physical transformation (i.e., solid to liquid state and back), intimate drug–polymer mixing, and/or enhanced surface area. Formation of crystalline or amorphous solid dispersions can be influenced by the rate of solidification of mixture and the rate of crystallization of drug, polymer, or both.

Drug and Polymer Exhibiting Miscibility in Fluid State

If the drug and polymer are miscible in their fluid state, then as discussed in the section titled Thermodynamic Perspective of Miscibility and Phase Separation in Solid Dispersions, the mixture may or may not undergo phase separation during solidification, thereby influencing the structure of solid dispersion.

Eutectic Mixtures

Eutectic mixtures are formed when the drug and polymer are miscible in their molten state, but on cooling, they crystallize as two distinct components with negligible miscibility. When a drug (A) and a carrier (B) are comelted at their eutectic composition defined by point Y, as shown schematically in Figure 18.4, the melting point of the mixture is lower than the melting point of either drug or carrier alone. While some researchers claim eutectics to be an intimate but inert physical mixture of the two components; others claim that the reduction in the melting point of eutectic mixtures is a direct evidence of molecular interaction between the drug and the carrier. At the eutectic composition (Y), both drug and carrier exist in a finely divided state, which results in higher surface area and enhanced dissolution rate of drug. Although not every carrier can form a eutectic with every drug, carriers such as polyethylene glycols (PEG), urea, and polyoxyethylene–polyoxypropylene (Pluronic®) have demonstrated eutectic formation to enhance dissolution rates of many poorly water-soluble drugs (Leuner and Dressman 2000).

Crystalline Solid Dispersion

A crystalline solid dispersion (or suspension) is formed when the rate at which drug crystallizes from drug–polymer miscible mixture is greater than the rate at which drug–polymer fluid mixture solidifies. Such a crystalline solid dispersion may differ from that described in the section titled Drug and Polymer Exhibiting Immiscibility in Fluid State, where even the drug–polymer fluid mixture is not miscible.

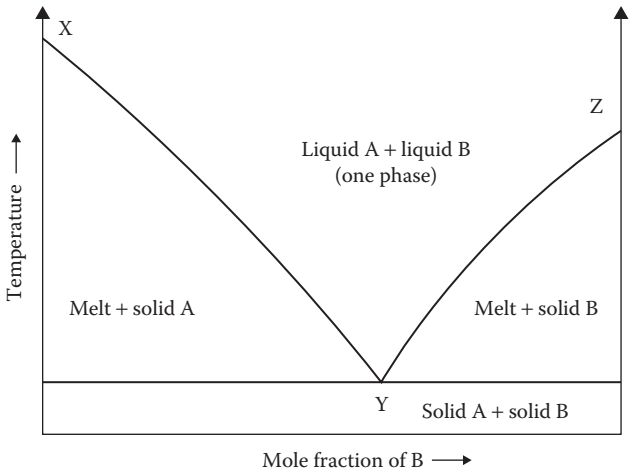

FIGURE 18.4 Phase diagram of a simple eutectic system. At temperatures below curve XY or YZ, either solid A [drug] or solid B [carrier] solidifies first from the molten mixture, respectively. At eutectic composition Y, both drug and carrier solidify simultaneously as a mixture of finely divided crystalline components.