TABLE 19.5
Examples of Changes in the Solid State of Drugs during Processing

Compound	Process	Reference
Barbitone	Milling	Chan and Doelker (1985)
Caffeine	Milling/compression	Chan and Doelker (1985)
Chlorpropamide	Milling	Chan and Doelker (1985)
Sulfabenzamide	Milling	Chan and Doelker (1985)
Sulfanilamide	Milling	Wall (1986)
Clotrimazole	Milling	Wall (1986)
Digoxin	Milling	Wall (1986)
Amiloride HCl	Milling/compression	Jozwiakowski et al. (1993)
Cephalexin	Milling	Matsumoto et al. (1991)
Fostedil	Milling	Takahashi et al. (1985)
Indomethacin	Compression	Matsumoto et al. (1991)
Piroxicam	Compression	Ghan and Lalla (1992)
Maprotiline HCl	Compression	Chan and Doelker (1985)
Chloroquine diphosphate	Compression	Bjaen et al. (1993)
Chloramphenicol palmitate	Milling	Kaneniwa and Otsuka (1985)
Ranitidine HCl	Milling	Chieng et al. (2006)
Sodium salicylate	Spray drying	York (1983)
Carbamazepine	Fluid-bed granulation	Everz and Mielck (1992)
Chloramphenicol palmitate	Heating	DeVilliers et al. (1991)

worst-case scenario; excipient addition may dilute the effect in actual formulations. Capsule filling uses little to no compression force, depending on the scale and machine design, and can be used when pressure-induced transformations are problematic. Jozwiakowski et al. (1993) calculated the percent conversion of amiloride HCl polymorph B into polymorph A under different compression forces and dwell times using a quantitative XRD method. For this drug, compression force had a greater impact than dwell time, as shown in Table 19.6. The percent conversion was a function of the compression force, but a four times increase in dwell time at the same compression force had no additional impact on the transformation. As expected, there is no change in the stable form (polymorph A) at the highest compression force.

Aqueous granulation in a high shear mixer or a fluid bed can cause hydrate formation, and the subsequent drying can cause desolvation. Carbamazepine was transformed from one anhydrate (form III) to another (form I) through a dihydrate intermediate when both of these processes were used (Everz and Mielck, 1992). The heat of drying can also cause the conversion of one form to another, as seen with chloramphenicol palmitate by DeVilliers et al. (1991).

TABLE 19.6
Transformation of Amiloride HCl Dihydrate Polymorphs during Compression

Initial Polymorph	Compression Variable (Force/Dwell Time)	Conversion (%)
B	1,100 psi/30 s	6
B	3,000 psi/30 s	41
B	3,000 psi/2 min	35
B	12,000 psi/2 min	69
A	12,000 psi/2 min	0

Source: Jozwiakowski, M. J., et al. *Int. J. Pharm.*, 91, 195–207, 1993.