Investigating the effect of Paracetamol crystal properties on quality of tablets using continuous manufacturing

Nastaran Ghazi, Zhiwei Cao, Zhanjie Liu, San Kiang, Alberto Cuitino

Rutgers, The State University of New Jersey

GOALS

Research objective

Create an integrated model to predict the required properties of the API based on the desired behavior of the drug Product

Research

Flow-sheet models is developed to produce batches of API with different crystal variables eg. **size, agglomeration and shape.** This research will investigate the influence of changing these variables on the properties of final drug products.

Phase 1: : exploring the effect of API's **crystal size** on secondary manufacturing and final product

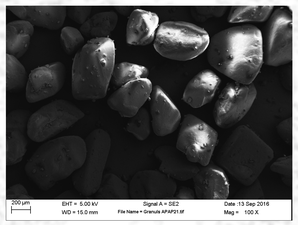
A: 100% API tablet

B: 70% API+30% MCC tablets

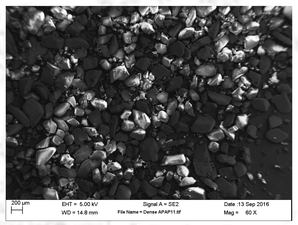
C: Complete formulation

Phase 2: In this phase we plan to look at more complex crystal types: surface modification and then co-crystals (FUTURE WORK)

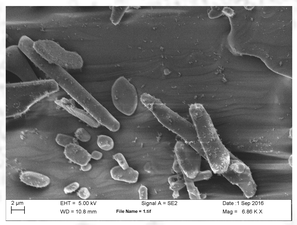
SEM images of the Paracetamol crystals used in **Phase 1**



Paracetamol Granular (mean 450 µm)



Paracetamol Dense Powder (mean 175 µm)



Paracetamol Powder + Sio (mean 45 µm)

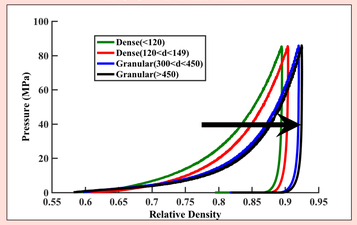
NSF Engineering Research Center for Structured Organic Particulate Systems (C-SOPS)

RESULT

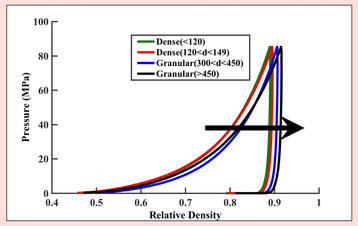
Phase 1:A&B exploring the effect of API's **crystal size** on secondary manufacturing and final product

The effect of size on compaction behavior

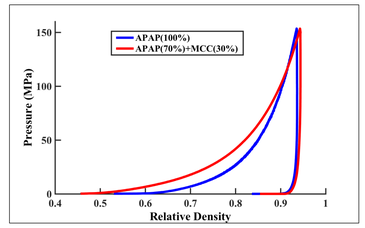
100% APAP



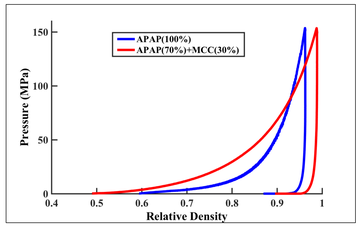
70% APAP+ 30% MCC



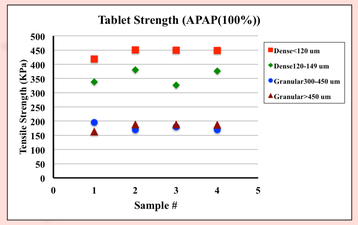
APAP crystal size <120 µm

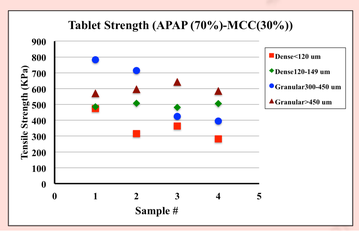


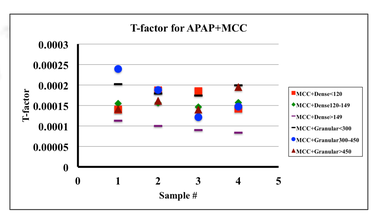
APAP crystal size >450 µm

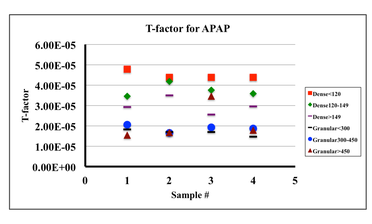


Tablet mechanical strength









T-factor: comparative factor calculated based on typical parts of the punch force/displacement-profile and properties of the resulting compact *N. Rasenack, B.W. Mu ller / International Journal of Pharmaceutics* 244 (2002)

$$T = \text{Plastic def} \times \text{energy}_{total} \times F_c / F_{max} \times s_{F\max(up)} \times e$$

Plastic def : Percentage of the plastic energy

Crushing strength F_c (N) : Stability of the compact

$s_{F\max}$ (mm) : Displacement of upper punch in F_{max}

Total energy(Nm) : Plastic and elastic energy

F_{max} (kN) : Upper punch force (maximum)

e (cm^3): Volume (true) tableted

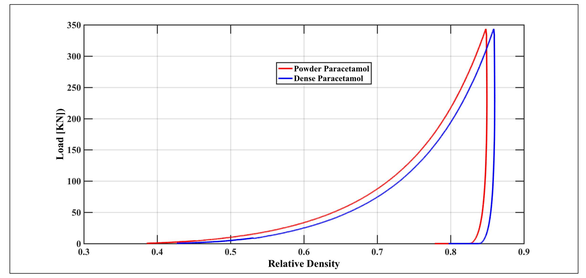
Phase 1: C

Optimized Formulation

Ingredient	mg/Tablet	purpose
Paracetamol	500	API
Avicel PH102	123.9	Exipeint
Kolidon VA 64	50	Dry binder
Kolliden CL 30	4	Disintegrant
Magnesium Stearate	1	Lubricant
Aerosil	4.7	coating
Polyethylene glycose 4000 (PEG)	16.5	Binder

T. Martinello rt.al/International Journal of Pharmaceuticas (2006)

The effect of size on compaction behavior of complete formulation



Future Work: By gathering and analysing all information from phase 1 and 2, we will develop libraries of raw materials with controlled properties that could be used for process characterization studies

www.ercforsops.org

RUTGERS THE STATE UNIVERSITY OF NEW JERSEY · PURDUE UNIVERSITY · NJIT New Jersey's Science & Technology University