(cooled stream 3) is recycled.[219] Such a hybrid process setting requires 34% and 45% of the number of stages and vapor boilup, respectively, given that the composition of B in stream 1 should be approximately 10 mol% above the eutectic composition to be crystallized.[219] An abundance of work exists on hybrid distillation–crystallization processes.[183,184,186,187,219,221] However, although melt crystallization can be operated continuously[222,223,225] (see also Chapter 11) or semi-continuously, the majority of examples in literature use a static layer melt crystallization process.

7.4.2 Process Integration

Originally conceived as a purification and separation process, crystallization has also become an important technique in particle design from macro to nano-sized particles. Generally, crystallization processes are tailored (i) to obtain the product purity needed with maximized yield and (ii) to improve the downstream operations such as filtration, drying, handling, milling, powder mixing, and tableting. Besides processing, physicochemical properties of the final drug product, such as dissolution rate and bioavailability, also depend on the size and the morphology of the crystals.[143,226,227] Up to date, solid dosage forms (*e.g.*, tablets, capsules) are the most convenient and industrially relevant drug delivery form for peroral administration due to their low cost, good stability, and patient-friendly administration.[228,229] On this account, appropriate flowability and handling properties of pharmaceutical powders in downstream processing such as direct tablet-compression or capsule-filling are paramount. Conventionally, milling and granulation/agglomeration are often employed as unit operations subsequent to crystallization either for better bioavailability or for improving flowability, compressibility, and content-uniformity by avoiding demixing of powders when transported. Despite the fact that milling and granulation improve the overall crystal size, it comes often at the expense of a wider CSD[24] and can only be performed on mixtures that are not moisture sensitive and may potentially cause polymorphic transformations of the API.[230–232] However, instead of operating crystallization, milling, and granulation separately, process integration by spherical crystallization (crystallization combined with agglomeration)[233] as well as wet milling combined with crystallization[234] generate synergistic effects that permit some of these challenges to be overcome and minimize equipment cost, process time, and energy compared to when they are operated as stand-alone unit operations.[235]

7.4.2.1 Spherical Crystallization

Spherical crystallization, developed by Kawashima *et al.*[233] using salicylic acid, is a method that increases the size of crystals by transforming the crystals directly into compact spherical particles through agglomeration during the crystallization process leading to improved crystal handling properties. Thus, spherical crystallization is inherently a PI technique due to its