may be adjusted accordingly or the volatility of the product modified by the addition of a less volatile component, such as glycerol.

Filling pressurized metered-dose inhaler canisters

Canisters are filled either by liquefying the propellant by reducing its temperature (cold filling) or by filling the vapour at elevated pressure (pressure filling).

In cold filling, active compound, excipients and propellant are chilled and filled at about −60 °C. Additional propellant is then added at the same temperature and the canister sealed with the valve. In pressure filling, a drug/propellant (CFC-11) concentrate is produced and filled at effectively room temperature and pressure (in fact, usually slightly chilled to below 20 °C). The valve is crimped on to the canister and additional propellant (e.g. CFC-12) is filled at elevated pressure through the valve, in a process known as gassing. Pressure filling is most frequently employed for inhalation aerosols. However, no HFAs have the properties (high boiling point: 23.7 °C) of CFC-11 so a single-stage pressure filling process has been developed for HFA-based formulations whereby a concentrated solution or suspension of drug in propellant, under pressure, is filled into canisters through the valve, followed by addition of further propellant.

Once filled, the canisters are leak tested by placing them in a water bath at elevated temperature, usually 50–60 °C. Following storage to allow equilibration of the formulation and valve components, the containers are weighed to check for further leakage, prior to spray testing and insertion into actuators.

Advantages and disadvantages of pressurized metered-dose inhalers

The major advantages of pMDIs are their portability, low cost and disposability. Many doses (up to 200) are stored in the small canister and dose delivery is reproducible. The inert conditions created by the propellant vapour, together with the hermetically sealed container, protect drugs from oxidative degradation and microbiological contamination. However, pMDIs have disadvantages. They are inefficient at drug delivery. On actuation, the first propellant droplets exit at a high velocity which may exceed 30 m/s. Consequently, much of the drug is lost through impaction of these droplets in the oropharyngeal areas. The mean emitted droplet size typically exceeds 40 μm, and propellants may not evaporate sufficiently rapidly for their size to decrease to that suitable for deep lung deposition. Vaporization of the droplets is hindered by the low volatility of CFC-11, which is present in concentrations of at least 25% in most CFC-based formulations. Evaporation, such that the aerodynamic diameter of the particles is close to that of the original micronized drug, may not occur until 5 seconds after actuation.

An additional problem with pMDIs, which is beyond the control of the formulator and manufacturer, is their incorrect use by patients. Reported problems include:

- failure to remove the protective cap covering the mouthpiece
- the inhaler being used in an inverted position
- failure to shake the canister
- failure to inhale slowly and deeply
- inadequate breath-holding following inhalation
- poor inhalation/actuation synchronization.

Correct use by patients is vital for effective drug deposition and therapeutic action. Ideally, the pMDI should be actuated during the course of a slow, deep inhalation, followed by a period of breath-holding. Many patients find this difficult, especially children and the elderly. The misuse of pMDIs through poor inhalation/actuation coordination can be significantly reduced with appropriate instruction and counselling. However, it should be noted that even using the correct inhalation technique, only 10–20% of the stated emitted dose may be delivered to the site of action.

Spacers and breath-actuated metered-dose inhalers

Some of the disadvantages of pMDIs, namely inhalation/actuation coordination and the premature deposition of large droplets high in the airways, can be overcome by using extension devices or ‘spacers’ positioned between the pMDI and the patient (Fig. 37.4), and thus these are frequently employed with a pMDI, for administering aerosol medications to young children (see also Chapter 43). The dose from a pMDI is discharged directly into the reservoir prior to inhalation. This reduces the initial droplet velocity, large droplets may be removed by impaction, efficient propellant