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Project Title: Predicting and managing API blend properties for batch and continuous manufacturing
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Problem Statement: Developing formulations for a new drug entity entails significant trial and error due to the uncertainties involved with the physical properties of the API. In particular, formulations with either very high or very low drug loadings that can be robustly processed via direct compression tableting route, which is highly preferred for continuous manufacturing (CM), is very challenging due to API cohesion. We propose to develop mechanistic and semi-empirical models that allow prediction of flow and other relevant bulk properties from material sparing particle and small sample based measurements. Such predictive framework along with dry coating toolbox can facilitate DC route for CM for a much wider range of drug loadings.

Objectives: The objective of this project are to develop models for: Estimating key cohesion parameter in form of granular Bond number for candidate API or excipient through models, validated based on material sparing measurements; predicting packing density and FFC based on the Bond number of individual constituents; blend property model along with a map that allows for predicting properties for any drug loading and thus determining the need for dry or wet granulation versus direct compaction. The results will also allow decision-making regarding the need for property enhancement based on dry coating and/or the need for value-added excipients, as well as the highest drug loading possible for a given API grade in direct compression batch or CM.

Methods and Materials: Our recent work has shown that particle cohesion, represented via granular Bind number may be estimated based on a few key measurements such as surface energy, surface roughness, and particle size. We have also shown that packing density, one key measure of powder bulk behavior can be predicted for different types of particles with or without surface modification. That also allows predicting ahead of time the impact of dry coating based surface modification without having to perform dry coating. More recently, we have extended this to predict the flow behavior, specifically, the flow function coefficient (FFC) based on the estimated granular number. In addition, preliminary work has shown that this approach may be extended to blends based on constituent powder properties. We propose to fully develop this approach to robustly predict bulk density and flow (FFC) of individual APIs and their blends. Predictive models will be utilized to assess the extent of flow and bulk density enhancements required or possible after dry coating with hydrophobic or hydrophilic silica at 30-100 % surface area coverage (SAC). Ultimately, we will build knowledge base and models for quality by design (QbD) of direct compaction (DC) CM using in-line dry coating for flow enhancements and expanding the scope of DC-CM.

Anticipated Impact: Development of proposed modelling framework can allow the determination of the highest API loading for a given set of properties of the API manufactured via batch or continuous manufacturing (CM) with and without API dry coating. Alternately, given the target API loading, such models can determine the API size that must be produced during API manufacturing, and/or if they need to be dry coated, and if special purpose excipients would be required. The models should also aid in the determination of surrogate APIs that can be used for testing purposes as a replacement for proprietary APIs. Consequently, it is anticipated that there will also be diminished trial and error procedures in the formulation and process development stages. Overall results from this project will lead to significantly reduced development time and improved product quality, while enabling quality by design.