**Development of model-based strategies to accelerate the experimental campaign for the production of oral solid dosage through direct compression**

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**Abstract**

Oral Solid Dosage (OSD) forms are widely used because they are easier to manufacture and transport with respect to other pharmaceuticals and they can be advantageous for patients, e.g. because dosage measurement is not needed. This impacts the market, too: Future Market Insights forecasts OSD market to grow from US$493.2 bn in 2017 to US$ 926.3 bn by the end of 2027 [9].

In this context, our study focuses on the production of solid tablets through direct compression: API, excipients and lubricants are fed to a blender and mixed for a precise blending time; then, the powder blend fills the dies of a tablet press and it is transformed into solid tablets thanks to the compression applied by the press punches. The only factor that facilitates tablets manufacturability is the lubrication step, which improves powder flowability [6] and prevents the powder from sticking to the die walls during compression [7,8].

Once the tablet has been ingested by the patient, it must be disintegrated, dissolved and absorbed in the desired point, usually in the gastrointestinal tract [3]. Such behavior is influenced by the manufacturing process, namely by lubrication and compression, and can be analyzed preliminarily through the assessment of tablets tensile strength, which is an intermediate property of the product. Different semi-empirical models have been proposed to describe the relation among these variables; for example, the Kushner and Moore model [4] relates tensile strength to the lubrication trough three parameters. Then, Nassar et al. [5] expanded the expression of two of those parameters in order to take into account the effects of powder compression in the tablet press.

The extended Kushner and Moore model is very useful to the purpose of accelerating the design and scale-up of lubrication units, however it requires a considerable amount of data to be calibrated. Usually, up to 9 blends with different lubrication extents are prepared and then compressed in a compaction simulator. This leads to an excessive consumption of API, which is the most expensive species involved and that may not be available during drug development.

In our study we tackled this issue by proposing a science-driven method to select experimental conditions called “model-based design of experiments” (MBDoE). Differently from trial and error approaches, MBDoE does not rely on the experts’ knowledge, but on the mathematical representation of the process given by the model. More specifically, it is an optimization problem which finds the “optimal” experiments, namely the experiments that allow to maximize the information about the system. The information content of data is quantified by the Fisher information matrix [1], which is strictly related to the uncertainty region of model parameters: indeed, experiments that maximize a scalar measure of the FIM allow also to minimize the uncertainty region of parameters after calibrating the model.

However, the classical formulation of the MBDoE optimization problem was not suitable for the system under study: since the extended Kushner and Moore model used to build the objective function is algebraic, the result of MBDoE was made of one optimal value of lubrication and one optimal value of solid fraction, therefore by one optimally lubricated and compressed tablet. However, it is not possible to perform only one compression point in the tablet press (i.e., to produce only one tablet). To overcome this limit, we adapted the Fisher information matrix calculation in order to get optimal “profiles” as MBDoE results, namely multiple optimal values of solid fraction for the optimal value of lubrication.

We applied the novel MBDoE approach to different drug formulations in order to test the methodology robustness in case of different drug behaviors in terms of lubrication sensitivity. The results were analyzed both in terms of parameters precision and model prediction accuracy: independently of the formulation considered, the model calibrated with three or four optimal profiles was characterized by statistically sound parameters estimates and by a good prediction of the tablet tensile strength, satisfying all the requirements set by the industry in this field. The high information content of the optimal experiments calculated though MBDoE allowed us to reduce the experimental burden up to 70% with respect to the standard industrial practice, thus cutting down the costs for materials and labor and the time to put new tablets formulations on the market.

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