the liquid through the valve orifice and atomize the suspension. The chlorinated hydrocarbon and the primary emulsion or suspension vehicle will evaporate, and the drug, in finely divided form, will be administered to the location of treatment (lung, skin).

In general the physical instability of aerosols can lead to changes in (a) total drug delivered per dose or (b) total number of doses that may be obtained from the container. It is intuitively obvious that the particle size range must be fine (i.e., the particles will have to pass through the valve).

In general the primary disperse system is filled into a seamless aerosol can, the valve assembly is attached, and the halogenated hydrocarbon is filled by pressure through the valve. The under-the-cap filling method has been described by Boegli et al. (1969). The halogenated hydrocarbon can, alternatively, be "liquid filled" at low temperature. For products that are moisture sensitive, this presents the problem of condensed ice and water in the product.

As far as "cleanliness of operation," aerosol lines are usually kept separate from conventional filling lines (Sciarra, 1974) (or the product is contract filled). Some attempts have been made to use ethylene oxide sterilization of the can (Joyner, 1969a, 1969b), and aseptic fillings (Harris, 1968; Sciarra, 1967) can be carried out.

6.1. Aerosol Testing

Some testing methods are official in the USP (XXI). The Chemical Testing Manufacturers Association has developed a series of tests described in the ASCM Handbook (Aerosol Guide, 1981).

Several test methods are used to detect physical aerosol instability, viz., (1) unit spray content, (2) color and odor, (3) rate of leakage, (4) moisture and trace catalytical substances, (5) particle size distribution, (6) spray characteristics, (7) moisture and trace catalytical substances, (8) pH, (9) delivery rate, (10) microbial limit tests, and (11) container compatibility.

Of the above, leak testing is official in the USP (XXI). This consists of obtaining the weight loss after at least 3 days of storage and converting it to loss per year. If plastic-coated glass containers are used, the test should be done at constant humidity. A faster method is to use an eudiometer tube described in the CSMA aerosol guide. This has the advantage of speed and also is advantageous in that it distinguishes between leakage from crimp versus leakage from valve gaskets.

For spray characteristics a qualitative measurement is to spray onto paper that is treated with a mixture of dye and talc, as described in the CSMA Aerosol Guide. There are also radiotracer techniques (Smith et al., 1984) and TLC graphic techniques (Benjamin et al. 1983). The Aerosol Guide, p. 77 also describes a method whereby the spray is sprayed through a pie shaped wedge onto a rotator.

Particle size analysis is the most important characteristic and hence the most important aerosol stability test. Sciarra states that particle sizes are between 1 and 10 μm and mostly between 3 and 5 μm. Particle size affects stability of delivery rate, effective dose, mass of drug delivered and of course the stability of the suspension itself. The methods used are microscopy, sedimentation methods, light scattering, cascade impactors, and liquid impingers. If the particle size distributions are determined by electronic methods (e.g., Coulter counter, Malvern), then allowance for solubility should be made.