concentration of anhydrous form (μg/ml), and *b* represents the intercept obtained by the extrapolation of the linear portion of the dissolution curve of the anhydrous form. The parameters k_t, k_r, and C_{SA} were calculated from the above-mentioned equations, and k_t, or the rate constant of the transport process, was calculated from the slope of the dihydrate curve using the solubility value for the respective dihydrate (C_{SH}) obtained from equilibrium solubility testing. C_{SA} was calculated from Equation 20.2 using the estimate of the slope of the initial segment and the k_t value calculated from Equation 20.2. The intercept of the final segment was calculated using Equation 20.4. The results are added in Table 20.10, where it is seen that in addition to the differences in the transition time point, variations in the value for the constant of phase transformation process (k_r) were also observed. The highest k_r value means that the sample has ability to undergo the fastest transformation from anhydrous to dihydrate form, consequently resulting in the highest IDR. In all examined samples, the highest k_r value was observed for CBZB and the lowest one was observed for CBZP. Considering these results, the correlation between the intrinsic dissolution parameters and the rate of transformation is promising and may help to determine the kinetics of transformation for each examined CBZ and eventually can help to predict its behavior in the final formulation by verifying these parameters in the preformulation stage.

The intrinsic dissolution parameters were used to estimate the solubilities of the samples. The calculated solubilities ranked CBZB > CBZP > CBZA and were in agreement with literature data of form III (Kobayashi et al., 2000), but were higher than the experimentally obtained equilibrium solubilities (measured after 72 h) because during the solubility measurements transformation of CBZ anhydrous to CBZ dihydrate took place.

The intrinsic dissolution rates were calculated from the initial part of each profile using Equation 20.5 (Kobayashi et al., 2000, Sethia and Squillante 2004):

$$\text{IDR} = \frac{C}{t} \cdot \frac{V}{S} = k \cdot C_s \tag{20.5}$$

where *S* is the surface area of the tablet (cm^2), *V* is volume of test solution (mL), *k* is intrinsic dissolution rate constant, and C_s represents solubility (mg/mL).

The obtained results have the same ranking as reported in the estimated solubility, that is, IDR CBZB (77.45 ± 2.04) > IDR CBZP (73.92 ± 2.00) > IDR CBZA (69.11 ± 1.96) (μg/min/cm^2). The IDR values of the dihydrates were nearly the same (between 22.43 and 23.09 μg/min/cm^2).

In conclusion, it is important to note that differences in the intrinsic dissolution rates of the samples were relatively small when described by a single value, however, they become important when the intrinsic dissolution behavior is described by a set of kinetic parameters. Considering that carbamazepine has narrow therapeutic index and very narrow dissolution range of acceptance criteria in the USP monograph, the variation in the kinetics of conversion from anhydrate to dihydrate form among different raw material of CBZ is important information. Therefore, the point of transformation as well as the kinetics of the phase transformation may be considered as critical parameters that should be investigated and monitored according to Q8 guidelines for drug substance.

Critical Process Parameters

The wet agglomeration process is the most common process for granulation and tableting of pharmaceutical powders. Conventional wet agglomeration uses a high-shear mixer granulator combined with a fluid-bed dryer or a fluid-bed granulator/dryer. Innovative semicontinuous processes such as the Glatt Multicell™ production line described earlier also use high-shear mixer/granulator in combination with fluid-bed dryer.

To design the process of wet agglomeration in order to limit or eliminate product variability, a mechanistic approach to the critical process parameters is required. A critical process parameter is the process parameter that must be controlled within the design space (i.e., within predetermined limits) to ensure the performance of the product.