The k values can be plotted as an Arrhenius plot, i.e., one may, after short periods of time, at elevated temperature, calculate an extrapolated k value at room temperature. By sampling daily at 55°C, one can determine the Y value ($Y_{\text{lower limit}}$), which corresponds to the poorest appearance that is acceptable. Since k is known for room temperature (k_{25}), it is possible to calculate a "shelf life date" (t^*) based on appearance from inserting $Y_{\text{lower limit}}$ into Eq. (10.54):

$$\ln\left\{1 - \frac{Y_{\text{lower limit}}}{Y_\infty}\right\} = -kt^* \tag{10.54}$$

9. SUSTAINED RELEASE PRODUCTS

There are several types of sustained release principles used in pharmaceutical products, and a detailed description is beyond the scope of this book. What will be done here is simply to state the types of dissolution profiles that can be expected, and how the parameters could change with time.

9.1 Coated Beadlets and Granules

The coated nonpareil seed is the original sustained release form invented by SKF in the 1950s. Here a drug is applied (in the form of a sugar syrup) to monodisperse sugar crystals. Drying is carried out after each application step, so that the drug eventually is in a sugar matrix around the original seed. This beadlet is then coated with either a semipermeable film or an impermeable film with a soluble filler. The latter, upon exposure to dissolution medium, will allow the soluble filler to dissolve, so that pinholes are created in the film. Liquid then diffuses in through the film (or the holes in it), becomes saturated on the inside of the beadlet, and the dissolved drug then diffuses out. The diffusion takes place under an (approximately) constant concentration gradient (the solubility of the drug in the medium), as long as there is undissolved material inside the beadlet (and the concentration is low in the outside fluid creating sink conditions). Once the last drug has dissolved, the concentration inside the beadlet will decrease, and the diffusion slows down. It is, therefore, often, difficult to get the last 5–10% of material to release from this type (and other types of sustained release) dosage forms.

There are, obviously, three stages in the dissolution (Fig. 32):

$0 < t < t_i$: Penetration of liquid into the pellet. t_i is the time it takes for this to complete, and it is denoted the lag time.

$t_i < t < t_f$: t_f is the point in time where all the drug inside the pellet has dissolved.

$t > t_f$: This is the final period where dissolution is slower.

The general dissolution pattern in the period $t_i < t < t_f$ is

$$\ln\left[\frac{M}{M_0}\right] = -k(t - t_i) \tag{10.55}$$

M is the mass not dissolved (and M_0 is the dose) and is obtained by multiplying concentration with dissolution liquid volume and subtracting this (the amount dissolved) from M_0. k is the dissolution constant and will be the smaller (and t_i