2.2 Whiskers

McVean et al. (1972) reported on the case of a parenteral solution (morphine) where "whiskers" occurred at the tip of the ampul in a large percentage of ampuls upon room-temperature storage.

This is a defect that will occasionally occur in a product. It is due to pinholes in the glass. The solution wicks out, and the liquid evaporates on the outside. The solid that is formed serves to wick out more solution, and long crystals or "whiskers" may occur. One might ask why the pinholes have not been detected in the dye test used for autoclaved ampuls. There are two reasons. One is that the hole may be too small for detection (about 0.5 μm is the detection limit). The other is that the ampul was tight at the time of manufacture, but the heat sealing line was run too rapidly, or the flame temperature was incorrect, so that the glass did not have time to anneal properly, and the strain caused the crack during storage (not immediately after manufacture).

2.3 Cloud Times

Sometimes a cloud will appear in a product as the storage time progresses, and this is most often due to chemical changes in the system. If for instance an ester (e.g., polysorbate, which is a fatty acid ester) hydrolyzes, then the produced acid may be poorly soluble. If the solubility is denoted S, then the following holds: If the reaction in general is written

$$A + H_2O \rightarrow B \tag{10.3}$$

where A is a drug of initial concentration A_0 and B is the decomposition product with solubility S (which is assumed to be limited). Assuming first order, the concentration of B is then given by

$$[B] = A_0[1 - \exp(-kt)] \tag{10.4}$$

At time t^* the solubility will be exceeded, and t^* is what is denoted the cloud time. t^* is given by

$$S = A_0[1 - \exp(-kt^*)] \tag{10.5}$$

or

$$\ln\left[1 - \frac{S}{A_0}\right] = -kt^* \tag{10.6}$$

If $A_0 \gg S$ then this simplifies to

$$t^* = \frac{S}{kA_0} \tag{10.7}$$