8.6. Percolation Thresholds

When a solid is compressed, then one might imagine that at "full" compression, the tablet would be similar to a perfect crystal, in that there would be no void space left in it. This is never achieved, however, and the fraction of void is called the porosity. This may be visualized as isolated pockets of void space or, as the porosity increases, strings of void, eventually terminating at the surface. The porosity at which this latter situation is achieved is denoted the threshold value.

Threshold values for a drug and its excipients in combination are important because they govern such properties as dissolution, hardness, and disintegration. For this purpose, percolation studies are often employed in pharmaceutical research.

Leuenberger and Leu (1992) and Leu and Leuenberger (1993) introduced the concept of drug percolation to the pharmaceutical sciences. By this, a pharmaceutical system is described as a bond/site system. In this concept, a cluster is defined as a group of nearest neighbor sites where all positions consist of the same component. There is a concentration where there is maximum probability that the clusters will start to percolate, and this is the percolation threshold. If the measured porosity of the tablet is denoted ε_m and (after dissolution) the porosity created by loss of dissolved matter is denoted ε^*, then the so-called β property is

$$\beta = -c\varepsilon_c + c\varepsilon \tag{10.44}$$

where $\varepsilon = \varepsilon_m + \varepsilon^*$ is the initial + developed (matrix) porosity, c is a constant, and ε_c is the critical porosity threshold for percolation. This ties in with the Higuchi type plot, the slope of which is b, and β is defined as

$$\beta = \frac{b}{[2A - \varepsilon S]^{1/2}} \tag{10.45}$$

where A is the drug load (g/cm^3 of total tablet) and S is solubility. When porosity is plotted versus β value, then a straight line ensues that cuts the x-axis at the percolation porosity.

The threshold for drug percolation may be obtained when more drug is available than that described in Chapter 9. Soriano et al. (1998) have described percolation methods that are done primarily by conducting dissolution studies with drug substance at various concentrations. They employ the method of Bonny and Leuenberger (1993) and Leuenberger and Leu (1992) for this purpose.

8.7. Multipoint Determinations

In post NDA testing, there is some reason for not carrying out dissolution at more than one time point, because of both human resources and equipment. In pre-NDA situations, however, as described e.g. by Prandit et al. (1994), the importance of carrying out multiple time points in dissolution cannot be stressed enough. Conclusions are difficult to reach if this is not done.

For instance Prandit et al. (1994) reported that aging affected the dissolution of nalidixic acid tablets and concluded that the effect was not attributable to an increase in disintegration time (as measured in a dissolution apparatus). Published data often