

For the freeze-thaw test, the question is what the minimum temperature should be, temperatures from -5° to $+5^{\circ}\text{C}$ being the most common. -5°C frequently gives rise to phase separation and irreversible changes that would not be seen in usual temperature ranges (Nakamura and Okada, 1976), but again, such tests may be used to select a "presumably best" formula from a series of preparations in product development. Results of a typical freeze-thaw cycle are shown in Fig. 10.

Centrifugation has been used by some investigators (Tingstad, 1964; Hahn and Mittal, 1979; and Ondracek et al., 1985). The general idea is that g can be increased in the terminal velocity predicted by Stokes's law (Eq. 11), but often the stresses caused by centrifugation may cause coalescence, which would not occur during normal collision stress.

Some investigators claim fair success in predictions by this means, but as Davis (1987) cautiously states, "as a general rule it can be stated that systems that withstand accelerated stress conditions should be stable under normal storage conditions. However the corollary is not necessarily true." That is, if the preparation fails the test it *may* still be all right, but if it passes the test it should be all right. Although this may be true overall, one can visualize that if a preparation is centrifuged right after manufacture, then the stress does not include the chemical changes (surfactant decomposition for instance) that occur on storage, and in this respect it may give too optimistic a prediction.

Buscall et al. (1979) have measured phase separation at several different centrifugal g s and have established from these data a so-called coalescence pressure. This (again recalling that the test does not account for chemical changes on storage) may be an appropriate parameter.

One predictive method in formulation is the correlation afforded by coalescence rates (Fig. 11), and this is rational in selecting the "best" of many formulations; in general the system with the highest phase inversion temperature is the best. The (nonchemical stability dictated) coalescence rate could theoretically be calculated prior to storage, and the difference between observed and calculated then attributed to chemical stability causes.

For emulsions, it should again be pointed out that rapid creaming and flocculation does not necessarily mean rapid coalescence. For emulsions there have been reports (Rhamblhau et al., 1977) that attempted to tie zeta-potentials to emulsion behavior on storage, but the generality of such an approach has been questioned (Davis, 1987).

The shaking test is usually carried out at 2–3 hertz (Davis, 1987), and the philosophy here is to intensify the collision frequency between globules (and to some degree also the intensity). This is therefore considered an accelerated test, but it actually is part of the product life (transportation). In any event, it should be included in protocols and simply reported.

6. AEROSOLS

Sciarra has reviewed pharmaceutical and cosmetic aerosols (1974). Aerosols are solutions, primary emulsions, or suspensions (i.e., suspensions in a suitable solvent such as ethanol) of active principle in chlorinated hydrocarbons, contained in a pressure can. Either a dip tube or a metering device connects the pressurized liquid contents to the valve. Upon activation of this, the internal pressure will force