TABLE 19.11
Glass Transition Temperature (T_g) of Amorphous Sucrose versus Water Content

Absorbed Water (% w/w)	Glass Transition (°C)
0.00	74
0.99	60
1.47	58
1.98	50
3.13	32

Source: Saleki-Gerhardt, A. and Zografi, G. *Pharm. Res.*, 11: 1166–117, 1994.

When a substance lowers the glass transition temperature of another, it is referred to as a plasticizer. Water has a glass transition temperature of −138°C (Sugisaki et al., 1968), which is low enough that it plasticizes pharmaceutical systems. This is a desired effect when the water content of excipients plasticize the material to enhance compressibility. When water is inadvertently introduced to a metastable system containing an amorphous drug, it can reduce the glass transition temperature into the range where the propensity to crystallize is higher. Table 19.11 (Saleki-Gerhardt and Zografi, 1994) shows how small amounts of absorbed water can change the physical stability of amorphous sucrose by lowering the glass transition temperature closer to room temperature. When partially amorphous materials are created by processing energy, nearly all the measured water content is concentrated in the amorphous regions, which can significantly magnify this effect. Chemical instability and crystallization of amorphous forms can be caused by the absorption of small amounts of atmospheric water by this mechanism. Matsuda and Kawaguchi (1986) found that amorphous oxyphenbutazone crystallized much faster when exposed to ambient humidity. In this case, it crystallized as the anhydrate at lower humidity and to the hemihydrate or monohydrate at moderate to high humidities. Strydom et al. (2009) demonstrated this conversion with an amorphous form of stavudine. The transformation from amorphous to hydrate was seen at relatively low relative humidity (>30%). Furthermore, stability studies at elevated temperature (100°C) indicated that the amorphous solid transforms to form III (hydrate) in the presence of moisture or to form II (anhydrous) in the absence of moisture.

To market an orally available dosage form of an amorphous solid, the drug must remain in the noncrystalline state for the shelf life of the product for predictable absorption. Applying the general rule of 50°C below T_g to inhibit molecular mobility, this means the T_g of the system should be more than 70°C–80°C. For solid dosage forms, excipients with higher glass transition temperatures can be added, which result in antiplasticization. This is why coprecipitates (the subject of Chapter 18) containing amorphous drugs and PVP (T_g = 280°C) are often physically stable enough for use in dosage forms. Yoshioka et al. (1995) have shown that indomethacin crystallization can be inhibited by the addition of 20% PVP, which raises the glass transition temperature from 50°C to 66°C and the crystallization temperature from 97°C to 135°C. Fukuoka et al. (1989) applied the same principle in using salicin (T_g = 60°C) to stabilize phenobarbital (T_g = 48°C) and phenobarbital to stabilize antipyrine (T_g = −17°C).

Coamorphous binary mixtures of small molecules are a potential strategy to increase the dissolution of a drug substance while simultaneously improving the stability of the amorphous state. Löbmann et al. (2011) investigated a coamorphous combination of naproxen and γ-indomethacin at molar ratios of 2:1, 1:1, and 1:2. Intrinsic dissolution testing showed an increase in dissolution rate for the amorphous indomethacin compared to the crystalline γ-indomethacin and a further increase was seen with its coamorphous forms. Similar results were seen with naproxen and it was found that naproxen could be made amorphous in combination with γ-indomethacin but not