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All you need is two tablets – How axial recovery is the key to a precise out-of-die tablet density prediction

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AIM

The aim of this work was to develop a mechanistic model to precisely predict the out-of-die density profile of a material using minimal mathematical effort and a minimal number of actual compacted tablets. Axial recovery is the main reason for density changes after compression and by getting a better understanding of this mechanism, a mathematical model can be developed.

MATERIAL AND METHODS

Compaction data were collected from two different compaction simulators at two different universities (University of Minnesota - UMN and University of Copenhagen - UCPH). Data of previous compaction projects were hereby kindly provided by colleagues. Different methods to control the compaction were used (fixed thickness an fixed load) and the elastic recovery was determined right after ejection (UMN) and after 24h of relaxation (UCPH). More than 50 diverse materials, blends and final formulations were evaluated.

CONCLUSION

By understanding the axial recovery, it was possible to develop a precise model to predict tablet density using linear regression relationship between two physical tablets.

RESULTS

PART I: Understanding axial recovery

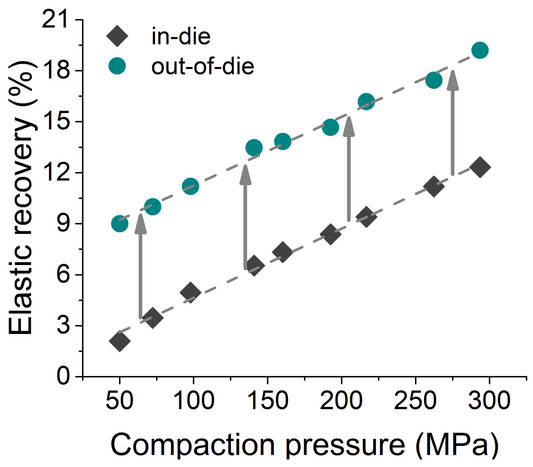

Fig.1: *elastic recovery of microcrystalline cellulose*

Analysis of >50 materials, blends and final formulations showed that:

1. in-die elastic recovery linearly depends on compaction pressure (*P*)
2. Out-of-die elastic recovery is independent of *P* (Fig. 1)

The total elastic recovery is split into 'in-die' and 'out-of-die' components, which are collected using a compaction simulator and manual measurement of tablet thickness and diameter, respectively.

PART II: Predicting tablet density

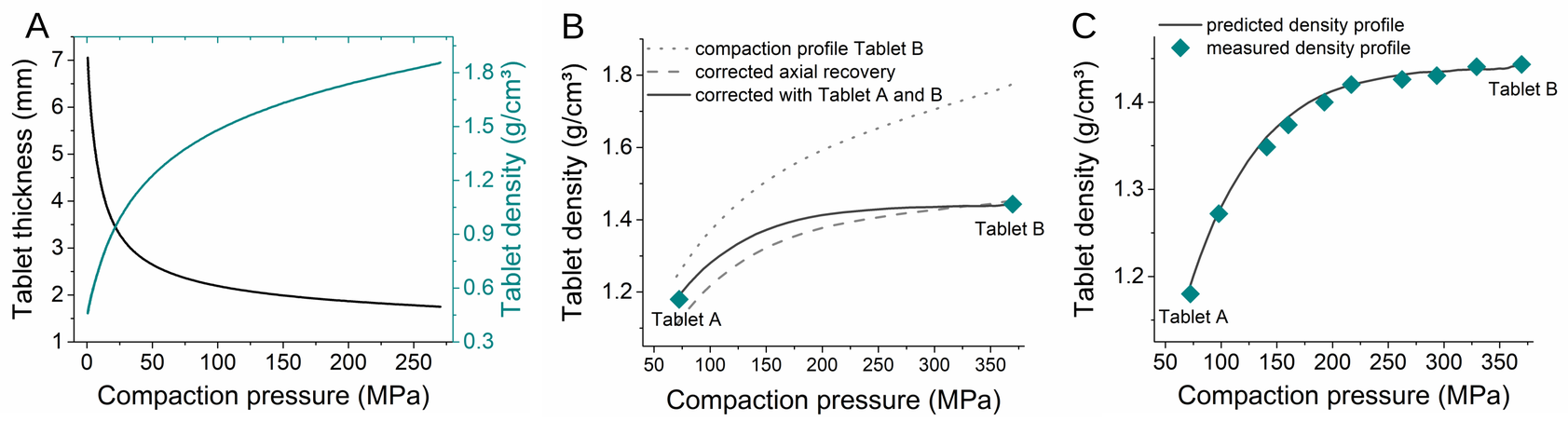

Fig.2: *A. Force distance profile of tablet B calculated to force- density profile. B. Different steps of the prediction C. Comparison of predicted and measured density profile (example microcrystalline cellulose)*

Prediction steps:

1. Two tablets are compressed, tablet (A) at a low *P* and tablet (B) at a high *P* (e.g. 50 - 350 MPa)
2. The pressure - density profile is obtained from force in-die thickness data of B (Fig. 2A)
3. Tablets A and B are used to establish linear axial recovery relationship (in-die and out-of-die)
4. In-die density profile (Fig. 2A) is corrected for elastic recovery to obtain out-of-die profile (Fig. 2B)
5. Radial recovery can be corrected if desired, but it does not significantly improve prediction accuracy
6. The densities of Tablets A and B are used to make the final correction of the out-of-die density profile

Prediction of the density profile was successful for most pharmaceutical materials with different properties (plastic, elastic and brittle). Problems were seen for materials that did not form intact tablets.

POTENTIAL APPLICATIONS

Having a material saving approach to predict the density profile of an API or formulation is of great advantage in early product development, where only very limited amount of material is available.

1. Based on the Ryshkewitch-Duckworth relationship between strength and porosity (1), it is possible to predict the full compactibility profile based on the tensile strength and porosity of the two tablets.
2. Accurate true density of a material can be derived from the predicted tablet density – *P* data (2).

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