PROCESS INTENSIFICATION ENABLING DIRECT COMPRESSION FOR PHARMACEUTICAL MANUFACTURING: FROM SPHERICAL AGGLOMERATION TO PRECISE CONTROL OF CO-AGGLOMERATION

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Spherical Agglomeration (SA) is a novel process intensification strategy for particulate manufacturing. In the context of pharmaceutical manufacturing, it has the potential to reduce the number of unit operations in downstream processing from seven to three, which significantly reduces the manufacturing cost. However, SA process development for a new API in the drug pipeline is still a challenging exercise, which has impeded its practical implementation. The major bottleneck lies in the lack of fundamental understanding of the mechanistic principles underlying agglomeration of primary crystals, which can enable rational process design. In addition, most SA processes reported in literature focus on only the active ingredient, which does not eliminate the blending and wet granulation unit operations. The major purposes of this thesis are to (i) develop a first principle mathematical framework which can identify the fundamental agglomeration mechanism (ii) develop a model based online optimization framework, which can control the process, even in the presence of uncertainties (iii) develop a rational framework for co-agglomerating APIs and excipients, guided by process analytical technology tools (iv) utilize dynamical optimization to ensure product specifications are met viz. particle size, product purity. It is believed that the novel technology developed in this thesis will lay the groundwork for fast and robust process development of co-agglomerating APIs and excipients in the future, thereby enabling one-step direct compression. The large-scale development and deployment of this technology developed in this thesis will significantly reduce the time to market and the manufacturing costs for new APIs, thereby ensuring higher accessibility of life-saving drugs. This can also potentially have widespread economic ramifications, with millions of dollars of cost-savings for the pharmaceutical industry, thereby improving economic productivity.