The clearance of particle-loaded macrophages occurs over a period of days or weeks.

Hydrophobic compounds are usually absorbed at a rate dependent on their oil/water partition coefficients, whereas hydrophilic materials are poorly absorbed through membrane pores at rates inversely proportional to molecular size. Thus, the airways' membrane, like the gastrointestinal tract, is preferably permeable to the unionized form of a drug. Some drugs, such as sodium cromoglicate, are partly absorbed by a saturable active transport mechanism, whilst large macromolecules may be absorbed by transcytosis. The rate of drug absorption, and consequently drug action, can be influenced by the formulation. Rapid drug action can generally be achieved using solutions or powders of aqueous soluble salts, whereas slower or prolonged absorption may be achieved using suspension formulations, powders of less soluble salts or novel drug delivery systems such as liposomes and microspheres.

Formulating and delivering therapeutic inhalation aerosols

There are currently three main types of aerosol-generating device for use in inhaled drug therapy: pressurized metered-dose inhalers, dry powder inhalers and nebulizers.

Pressurized metered-dose inhalers

Pressurized metered-dose inhalers (pMDIs), also referred to as metered-dose inhalers (MDIs), were introduced in the mid-1950s and are the most commonly used inhalation drug delivery devices. In pMDIs, drug is either dissolved or suspended in liquid propellant(s) together with other excipients, including surfactants, and presented in a pressurized canister fitted with a metering valve (Fig. 37.2). A predetermined dose is released as a spray on actuation of the metering valve. When released from the canister, the formulation undergoes volume expansion in the passage within the valve and forms a mixture of gas and liquid before discharge from the orifice. The high-speed gas flow helps to break up the liquid into a fine spray of droplets.

Containers

Pharmaceutical aerosols may be packaged in tin-plated steel, plastic-coated glass or aluminium containers. In practice, pMDIs are generally presented in aluminium canisters, produced by extrusion to give seamless containers with a capacity of 10–30 mL. Aluminium is relatively inert and may be used uncoated where there is no chemical instability between container and contents. Alternatively, aluminium containers with an internal coating of a chemically resistant organic material, such as an epoxy resin or polytetrafluoroethylene (PTFE), can be used.

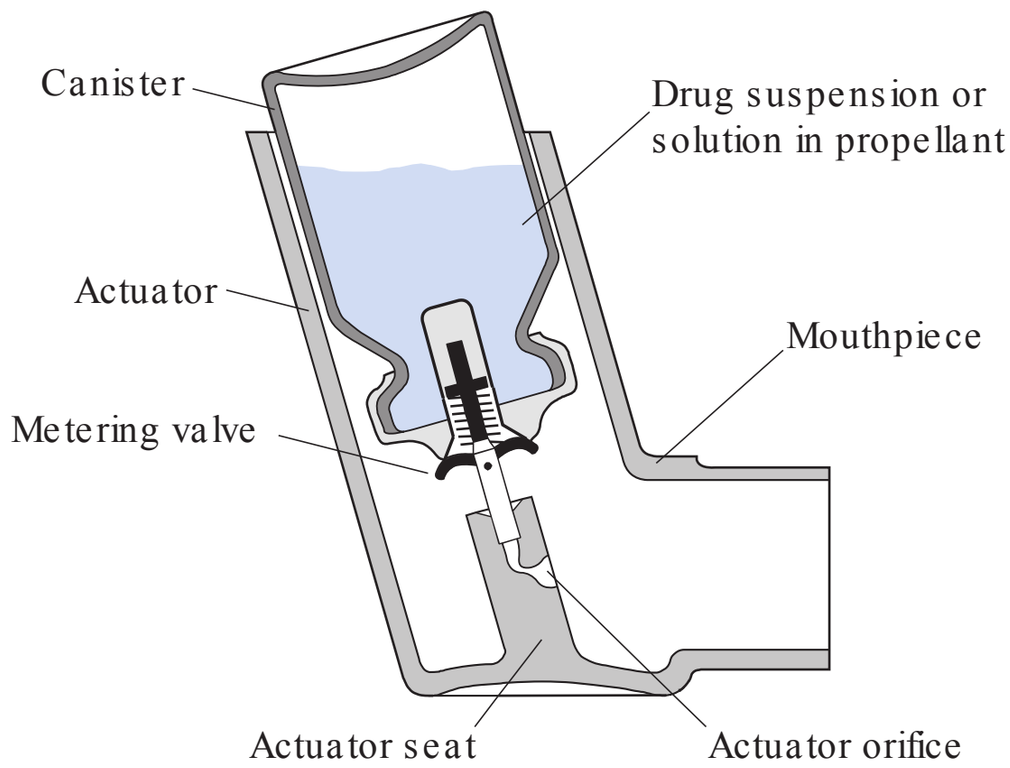

Fig. 37.2 • The pressurized metered-dose inhaler.

Propellants

The propellants used in pMDI formulations are liquefied gases, traditionally chlorofluorocarbons (CFCs) which are now largely replaced by hydrofluoroalkanes (HFAs). At room temperature and pressure, these are gases but they are readily liquefied by decreasing temperature or increasing pressure. The head space of the aerosol canister is filled with propellant vapour, producing the saturation vapour pressure at that temperature. On spraying, medicament and propellant are expelled and the head volume increases. To reestablish the equilibrium, more propellant evaporates and so a constant pressure system with consistent spray characteristics is produced. The CFCs currently employed in pMDI formulations are trichlorofluoromethane (CFC-11), dichlorodifluoromethane (CFC-12) and dichlorotetrafluoroethane (CFC-114). Formulations generally comprise blends of CFC-11 and CFC-12 or CFC-11, CFC-12 and CFC-114 (Table 37.1), together with a surfactant such as a sorbitan ester, oleic acid or lecithin, which acts as a suspending agent and lubricates the valve.