TABLE 6.3

Thermodynamic Rules for Polymorphic Transitions

Enantiotropy	**Monotropy**
Transition < melting I	Transition > melting I
I stable > transition	I always stable
II stable < transition	—
Transition reversible	Transition irreversible
Solubility I higher < transition	Transition I always lower
Solubility I lower > transition	—
Transition II → I endothermic	Transition II → I exothermic
$\Delta H_f^I < \Delta H_f^{II}$	$\Delta H_f^I > \Delta H_f^{II}$
IR peak I before II	IR peak I after II
Density I < II	Density I > density II

are related. At a transition point, with the temperature and the pressure fixed, it is possible for interconversion to take place between two polymorphs only in the case where the structures of the polymorphs are related. If complete rearrangement is required by atoms or molecules during transformation, no point of contact for reversible interconversion exists. Therefore, the existence of enantiotropes or monotropes in thermodynamics and phase theory corresponds to related or unrelated lattice structures in structural theory. Transformation between polymorphs that have completely different lattice structures exhibits dramatic changes in properties. The difference in energy between polymorphs is not always considerable, as shown with diamond/graphite. In most cases, polymorphs in this category are required to break bonds and rearrange atoms or molecules, and consequently, the polymorphs have a monotropic relation.

For the study of polymorphs that are structurally related, the structural relationships between the polymorphs should be established first; second, it should be explained why a particular substance is able to arrange its structural units in two closely related lattices, and finally, there should be a description of the manner and conditions under which rearrangement of the units from one lattice type to another can happen. It is the physical form of the drugs that is responsible for its degradation in the solid state. Selection of a polymorph that is chemically more stable is a solution in many cases. Different polymorphs also lead to different morphology, tensile strength and density of powder bed, which collectively contribute to the compression characteristics of materials. Some investigation of polymorphism and crystal habit of a drug substance, as it relates to pharmaceutical processing, is desirable during its preformulation evaluation, especially when the active ingredient is expected to constitute the bulk of the tablet mass.

Various techniques are available for the investigation of the solid state. These include microscopy (including hot-stage microscopy, HSM), infrared spectrophotometry (IRS), single-crystal X-ray and X-ray powder diffraction (XRPD), thermal analysis, and dilatometry.