continuous crystallization and the effects of all transport phenomena and kinetic effects have significant impact on the process, which have been demonstrated and addressed. Continuous crystallization and process stability, spontaneous nucleation (bulk nucleation) at high supersaturation ratio, secondary nucleation and mixing, particle–impeller attrition, and heterogeneous nucleation rate are critical aspects to be controlled and monitored. Understanding the mechanisms driving epitaxy at a molecular level is critical for controlling epitaxial nucleation and growth of crystals. Of particular interest for this concept, the induction time, preferential nucleation rate, and final properties of the composite are highly affected by the mechanisms driving epitaxy and proper API-excipient selection. Therefore, understanding the mechanisms controlling epitaxial ordering is fundamental for controlling the final properties of the crystalline material.

Numerous studies investigated epitaxial ordering on crystalline and other highly ordered surfaces to understand the effect of lattice matching, functional group matching (surface functionality), and interaction energy.[86] The explanations rely on a partial or total matching between the two opposing lattice planes, which significantly lowers the nucleation free energy barrier and eventually promotes nucleation. Alternately, molecular dynamics modelling could demonstrate that molecular functionality and chain orientation, in such a manner as to utilize as many hydrogen bonding groups as possible to stabilize the prenucleation aggregate of crystalline substrates, are dominant in promoting heterogeneous nucleation of a model API.

Figure. 1.7 demonstrates the surface chemistry and molecular interaction (bond matching) between the solute crystal and excipient (crystalline or polymeric). The hydrogen bond propensity and bond formation potential between the active groups on the exposed surface of excipient and also chemical bonds at different faces of the solute crystal promote preferential nucleation and crystallization. In this way, the solute molecules prefer to interact and form local nuclei on a certain side of the excipient, in competition with other surfaces (*i.e.* mixer blade, crystallizer glass wall...) or homogeneous bulk nucleation. Therefore, the nucleation and crystal growth on the surface of the excipient benefit from both the heterogenous nucleation and surface Gibbs free energy and also chemical bond formation and surface chemistry.

Heterogeneous nucleation by definition can occur on any foreign particle, such as dust, which is the distinction between homogeneous and heterogeneous nucleation. The presence of excipient crystals in the crystallization solution enhances the nucleation and yields the epitaxy. As mentioned previously, the difference in excipient selection is based on the matching ranking matrix, which is driven from molecular dynamic modeling and induction time measurement experiments. Yazdanpanah *et al.* performed an experiment with two different excipient crystals (sodium chloride and D-mannitol) at the same supersaturation ratio of solute solution (acetaminophen), and demonstrated by molecular dynamic calculations and experimental results