Discrete Element Model for a Microscale Tablet Development System and Drug Release Prediction

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Background

- Digital Medicine Manufacturing (DM^2) is an integrated, automated tablet manufacturing and testing system (Fig. 1).
- Integration of models with automated processes enables the prediction of critical quality attributes with several advantages. (Fig. 2).
- Discrete Element Model (DEM) is a modelling tool utilising mathematical simulations to mimic real-life counterpart of particle movement and interactions and visualise their behaviour.
- Successful implementation of DEM can create digital twins of a desired process and accelerate drug development while improving agility.

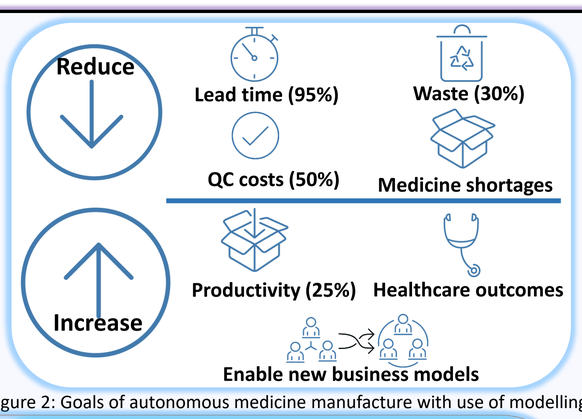


Figure 2: Goals of autonomous medicine manufacture with use of modelling

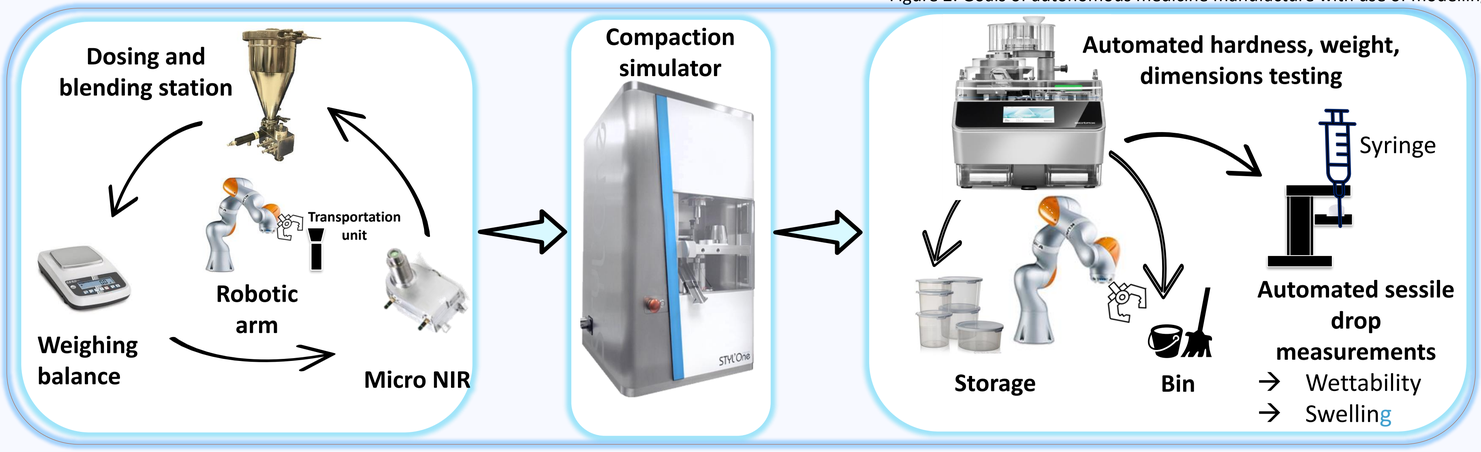


Figure1 : Overview of DM^2 project highlighting the different phases of the autonomous table-top microfactory used in this project.

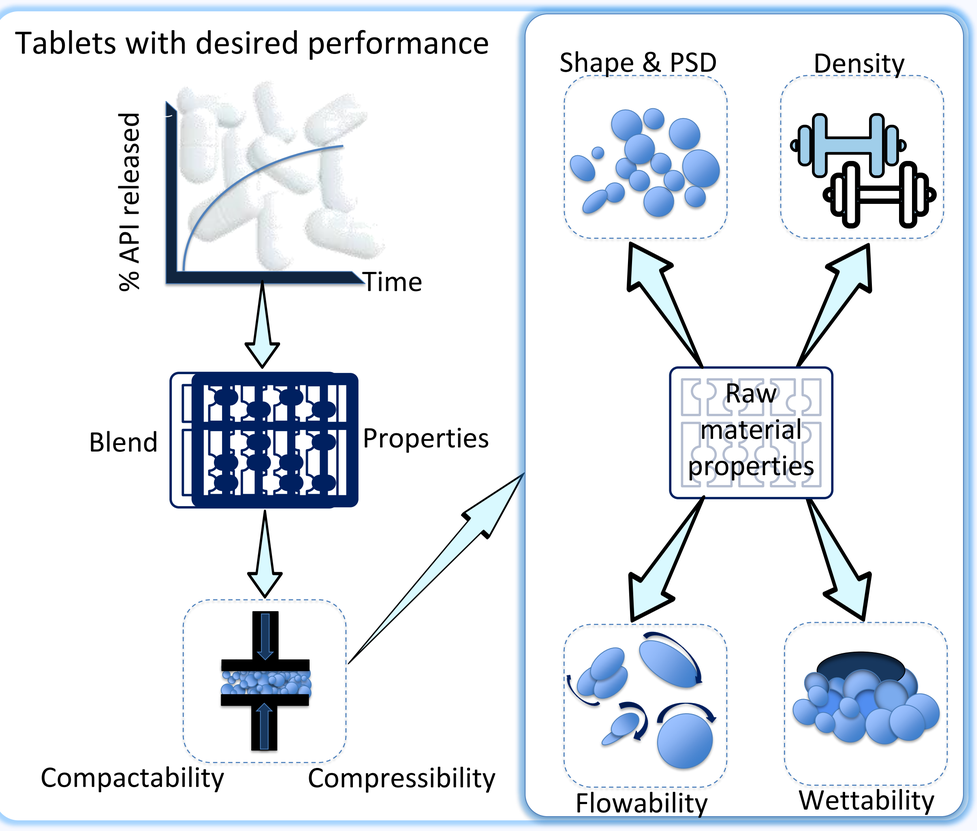


Figure 3: Breakdown of target material properties affecting the extent of drug release from a tablet

Aims & Objectives

Multiple steps are required to achieve desired drug release profile, most importantly calibration of frictional coefficients of DEM particle (Fig 4)

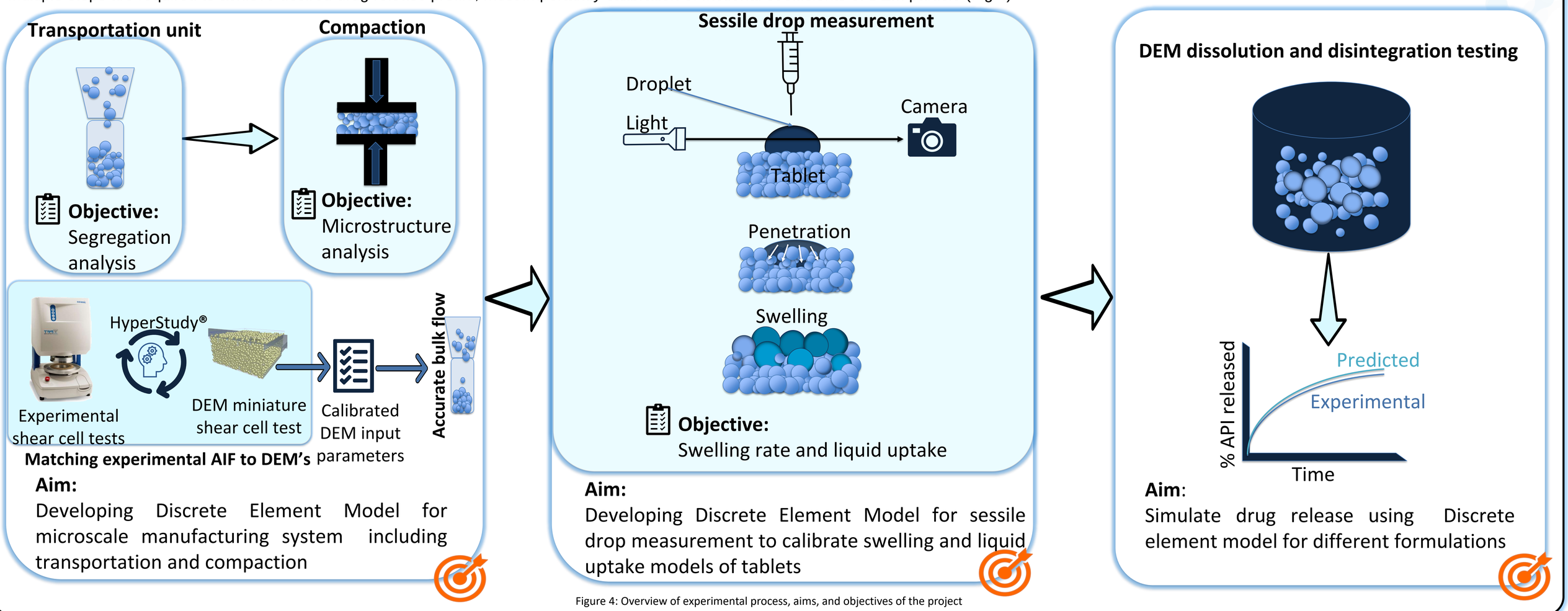
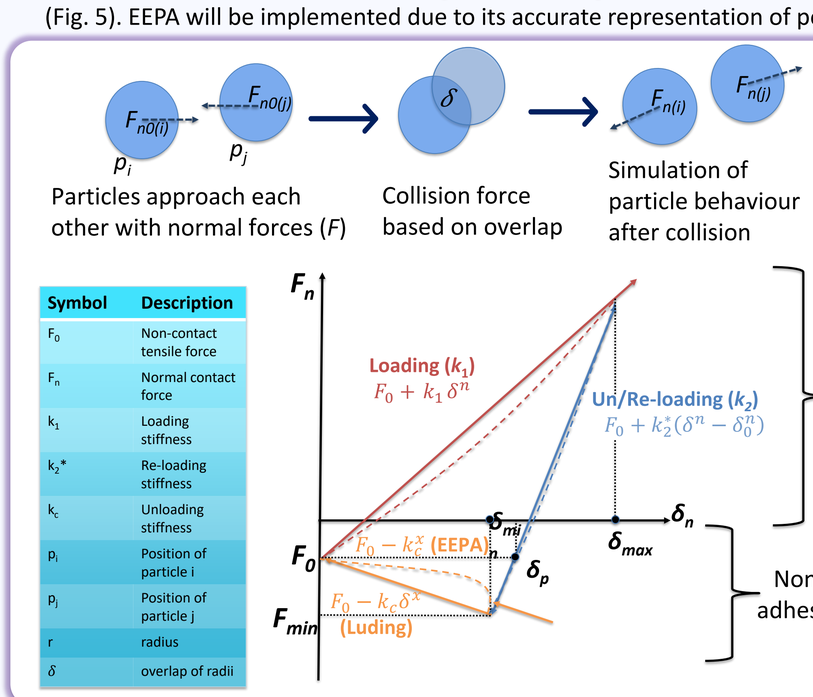


Figure 4: Overview of experimental process, aims, and objectives of the project

Methods

- Two models used in simulation, Luding[1] and Edinburgh Elasto-Plastic Model[2] (EEPA) (Fig. 5). EEPA will be implemented due to its accurate representation of powders[2]



Symbol	Description
F_0	Non-contact tensile force
F_n	Normal contact force
k_1	Loading stiffness
k_2*	Re-loading stiffness
k_c	Unloading stiffness
p_i	Position of particle i
p_j	Position of particle j
r	radius
δ	overlap of radii

Figure 5: A summary of Discrete Element Model (DEM)

Mathematical model

- Calculation of particle behaviour is based on single time-steps in repetition (Fig. 6).

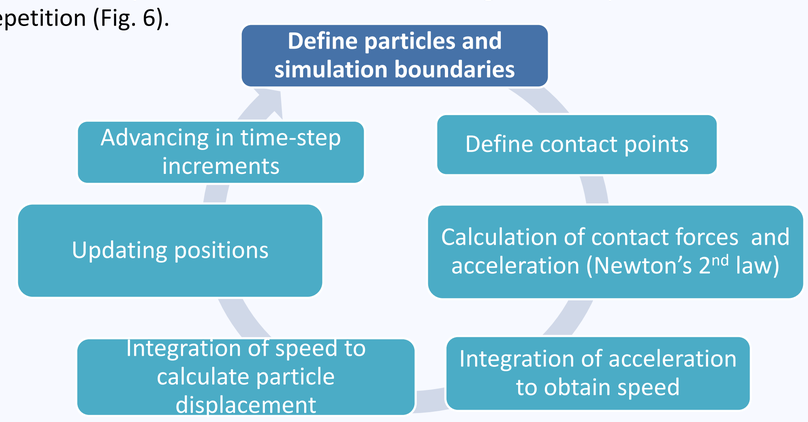


Figure 6: Simplified process of Discrete Element Model (DEM)

Calibration process

- Proper calibration of frictional parameters (Fig. 4) through Angle of Internal Friction (AIF) obtained through Brookfields PFT and through DEM will be matched through Altair Hyperstudy® allowing rapid Design of Experiments (DoE)
- Hyperstudy® outputs frictional coefficients under investigation that matches the AIF of DEM particles to the experimental one.
- Matched results yield effective parameter outputs to be fed into each step (Fig. 4)

Setup

- A digital twin of the microfactory (Fig. 7) is used to predict tablet performance.

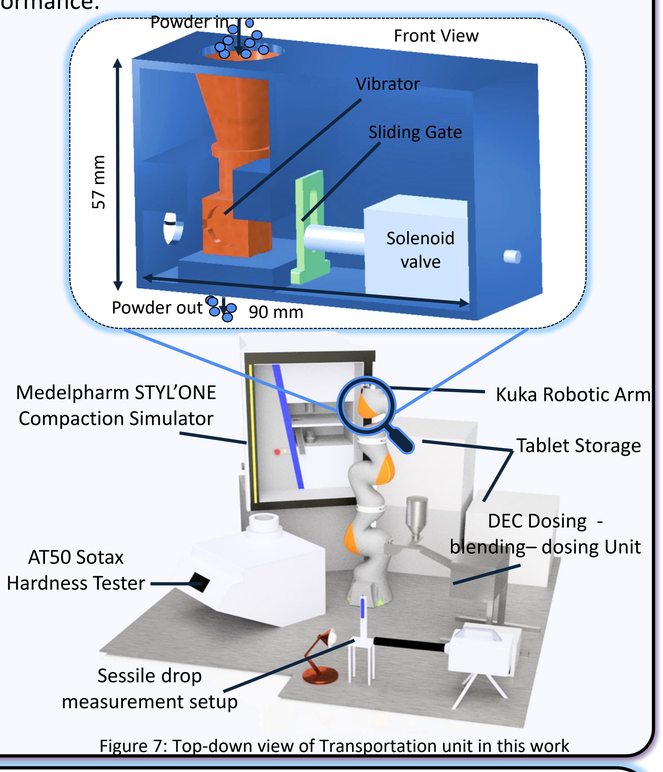


Figure 7: Top-down view of Transportation unit in this work

Preliminary results

- Visualisation of powder behaviour demonstrates accuracy with experimental near-infrared analysis 1% binary blend of paracetamol and lactose done in the lab (Fig. 8).
- DEM can aid in developing understanding of particle-level behaviors of a micro scale blend with more accurate calibration of the system using established characterisation tools.

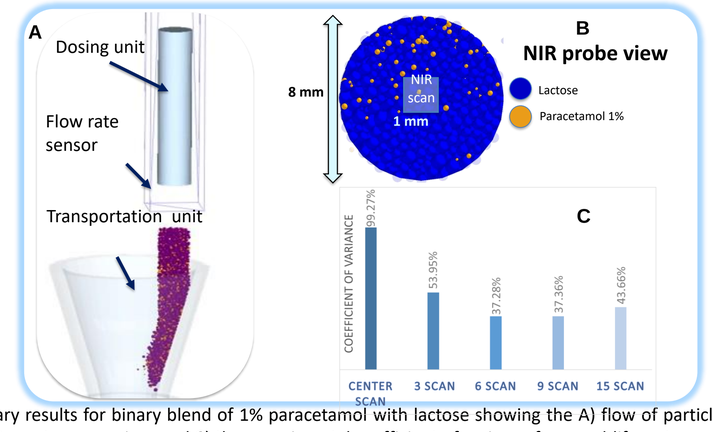


Figure 8: Preliminary results for binary blend of 1% paracetamol with lactose showing the A) flow of particles, B) resultant near-infrared (NIR) spectroscopy view, and C) the experimental coefficient of variance from real-life raster scan.

Future direction

- Establishing a systematic workflow to calibrating individual raw materials using lab-based characterisation techniques.
- Conducting automated DoE to extract parameters for further down-stream simulation of the autonomous development system.
- Identifying ideal simulation boundaries through down-scaling of instruments to reduce computational load (Fig. 9).
- Achieving calibrated bulk extends the exploration to different blends in order to validate braw material properties in different blends

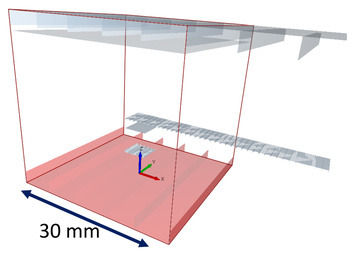


Figure 9: DEM shear cell scaled down to reduce computational burden

DEM Demo:

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References:

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