which, within the respiratory tract, enables small particles (<0.5 μm) to move towards and be deposited on the walls of the various sections of the respiratory tract. This is not a significant contributor for the deposition of particles from therapeutic aerosols.

Electrostatic precipitation

This is a phenomenon in which the charge on the surface of a particle may affect the resultant deposition, i.e. a charged particle interacts with a site within the respiratory tract that possesses an opposite charge. Typically, this mechanism is not important for particles of MMAD that are greater than circa 4 μm . Furthermore, the charge on particles may induce an interaction with the plastic surfaces of containers/spacers/inhalers and may therefore compromise the effective delivery of the particles to the required site within the respiratory tract.

Tip

The region of deposition of the inhaled particles/droplets within the respiratory tract directly affects the clinical performance of the dosage form. Therefore, it is important that the formulation scientist designs the dosage form to ensure that, following inhalation, the particle/droplet size is of the correct MMAD to reach the target site within the respiratory tract.

Formulation of respiratory dosage forms

There are three main types of delivery system for respiratory dosage forms: (1) metered-dose inhalers (MDIs); (2) dry-powder inhalers; and (3) nebulisers. The formulation and design of these systems are described in this section.

Metered-dose inhalers

MDIs are a commonly used system – in use for over 50 years – for the delivery of therapeutic agents to the respiratory tract. The

advantages and disadvantages associated with the use of MDIs are detailed below.

Advantages

- portable (which is particularly useful for the treatment of acute respiratory conditions, e.g. breathlessness in asthma patients)
- low-cost dosage form
- hermetically sealed and therefore oxidation of the therapeutic agent and microbial contamination are minimised
- effective treatment of respiratory disorders.

Disadvantages

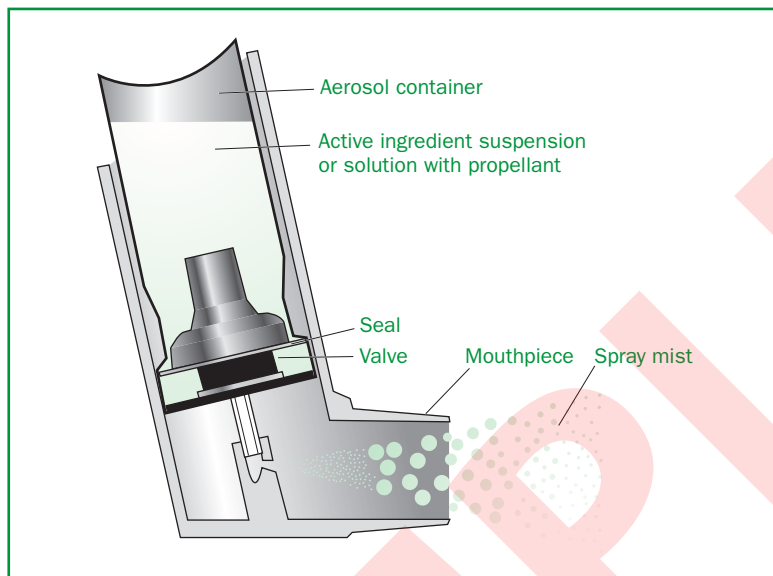
- MDIs most frequently contain *dispersed* drug and therefore problems may arise concerning the physical stability of the formulation.
- Frequently there is ineffective use of drug. Typically the majority of drug that is emitted from the aerosol fails to reach the proposed site of pharmacological action. This point is further addressed later in this chapter.
- Clinical efficacy is often dependent on the ability of the patient to use the MDI correctly: efficacy is lowered by the inability of the patient to synchronise inhalation and actuation of the dosage form.

The main components of MDIs are the container, the metered valve and the formulation (within the container), as illustrated in Figure 8.2.

Formulation and operation of an MDI

The formulation component of MDIs comprises two parts: the propellant and the therapeutic agent (which may be present as a solution or, most commonly, as a suspension). Following actuation, a mixture of the propellant and the therapeutic agent is released into the oral cavity of the patient in the form of droplets (circa 40 μm MMAD). The volume of product (typically 25–100 μm) dispensed from the MDI during the actuation process is controlled by a *metering valve*. In this, the depression of the stem of the canister (containing the formulation) facilitates the release of a volume of product into the mouthpiece of the device. Release of the downward pressure on the stem of the canister allows the free volume within the metering valve to be replenished. Removal of liquid propellant following actuation results in a momentary change in the vapour pressure within the canister. To correct this, liquid propellant evaporates to occupy the free volume within

Figure 8.2 Illustrated cross-section through a metered dose inhaler showing the location of the formulation and the design of the container.



the canister, thereby maintaining a constant vapour pressure and hence operating pressure.

When formulated correctly the propellant will rapidly evaporate following exposure to atmospheric conditions and the droplets are reduced to solid particles of therapeutic agent, which may then be deposited at the required site in the respiratory tract. The reader will be aware of the particle size requirements for penetration into the lower regions of the respiratory tract and therefore to ensure that the therapeutic agent reaches the required site. There are three prerequisites for this process to occur successfully:

1. The particle size of the therapeutic agent that has been incorporated into the formulation must exhibit the required diameter and polydispersity. Reduction in the particle size to achieve the required diameter is most commonly performed using milling techniques (Chapter 11). It is difficult to achieve the required polydispersity using such techniques.
2. Following shaking of the MDI (prior to use), the drug particles must be readily resuspended. Aggregation of drug particles will increase their effective size and will lead to deposition at the incorrect region of the respiratory tract and, if the size of the aggregate is sufficiently large, clogging of the nozzle of the MDI.

3. As highlighted previously, the formulation exits the MDI as a droplet composed of the dispersed therapeutic agent with the liquid propellant. The purpose of the propellant is therefore to provide sufficient pressure to deliver the dose of drug from the MDI to the upper respiratory tract. However, it is essential that evaporation of the propellant occurs rapidly to ensure that the solid drug particle is free to travel to the lower regions of the lung.

Based on these three requirements, the formulation of MDI involves consideration of the properties of both the propellant and the therapeutic agent.

- *Propellants used in MDI.* The purpose of the propellant is twofold: to provide the driving pressure to force the therapeutic agent from the MDI to the upper respiratory tract and, secondly, to exhibit the required evaporation rate to facilitate particle delivery to the required site within the respiratory tract. Both the pressure within the metal canister of the MDI and the subsequent rate of evaporation of the propellant are functions of the partial vapour pressure of the propellants within the canister. To achieve these required properties mixtures of propellants are used. Currently there are two main classifications of propellants used, as follows: (1) chlorofluorocarbons (CFCs) and (2) hydrofluorocarbons.
 - *CFCs.* CFCs have been used as propellants for many years; however, due to concerns with their contribution to the depletion of the ozone layer, their use has been prohibited in all aerosols, with the exception of MDIs (under the proviso that no suitable alternatives are available). The main examples of these that have been or are being used as propellants in MDI, including their physicochemical properties, are shown in Table 8.1 and Figure 8.3.

Table 8.1 The physicochemical properties of propellants 11 (trichloromonofluoromethane), 12 (dichlorodifluoromethane) and 114 (dichlorotetrafluoroethane)

Propellant	Boiling point	Vapour pressure at 20°C	Freezing point
12	-29.8°C	568 kPa	-158°C
114	3.6°C	183 kPa	-94°C
11	23.7°C	89 kPa	-111°C

Propellant 12 may be used as the sole propellant in MDI formulations; however, propellants 11 and 114 are generally used in combinations with other propellants. For example, blends of

propellants 11 and 12 or propellants 11, 114 and 12 are used in MDI to provide the correct range of vapour pressures (103–484 kPa) at room temperature and hence provide the required expulsion pressure, droplet size distribution and evaporation rate to ensure optimal clinical performance. Furthermore, mixtures of propellants may be required to ensure the surfactants that are used to stabilise the dispersed drug particles are soluble in the propellant. This is an important consideration in the formulation of a stable MDI product.

Calculation of the vapour pressure of propellant mixtures is performed using *Raoult's law*, which states that the vapour pressure of a mixture of propellants (p_{total}) is simply the sum of their partial vapour pressures (e.g. p_1 and p_2 for propellants 1 and 2, respectively).

$$p_{\text{total}} = p_1 + p_2$$

The partial vapour pressure of each component is the product of the mole fraction of that component (χ) and the partial vapour pressure of the propellant (p_i^0):

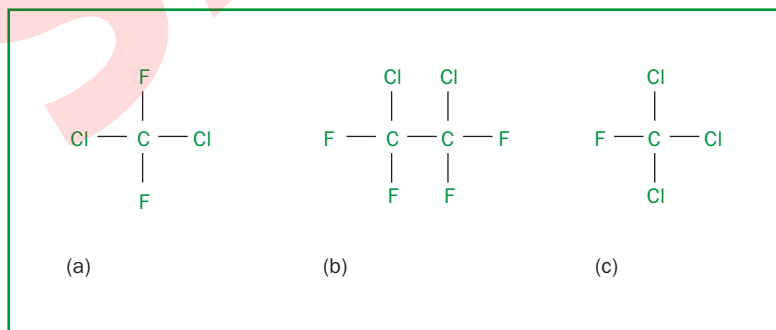
$$p_1 = \chi_1 \times p_1^0$$

This equation can be used to calculate the total vapour pressure of a mixture of propellant 11 and propellant 12 (60:40 ratio), as follows:

- *Determination of the mole fraction of each propellant in the mixture*
Propellant 11 (molecular weight 137.50 g/mol)

$$n_{11} = \frac{60}{137.5} = 0.44$$

Figure 8.3 Structural formulae of (a) dichlorodifluoromethane (propellant 12), (b) dichlorotetrafluoroethane (propellant 114) and (c) trichloromonofluoromethane (propellant 11).



Propellant 12 (molecular weight 121.00 g/mol)

$$n_{12} = \frac{40}{121} = 0.33$$

Total number of moles of propellant

$$n_{\text{total}} = n_{11} + n_{12} = 0.44 + 0.33 = 0.77$$

Mole fraction of propellant 11

$$\chi_{11} = \left(\frac{n_{11}}{n_{11} + n_{12}} \right) = \frac{0.44}{0.44 + 0.33} = 0.57$$

Mole fraction of propellant 12

$$\chi_{12} = \left(\frac{n_{12}}{n_{11} + n_{12}} \right) = \frac{0.33}{0.44 + 0.33} = 0.43$$

- *Determination of the partial vapour pressures of each component in the mixture*

Partial vapour pressure of propellant 11

$$p_{11} = \chi_{11} \times p_{11}^0 = 0.57 \times 89 = 50.86 \text{ kPa}$$

Partial vapour pressure of propellant 12

$$p_{12} = \chi_{12} \times p_{12}^0 = 0.43 \times 568 = 243.43 \text{ kPa}$$

- *Calculation of the total vapour pressure within the canister*

$$p_{\text{total}} = p_{11} + p_{12} = 50.86 + 243.43 = 294.29 \text{ kPa}$$

As the reader will observe, the partial pressure of the propellant mixture may be readily manipulated by altering the ratio of the individual propellants. The partial vapour pressure of the mixture is an important consideration in the formulation of aerosols. The vapour pressure is responsible for the expulsion of the defined volume of product from the aerosol. If the pressure is too high, impaction of the expelled droplet/particle on to the surfaces of the upper respiratory tract will occur, thereby diminishing the clinical performance of the MDI. Reduction of the partial vapour pressure of the system may be achieved by increasing the mole fraction of a less volatile propellant (e.g. propellant 11) into the formulation. However, as the mole fraction of a less volatile propellant is increased, the rate of evaporation of the propellant following actuation

decreases and, hence, this may reduce the percentage of the actuated dose of the therapeutic agent that reaches the lower airways.

- *Hydrofluorocarbons (HFCs)*. HFCs were developed to address the deleterious effects of CFC propellants on the ozone layer. Unfortunately, although the effects on the environment are lower than for CFCs, these propellants are also damaging to the ozone layer. In spite of this HFCs represent a significant evolution in the development of propellants that are ozone-friendly. Two examples of these that are employed in MDIs are heptafluoropropane and tetrafluoroethane (Figure 8.4).

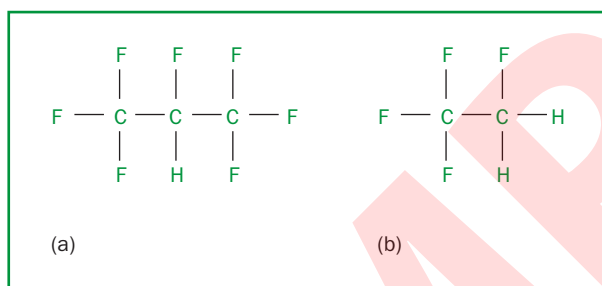


Figure 8.4 Structural formulae of selected hydrofluorocarbons used as propellants in metered dose inhalers: (a) heptafluoropropane; (b) tetrafluoroethane.

Both heptafluoropropane and tetrafluoroethane may be employed as propellants for MDIs. One potential problem with their use is their extremely hydrophobic properties. As a result, the solubility of the commonly used surfactants (sorbitan trioleate, oleic acid, sorbitan sesquioleate) may not be sufficiently high to stabilise the formulation.

The physicochemical properties of the HFC propellants are similar to CFC, reflecting their applicability as propellants for MDIs. These are summarised in Table 8.2. As before, modification of the vapour pressure of the propellant system may be achieved by blending the HFC propellants (according to Raoult's law).

Table 8.2 Physicochemical properties of selected hydrofluorocarbon propellants

Propellant	Boiling point	Vapour Pressure	Freezing point
Tetrafluoroethane	-26.2°C	569 kPa (at 20°C)	-108°C
Heptafluoropropane	-16.5°C	398 kPa (at 20°C)	-131°C

There are other formulation considerations for MDI. These are summarised below.

The physicochemical properties of the therapeutic agent

There are two key physicochemical properties that affect the stability and clinical performance of MDI – the solubility of the therapeutic agent in the propellant system and the MMAD (and polydispersity) of the dispersed particles. If the drug shows limited solubility in the propellant that is susceptible to changes in storage conditions, this may result in fluctuations in the solubility of the drug in the propellant that may, in turn, result in recrystallisation of the drug. This will result in the generation of larger particles. It is additionally important that the MMAD (and polydispersity) of the therapeutic agent that is to be incorporated into the propellant system is within the inspirable size range (remembering that the MMAD of particles that will be deposited in the lower airways is circa 1–5 μm). The drug particle size should be manipulated to the required size fraction by milling techniques.

Maintenance of the physical stability of the MDI

Most commonly the therapeutic agent is present in the MDI as dispersed particles within the liquid propellant and therefore there are similar concerns regarding the physical stability of the formulation. Irreversible aggregation of the particles (caking) will result in problems regarding both the successful deposition of drug within the respiratory tract and the successful discharge of the particles through the orifice of the MDI. To obviate these problems surface-active agents of low hydrophile–lipophile balance are incorporated into the liquid propellant which will adsorb to the dispersed particles and, in so doing, will stabilise the drug suspension (see Chapter 3 for a full description of the mechanism of stabilisation). Examples of surface-active agents that are used for this purpose (generally in concentrations ranging from 0.1% to 3.0% w/w) include:

- sorbitan trioleate
- sorbitan sesquioleate
- oleic acid.

Unlike suspensions designed for oral application, enhancement of suspension stability by modification of the viscosity of the liquid propellant phase is not performed for MDI.

Enhancement of drug solubility in the propellant

In some aerosol products, e.g. those for topical administration, the pharmaceutical scientist may wish to dissolve the therapeutic agent in the propellant mixture. For this purpose ethanol is frequently added as a co-solvent to facilitate this demand. This approach is infrequently used for MDI as the presence of ethanol

will result in the generation of droplets after actuation that require a longer period to evaporate (due to the vapour pressure of ethanol being substantially lower than that of the propellant mixture). This may affect the clinical performance of the MDI.

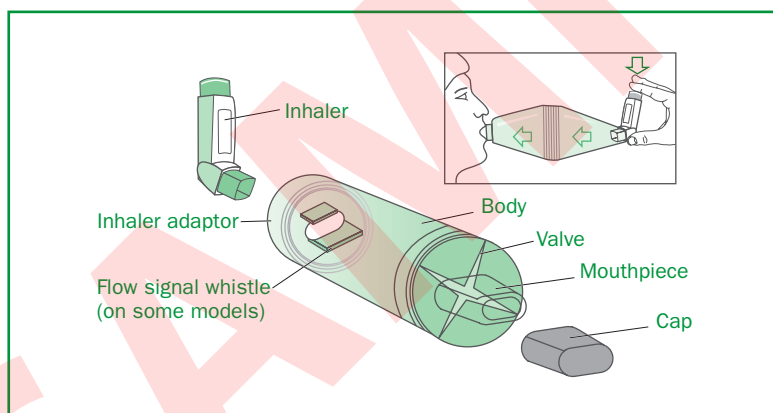
Spacer devices for MDIs

Previously in this section, the importance of the evaporation rate of the propellant after actuation to the subsequent deposition of the therapeutic agent within the respiratory tract was detailed. Furthermore, the reliance of conventional MDI on the ability of the patient to coordinate actuation and inhalation was discussed. One method by which these two problems may be minimised is the use of spacer devices (Figure 8.5).

Tip

Formulations that are delivered to the respiratory tract using metered-dose inhalers are generally composed of the drug (dispersed or dissolved), a surfactant(s), the propellant(s) and, occasionally, a co-solvent (to enhance drug solubility within the propellant).

Figure 8.5 Diagrammatic presentation of a spacer device, showing the clinical use of the spacer with the MDI.



Following actuation the propellant droplets (containing suspended particles of therapeutic agent) will reside within the spacer device, thereby facilitating evaporation of the propellant and allowing the patient to inspire the dose of drug without the need for coordination between actuation of the MDI and inhalation. One disadvantage of spacer systems is their size (rendering them conspicuous in use and relatively non-portable).

Manufacture of MDIs

There are two methods by which MDIs are manufactured: (1) pressure filling; and (2) cold filling.

Pressure filling

In this method the therapeutic agent (and excipients) is mixed with a portion of a propellant which possesses a relatively high boiling point and low vapour pressure, e.g. trichloromonofluoromethane (23.7°C and 89 kPa, respectively) at or below 20°C. This drug/propellant slurry is then filled into the canister and the canister is then crimped with the attached valve. The second more volatile propellant is then filled into the canister through the valve under pressure until the correct propellant blend is attained. Although this technique is straightforward, it is dependent on the use of a less volatile propellant whose boiling point is greater than that of the temperature in the mixing area.

Cold filling

In cold filling the drug (and excipients) and propellants are mixed under cold conditions (circa -30°C) and filled into the canister (which is subsequently crimped with the attached valve). Propellant is then added into the canister through the valve at this low temperature until the correct mass has been added.

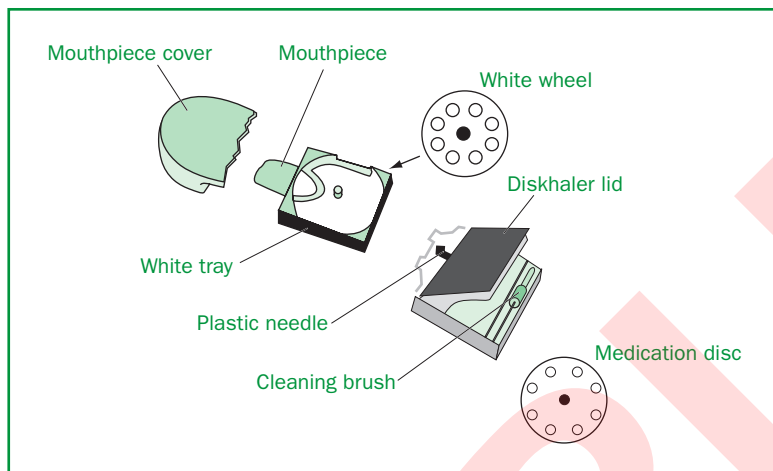
Dry-powder inhalers

DPIs are respiratory dosage forms in which a powder (containing the therapeutic agent) is inhaled into the respiratory tract. The flow of the powder is activated whenever the patient inhales and therefore no propellant is required. It has been reported that MDIs are more efficient respiratory delivery systems than their dry-powder comparators.

There are a number of designs of these systems:

- *Inhalers in which the drug (and excipients) are present within a hard gelatin capsule.* In these the hard gelatin capsule (containing the therapeutic agent) is located inside the device. Prior to use the gelatin capsule is pierced in two locations to enable airflow through the capsule. As the patient inhales, a rotor is activated, resulting in turbulent airflow (>35 l/min), which carries the powder to the patient.
- *Inhalers in which the drug (and excipients) are present within a blister pack.* In these systems, a multidose unit comprising four or eight individual doses is located within a circular device containing a mouthpiece (Figure 8.6). After the device has been assembled the lid is elevated and the individual disc containing the therapeutic agent (and excipients) is pierced. Inhalation by the patient results in the passage of air through the device, which delivers the bioactive powder to the patient.
- *Inhalers in which the drug (and excipients) are present within the inhaler.* In these systems the inhaler is preloaded with

Figure 8.6 Diagrammatic representation of a diskhaler device, illustrating the individual components and assembly.



multiple doses of drug. As before, the packaging containing each dose is broken and the therapeutic agent (and excipients) are carried to the patient during inhalation. These systems may be replenished with drug by incorporating a replacement reservoir. In an alternative strategy the drug (*without excipient*) is located within a reservoir (not as individual units). The device is activated (e.g. by twisting the base), resulting in the passage of drug into a chamber. As before, when the patient inhales, air is drawn through the device and the powdered drug will be delivered to the patient.

Formulation considerations for DPIs

The formulation of DPIs is relatively straightforward, particularly when compared to MDIs. The major formulation concerns for DPIs are as follows:

- **Therapeutic agent.** As before, the particle size (MMAD) of the therapeutic agent should be less than 5 μm .
- **Excipients.** Excipients are used in the majority of DPIs for two main reasons:
 - *To facilitate production.* As the dose of therapeutic agent in the DPI is generally low, the addition of an inert excipient may be used to enhance the quality of the filling process.
 - *To improve the flow properties of the therapeutic agent during inhalation.* To ensure optimum clinical efficacy,

Tip

DPIs do not use a liquid propellant. The powder enters the respiratory tract as the patient inhales air through the device.

it is essential that following inhalation the flow properties of the therapeutic agent are sufficient to enable the dose of drug to be efficiently removed from the device. If the drug particles are aggregated or if there is an interaction between the drug and the plastic interior of the device, this will result in both a variable and inaccurate dose of drug being delivered to the patient. Therefore, to address this problem the therapeutic agent is frequently mixed with an inert excipient, most commonly lactose (MMAD 30–60 μm). The larger particle size of the excipient ensures that it does not enter into the lower airways. Within the device the drug particles are adsorbed on to the larger lactose particles and, in so doing, their flow properties are improved. It is essential, however, that dissociation of the drug/carrier interaction occurs prior to impaction of the lactose carrier within the oral cavity/pharynx.

The interaction between the therapeutic agent and the carrier is dependent on several factors, including:

- the surface areas of the particles
- the surface energies of the particles
- the morphologies of the particles.

These factors are dependent (to a large degree) on the techniques used to process the powders, in particular, the milling conditions (Chapter 11).

Solutions for nebulisation

Nebulisation involves the application of energy (either a high-velocity gas or by the use of ultrasonic systems) to a solution of a therapeutic agent and results in the formation of droplets of solution, which are then inspired by the patient through a facemask. The energy source is provided by a nebuliser (most commonly a jet or ultrasonic nebuliser). The use of nebulisers is generally reserved for the treatment of acute conditions (e.g. acute asthma, respiratory infection) or in those patients who have difficulties using other respiratory dosage forms.

Formulation of solutions for nebulisation

The general formulation considerations for solutions for nebulisation are similar to those described in Chapter 1 and therefore in this section only the particular formulation requirements for solutions designed for administration to the respiratory tract will be discussed.

Vehicle

The vehicle for solutions designed for nebulisation is water for injections (nebuliser solutions are sterile). Due to the possibility of acidic solutions (pH <5) causing bronchoconstriction, the pH of nebuliser solutions is greater than 5. This may be modified via the use of buffers (e.g. citrate, phosphate).

Co-solvents

Co-solvents may be used in nebuliser solutions to increase the solubility of the drug. However, as in other applications, care should be taken when selecting the concentration of these to ensure that there is no toxicity to the respiratory epithelia.

Examples of co-solvents that may be used include:

- propylene glycol
- glycerol
- ethanol.

Osmolality-modifying agents

The use of hypo- and hyperosmotic solutions within the respiratory tract has been linked to bronchoconstriction and therefore solutions designed for nebulisation should be formulated to be iso-osmotic. As described previously (Chapter 5), modification of the osmolality of nebuliser solutions may be performed by adding the appropriate ionic concentration of, for example, sodium chloride, potassium chloride, mannitol.

Miscellaneous agents

Other components that may be present in nebuliser solutions include:

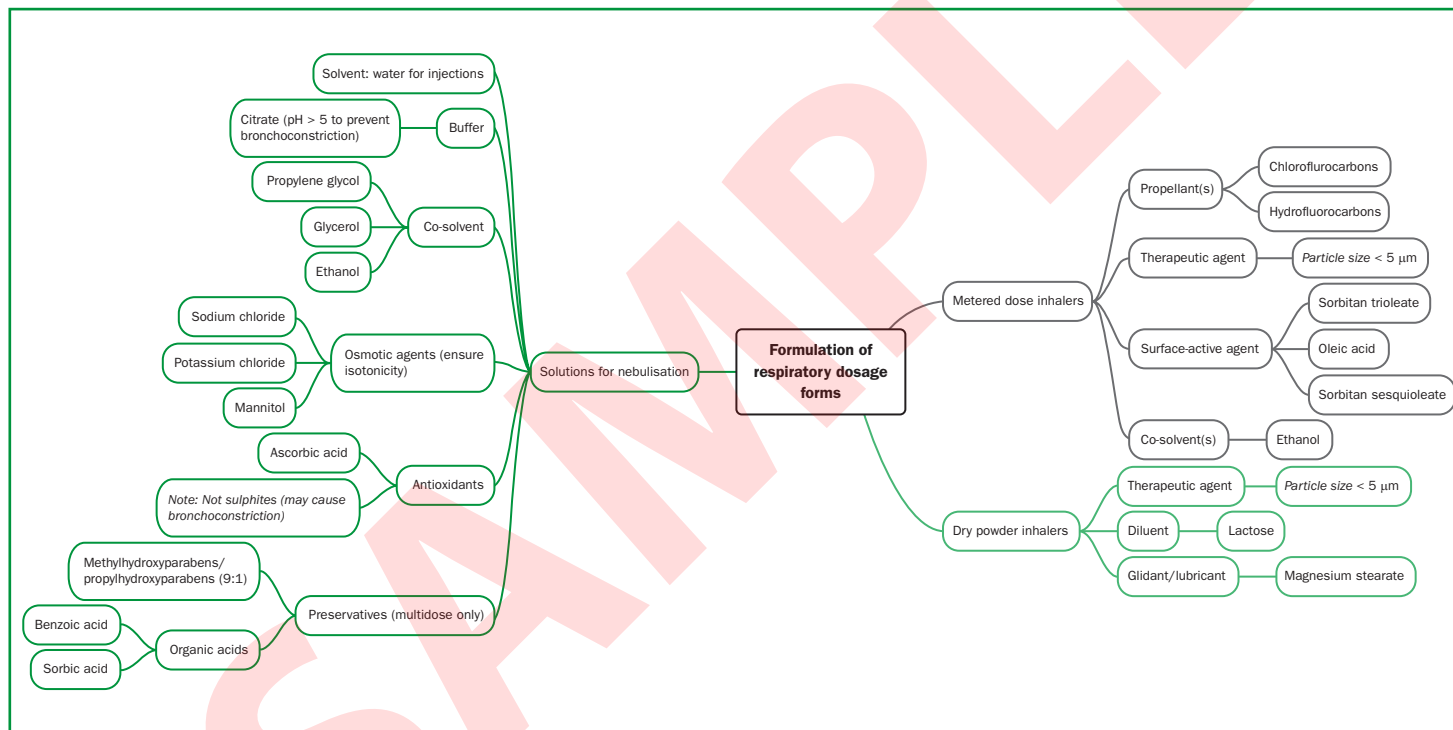
- antioxidants (water-soluble examples; however, it should be noted that sulphites may cause bronchospasm)
- preservatives: some multidose nebuliser solutions contain preservatives; however, the vast majority of formulations do not contain these excipients. Generally nebuliser solutions are packaged as single-dose vials/ampoules and, as such, do not require the addition of preservatives.

A diagrammatic representation of formulation considerations for respiratory dosage forms is shown in Figure 8.7.

Quality control of respiratory products

The three main categories of respiratory products have been defined in this chapter as (a) metered dose inhalers, (b) dry powder inhalers and (c) solutions for nebulisation. The details of the

Figure 8.7 Formulation considerations for respiratory dosage forms.



quality control of these products will focus primarily on the first two categories; the quality control of solutions for nebulisation being similar to that for other solutions (as described in previous chapters). Thus, the following analyses are typically applied to respiratory products following manufacture and over the designed period of the shelf-life:

- 1. Concentration of therapeutic agent:** Following manufacture the concentration of therapeutic agent must lie within 95–105% of the nominal concentration. Over the shelf-life of the product the concentration of drug must not fall below 90% of the nominal amount.
- 2. Appearance:** The appearances of these products are defined in a product specification, adherence to this being examined both following manufacture and storage.
- 3. Uniformity of dose:** Assessment of the uniformity of dose of respiratory products is performed by administering a dose from the product, which is transported by the application of a vacuum prior to deposition of the drug on to a collection unit (e.g. filter disc) and quantification using an appropriate analytical method. Collection of a series of doses is performed at different stages of the contents of the device, i.e. at the start (three doses), middle (four doses) and towards the end of the contents (three doses). Typically, the product will pass the test if in nine out of ten results (doses) the drug content lies between 75% and 125% of the average value and all doses range between 65% and 135% of the average content. If two or three values lie outside the 75–125% range then the test is repeated for two more inhalers. The test is passed if not more than three of the thirty doses (3 inhalers \times 10 doses each) lie outside the range 75–125% and no value lies outside the range 65–135%.
- 4. Number of deliveries per metered dose inhaler:** This test examines the number of deliveries from the inhaler and compares this to the number specified on the label. The total number of deliveries (actuators) must not be less than the number defined in the product specifications.
- 5. Fine particle dose and particle size distribution:** Given the importance of particle size in the performance of respiratory products, pharmacopoeial tests are available to characterise the particle size properties generated by such products. There are several methods that are used, namely the (a) glass impinger, (b) the metal impinger, (c) the multi-stage liquid impinger and (d) the Andersen sizing sampler. All three methods examine the deposition of particles/droplets within different chambers and attempt to generate information that relates to the possible clinical performance of these systems.

Movement of the dose through the device is performed using a vacuum. In these methods, the mass fractions of the dose collected at different stages of these devices are collected and quantified, this information being related to the fine particle dose (the mass of active ingredient that is less than $5\mu\text{m}$). The reader should consult the appropriate pharmacopoeias for a more detailed description of the design and operation of the various methods described above.

The reader should note that other tests, similar to those described in earlier chapters, are applied to solutions for nebulisation. Furthermore, the list of methods is indicative of the quality control methods that may be employed. The reader should consult the appropriate pharmacopoeias for a more detailed description of the above methods and others that have not been explicitly covered in this chapter.

Multiple choice questions

1. **Concerning respiratory drug delivery, which of the following statements are true?**
 - a. Delivery of therapeutic agents to the respiratory tract is performed primarily for the treatment of local conditions, e.g. asthma, infection.
 - b. The treatment of asthma involves the deposition of the therapeutic agent at the alveoli.
 - c. Systemic absorption of certain therapeutic agents occurs following respiratory delivery.
 - d. Respiratory drug delivery is associated with a slow onset of drug action.

2. **Regarding the physiology of the respiratory tract, which of the following statements are true?**
 - a. The diameters of the conducting airways decrease towards the alveoli.
 - b. Drug absorption from the respiratory tract occurs at the alveoli.
 - c. The surface area of the alveoli is $>100\text{ m}^2$.
 - d. The primary mechanism of elimination of particles $>5\ \mu\text{m}$ in diameter is expiration.

3. **Which of the following factors influence the deposition of particles within the respiratory tract?**
 - a. The size of the inspired droplets: increasing particle/droplet size results in greater deposition within the lower airways.
 - b. Humidity.
 - c. The vapour pressure of the propellant.
 - d. The patient's inhaler technique.

- 4. Concerning the formulation and use of metered-dose inhalers, which of the following statements are true?**
- Oxidation of drugs is minimised.
 - Metered-dose inhalers are usually formulated to ensure that the drug is soluble within the propellant system.
 - Metered-dose inhalers require the inclusion of a preservative.
 - Metered-dose inhalers may be easily formulated to contain water.
- 5. Concerning propellants for metered-dose inhalers, which of the following statements are true?**
- The vapour pressure remains constant throughout the lifetime of use of the inhaler.
 - The use of chlorofluorocarbons has increased in recent years.
 - The volume of propellant released upon actuation is controlled by a metering valve.
 - All metered-dose inhalers are filled under atmospheric conditions.
- 6. The following excipients are included in metered-dose inhalers for the following reasons:**
- Ethanol – to increase the vapour pressure of the propellant.
 - Tween 80 – to enhance the solubility of the therapeutic agent within the propellant.
 - Oleic acid – to stabilise the suspended drug in the propellant.
 - Antioxidants – to inhibit oxidative degradation of the therapeutic agent.
- 7. Concerning the formulation of dry-powder inhalers, which of the following statements are true?**
- Liquid propellants are not required.
 - The mass median aerodynamic diameter (MMAD) of the therapeutic agent should be less than 5 μm .
 - Lactose is commonly used to improve the flow properties of the powdered drug.
 - Following inspiration, both lactose and the powdered drug reach the site of action.
- 8. The advantages of metered-dose inhalers include:**
- Administration of high doses of therapeutic agent.
 - Convenience for the patient.
 - Requirement for patient's ability to coordinate actuation and inhalation.
 - Greater efficiency than nebulisers.

- 9. Concerning nebulisers, which of the following statements are true?**
- Nebulisers require either a compressed-gas source or an ultrasonic device.
 - Nebulisers are portable and convenient to use.
 - They require patient coordination.
 - They are suitable for the delivery of all drugs.
- 10. Regarding the formulation of solutions for nebulisation, which of the following statements are true?**
- The pH of nebuliser solutions is always greater than 5.
 - Propylene glycol may be employed as a co-solvent in nebuliser solutions.
 - Nebuliser solutions should be hypertonic.
 - In general, preservatives are not required in nebuliser solutions.
- 11. A metered-dose inhaler has been formulated containing a propellant mixture, a hydrophilic drug (salbutamol sulphate) and a surface-active agent (Tween 80). The boiling point of the propellant mixture is 6°C. Blockage of the exit orifice of the inhaler was observed following actuation of the device. Which of the following explanations would account for this observation?**
- The particle size of the dispersed drug within the metered-dose inhaler was too large.
 - The drug precipitated out of solution, the large crystals blocking the exit orifice.
 - The concentration but not the type of surfactant was inappropriate.
 - The concentration and the type of surfactant were both inappropriate.
- 12. Which of the following statements are true regarding the efficacy of metered-dose inhalers containing CFC propellants?**
- The efficacy of performance increases as the partial vapour pressure of the propellant increases (up to a defined partial vapour pressure).
 - The efficacy of performance increases as the concentration of surfactant increases (up to a defined concentration).
 - The efficacy of performance increases as the solubility of the drug in the propellant increases (up to a defined concentration).
 - The efficacy of performance increases as the diameter of the exit orifice increases.

- 13. Which of the following are advantages of a pressurised metered-dose inhaler?**
- Easy delivery of high doses
 - Convenience
 - No need for patient coordination
 - Greater efficiency than a nebuliser.
- 14. Which of the following statements are true concerning the physical properties of an aerosol?**
- Particles that have the same shape have the same aerodynamic diameter.
 - Particle density is important when determining aerodynamic diameter.
 - Particles between 1 μm and 10 μm are important for drug delivery to the airways.
 - The probability of inertial impaction is not related to particle velocity.
- 15. Which of the following statements are true concerning a metered-dose inhaler that has been formulated containing a water-soluble β_2 agonist, sorbitan trioleate and a HFC based propellant system?**
- Controlled flocculation of suspended drug particles will enhance both the physical stability and clinical performance.
 - Particle sedimentation does not occur upon storage.
 - Physical stability and clinical performance will be improved by the addition of Tween 80.
 - Controlled flocculation may be engineered by the addition of electrolytes.