quality, purity, potency, homogeneity, viscosity, specific gravity, particle size, microbial limits, and impurity profile. These tests do not provide any information about drug release properties of the product, stability of the product, or effects of manufacturing and processing variables on the performance of the finished dosage form.

## 18.2 IN VITRO RELEASE TESTING

IVR is one of several methods used to characterize performance characteristics of a finished topical dosage form. Important changes in the characteristics of a drug product or in the thermodynamic properties of the drug substance in the dosage form should be manifested as a difference in drug release. Drug release of semisolid dosage form is theoretically proportional to the square root of time when the drug release from the formulation is rate limiting. A plot of the amount of drug released per unit area (mcg/cm$^2$) against the square root of time yields a straight line, the slope of which represents the release rate. This release rate measure is formulation specific and can be used to monitor product quality. The IVR methodology for semisolid dosage forms is very well summarized in the Scale-Up and Post-Approval Changes (SUPAC-SS) guidance document of U.S. Food and Drug Administration (FDA) (1). The drug release methodology uses a vertical diffusion cell system (VDC) and is described briefly here.

- *Diffusion cell system*: A static diffusion cell system with a standard open-cap, ground-glass surface with 15-mm-diameter orifice and total diameter of 25 mm.
- *Synthetic membrane*: Appropriate inert, porous, and commercially available synthetic membranes such as polysulfone or cellulose acetate/nitrate mixed ester of appropriate size to fit the diffusion cell diameter (e.g., 25 mm in the preceding case).
- *Receptor medium*: Appropriate receptor medium such as aqueous buffer for water-soluble drugs or a hydroalcoholic medium for sparingly water-soluble drugs or another medium with proper justification.
- *Number of samples*: A minimum of six samples is recommended to determine the release rate (profile) of the topical dermatological product.
- *Sample applications*: About 300 mg of the semisolid preparation is placed uniformly on the membrane and kept occluded to prevent solvent evaporation and compositional changes. This corresponds to an infinite-dose condition.
- *Sampling time*: Multiple sampling times (at least five times) over an appropriate period to generate an adequate release profile and to determine the drug release rate (a six-hour study period with no fewer than five samples, i.e., at 30 minutes and one, two, four, and six hours) are suggested. The sampling times may have to be varied depending on the formulation. An aliquot of the receptor phase is removed at each sampling interval and replaced with fresh aliquot so that the lower surface of the membrane remains in contact with the receptor phase over the experimental period.
- *Sample analysis*: An appropriate validated, specific, and sensitive analytical procedure, generally high-pressure liquid chromatography (HPLC), is used to analyze the samples and to determine the drug concentration and the amount of drug released.
- *IVR rate*: A plot of the amount of drug released per unit membrane area (mcg/cm$^2$) versus square root of time should yield a straight line. The slope of the line (regression) represents the release rate of the product.

The relationship between drug release and square root of time has been shown to be linear and valid for topical formulations as long as the percentage of drug release is less than 30% of the drug applied in the donor chamber. This relationship holds true for topical formulations with either fully dissolved or suspended drug. An X-intercept typically corresponding to a small fraction of an hour is a normal characteristic of such plots.