Propellants HFA-134a (trifluoromonofluoroethane) and HFA-227 (heptafluoropropane) are non-ozone depleting, non-flammable HFAs, also called hydrofluorocarbons (HFCs), which are now used as alternatives to CFC-12 (see Table 37.1). However, these gases contribute to global warming and further replacements may be sought in the future.

HFA-134a and HFA-227 have some physical properties, including density, which are similar to those of CFC-12 and, to a lesser extent, CFC-114. However, they have presented major formulation challenges; in particular, they are poor solvents for the surfactants commonly used in pMDI formulation and no alternative to CFC-11 is currently available. Ethanol is approved for use in formulations containing HFAs to allow dissolution of surfactants, and is included in marketed HFA pMDI products. However, ethanol has low volatility and its inclusion may consequently increase the droplet size of the emitted aerosols.

Metering valve

The metering valve of a pMDI permits the reproducible delivery of small volumes (25–100 μL) of product. Compared to the non-metering continuous-spray valve of conventional pressurized aerosols, the metering valve in pMDIs is used in the inverted position (Fig. 37.3). Depression of the valve stem allows the contents of the metering chamber to be discharged through the orifice in the valve stem and made available to the patient. After actuation, the metering chamber refills with liquid from the bulk and is ready to dispense the next dose. A corollary of this is that the pMDI needs to be primed, i.e. the metering chamber must be filled, prior to the first use by a patient. pMDI valves are complex in design and must protect the product from the environment, while also protecting against product loss during repeated use. The introduction of HFA propellants with different solvent properties has necessitated the development of new valve elastomers. The valve stem fits into the actuator, which is made of polyethylene or polypropylene. The dimensions of the orifice in the actuator play a crucial role, along with the propellant vapour pressure, in determining the shape and speed of the emitted aerosol plume.

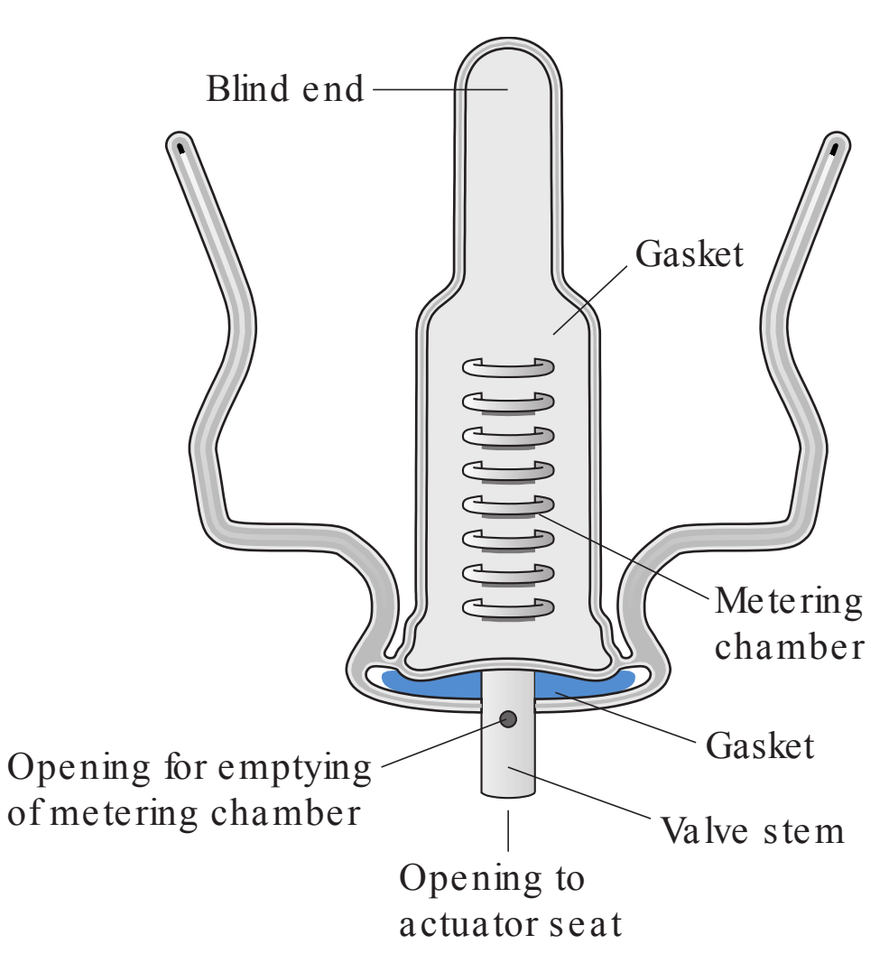

Fig. 37.3 • The metering valve.

Formulating pressurized metered-dose inhalers

Pressurized aerosols may be formulated as either solutions or suspensions of drug in the liquefied propellant. Solution preparations are two-phase systems. However, the propellants are poor solvents for most drugs. Cosolvents such as ethanol or isopropanol may be used, although their low volatility retards propellant evaporation. In practice, pressurized inhaler formulations have traditionally been almost exclusively suspensions. These three-phase systems are harder to formulate and all the problems of conventional suspension formulation, such as caking, agglomeration, particle growth, etc., need to be considered. Careful consideration must be given to the particle size of the solid (usually micronized to between 2 and 5 μm), valve clogging, moisture content, the solubility of active pharmaceutical ingredient in propellant (a salt may be desirable), the relative densities of propellant and drug, and the use of surfactants as suspending agents, e.g. lecithin, oleic acid and sorbitan trioleate (usually included at concentrations between 0.1 and 2.0% w/w). These surfactants are very poorly soluble (<0.02% w/w) in HFAs and so ethanol is usually employed as a cosolvent, though alternative surfactants are being developed. Solution formulations of some drugs, such as beclometasone dipropionate are now available. Evaporation of HFA propellant following actuation of these formulations results in smaller particle sizes than with conventional suspension formulations of the same drug, with consequent changes in its pulmonary distribution and bioavailability. The dose