can be influenced by the supersaturation, the nature of the solvent, the presence of impurities, the fluid dynamic regime *etc.*; at industrial level, the crystalline habit plays a crucial role in downstream processes such as filtration, washing, drying, flow, compaction, dissolution, and packaging.[32]

Polymorphism is the ability of a solid substance to exist in at least two different crystalline arrangements of the molecules having the same chemical composition; the term pseudo-polymorphism is used to describe the ability of crystals to incorporate variable quantities of solvent with a defined stoichiometry. Polymorphism often plays a significant role in the preparation of active pharmaceutical ingredients (APIs) and other products of the pharmaceutical industry, since different polymorphs can exhibit important differences in solubility, dissolution rate, stability, melting point, density and many other properties that significantly affect the efficacy, bioavailability and safety of APIs.[33]

According to the Ostwald step rule,[34] a crystalline system evolves from the least stable (more soluble, highest Gibbs free energy barrier) to the most thermodynamically stable form (less soluble, lowest Gibbs free energy barrier). In some cases, if the energy of the system is not sufficient to overcome the nucleation barrier of unstable polymorphs, only the stable form is obtained.

A practical implication of Ostwald's rule is that – when manipulating in an appropriate way the energy barrier to nucleation – different polymorphs can be isolated. Referring to the energy/reaction coordinate diagram for a dimorphic system in Figure 8.8, the reduction of the activation energy induced by heterogeneous nucleation on a membrane can enable the formation of both polymorphs A and B.

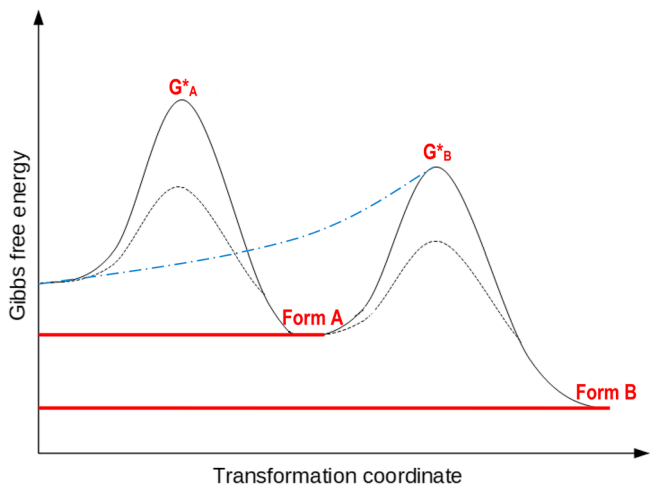

Figure 8.8 Schematic representation of the path for a solution mediated phase transformation from an unstable form A to the thermodynamically stable form B. Two pathways are possible: directly to the stable form (dot-dash line) or – if the energy of the system is sufficient to overcome the nucleation barrier for A – to form B *via* metastable form A. Membrane crystallization promotes heterogeneous nucleation, and the decrease of energy barrier can facilitate the appearance of polymorphic forms.