A material-sparing approach for sildenafil orally disintegrating tablet development

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Purpose: The development of an orally disintegrating tablet (ODT) product from solid form selection, to establishment of a reliable crystallization method, and to development of a manufacturable formulation and efficient scalable process by the traditional empirical development approach is time- and material-consuming. The purpose of this work was to develop an ODT of sildenafil (SIL) using a materials sparing and expedited development approach, enabled by the materials science tetrahedron principle and predictive technology. In addition to the typical challenges for developing a tablet, the SIL ODT development is also presented with the problem of bitter taste.

Methods: From the reported twenty-six solid forms of Sil, a sweet salt of sildenafil with an artificial sweetener, acesulfame (Acs), was selected to overcome the problem of bitterness of SIL. The solubility and lipophilicity data of SIL and Acs was considered for designing a crystallization process. The new SIL-Acs salt was characterized for thermal stability, hygroscopicity, dissolution rate (both intrinsic and powder), flowability, and tabletability. A direct compression (DC) tablet formulation was designed based on flow and compaction properties of Acs. Formulation and process parameters were then optimized based on powder flowability, tabletability, tablet disintegration time, and expedited friability.

Results: The crystallization process (between SIL free base and Acs free acid) from acetonitrile led to SIL-Acs salt anhydrous form with high phase purity and yield (91 %) even in the 4.0 g scale. Less than 100 mg of Sil-Acs was used for solid-state characterization to confirm its excellent thermal stability (T_m=200.2 ^oC), low hygroscopicity, and acceptable dissolution rate. A particle engineering approach, i.e., nanocoating, was employed to secure excellent flowability of the Sil-Acs ODT formulation to attain good manufacturability using the DC process. The wide range of design space for compression force suggested the flexibility in manufacturing Sil-Acs ODT with

fast disintegration time (less than 30s) and low friability (less than 0.8%) (Figure 1). The development of the scalable ODT formulation and process took only 2.7 g Sil-Acs.

Conclusion: A scalable SIL ODT, exhibiting high mechanical strength, fast disintegration, low hygroscopicity, and sweet taste, was successfully developed through a material-sparing approach. Guided by material science and assisted by predictive material characterization techniques, the development of a SIL ODT product from solid form selection only required unprecedented 5 g of drug and 2 weeks of time. This exemplifies the efficiency and power of material-science guided pharmaceutical product development.

Figure 1. Dependence of disintegration time and friability of Sil-Acs tablets on compaction force.