CMAC FUTURE MANUFACTURING RESEARCH HUB

EPSRC Engineering and Physical Sciences Research Council

cpi

Improving multicomponent tablet predictions – accuracy and accessibility

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Integrated Control in Powder Formulation meeting

National Formulation Centre, Sedgefield.

17th January 2019

1. Introduction

2. Compression model

3. Experimental work

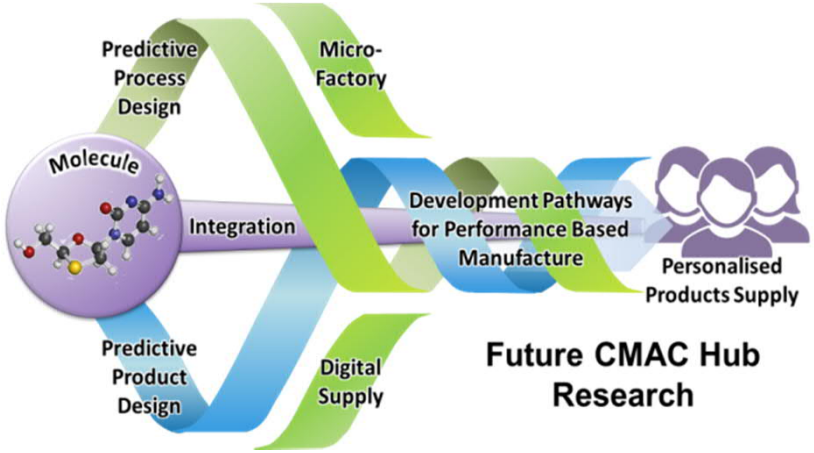
4. Parameter estimation and predictive model

5. Conclusions

Continuous Manufacturing and Crystallisation

Co-created with industry to address key manufacturing challenges and skills needs

- World leading manufacturing research platform
- A partnership approach for world-class:
  - Research
  - Training & Skills
  - Translation to industry & Impact
  - Facilities & Infrastructure



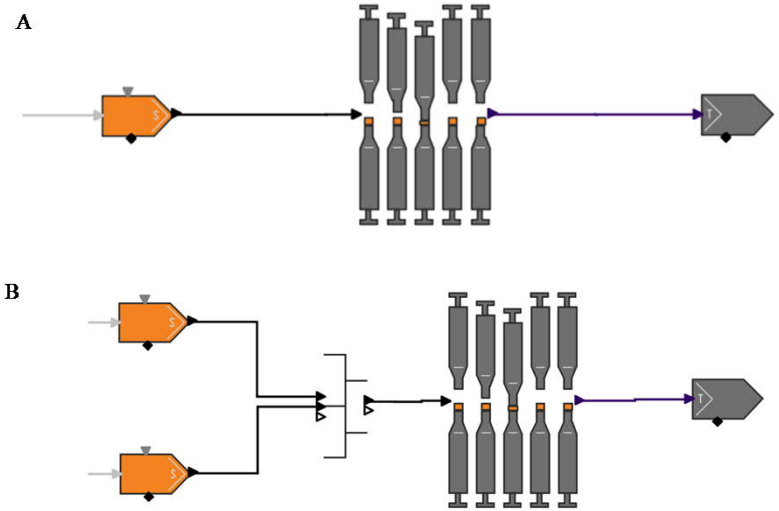
University of Strathclyde Glasgow · University of Bath · University of Cambridge · The University Of Sheffield. · Imperial College London · University of Leeds · Loughborough University

gsk · AstraZeneca · Novartis · Bayer · Lilly · Takeda · Roche · Pfizer

gPROMS (gFORMULATE)

gPROMS software environment

Basic gFORMULATE tablet compression arrangement



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Compression model

Gavi and Reynolds (2014) model

Tablet relative density (ρ_T^*): power law
- Variables: compression pressure (*P*)
- Parameter: tablet relative density at zero *P* (ρ_{T0}^*)
- Fitted parameter: compressibility constant (K_T)

$$\rho_T^* = \rho_{T0}^* P^{1/K_T}$$

Tablet tensile strength (σ_T): Ryshkewitch–Duckworth equation
- Variables: porosity (ε)
- Fitted parameter: bonding capacity (k_b)
- Fitted parameter: tensile strength at zero porosity (σ_{T0})

$$\sigma_T = \sigma_{T0} e^{-k_b \varepsilon}$$

Tensile strength computed via:
- Variables: thickness (h_T), diameter (d_T), compaction force (F_{comp})

$$\sigma_T = \frac{2}{\pi} \frac{F_{comp}}{d_T h_T}$$

Mixing rules for multicomponent tablets:
- k_b and σ_{T0} - gPROMS implemented (volume fraction-based)
- K_T - user-specified (also volume fraction-based)

$$\sigma_{T0,mix} = \sum_i \sigma_{T0,i} \phi_i \quad k_{b,mix} = \sum_i k_{b,i} \phi_i \quad K_{T,mix} = \sum_i K_{T,i} \phi_i$$

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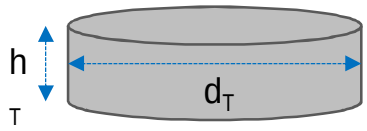
Tablet size, shape, weight and components

Flat-faced plain tablet



Various tablet weights
- 200 mg, 250 mg, 300 mg

Multiple excipient components
- Lactose (Pharmatose, GranuLac), cellulose (Avicel), HPMC (Affinisol)
  N-vinyl-2-pyrrolidone and vinyl acetate copolymer (Plasdone S630)

Active Pharmaceutical Ingredients (APIs)
- Aspirin, paracetamol, lovastatin

Various material grades
- Avicel PH-101, PH-102
- Pharmatose 50M, GranuLac 200M
- Lovastatin spherical agglomerates (LSA)

Formulation	Pharmatose® 50M	Avicel® PH-101	Lovastatin	LSA
A	80	20	-	-
B	70	30	-	-
C	60	40	-	-
D	50	50	-	-
E	70	20	10	-
F	60	20	-	10

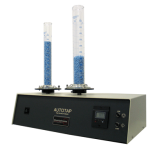
Material	Die filling method	Tablet target weight (mg)
Avicel® PH-101	A/M	200, 250
Avicel® PH-102	A	200, 250
Pharmatose® 50M	A	250, 300
Pharmatose® 50M internally lubricated (InLu) with Mg Stearate	A	250, 300
Pharmatose® 50M externally lubricated (ExLu) with Mg Stearate	M	300
GranuLac® 200M	M	250, 300
Affinisol™ (HPMC HME 15LV)	A	200, 250
Plasdone™ S-630	A	250
Aspirin agglomerates	A	300
Acetaminophen granular	A	250, 300
Lovastatin	M	200
Lovastatin externally lubricated (ExLu) with Sodium stearyl fumarate PG-100	M	200
Lovastatin spherical agglomerates (SAG)	M	200
Formulation A	A	250
Formulation B	A	250
Formulation C	A	250
Formulation D	A	250
Formulation E	M	200
Formulation F	M	200

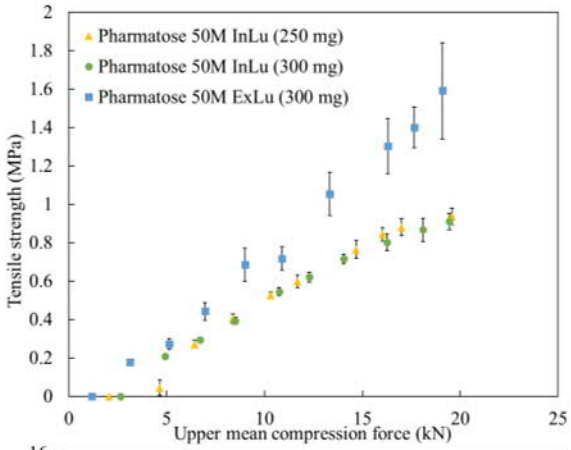
Equipment

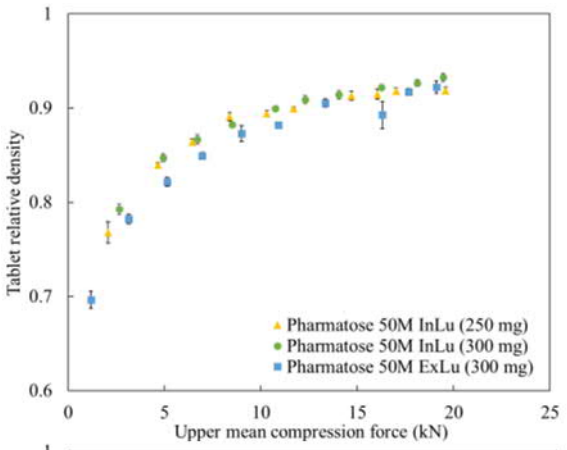
Tapped density: Autotap™, Quantachrome
True density: MicroUltrapyc 1200e, Quantachrome
Particle size: Qicpic, Sympatec
Tablet hardness: HC6.2, Kraemer Electronik

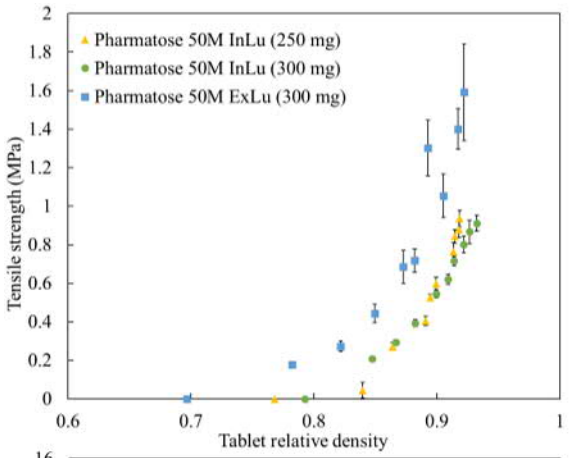
Tablet press: Korsch XP1, Korsch AG
- Single-punch tablet press
- 9 mm, flat-faced punch
- Operated in single-stroke mode

Recorded data
- Upper punch compression force (range: 0.5 – 20 kN)
- Lower punch compression force
- Ejection force
- Upper punch displacement
- Lower punch displacement




Pharmatose 50M InLu (250 mg)
Pharmatose 50M InLu (300 mg)
Pharmatose 50M ExLu (300 mg)
Tensile strength (MPa)
Upper mean compression force (kN)


Pharmatose 50M InLu (250 mg)
Pharmatose 50M InLu (300 mg)
Pharmatose 50M ExLu (300 mg)
Tablet relative density
Upper mean compression force (kN)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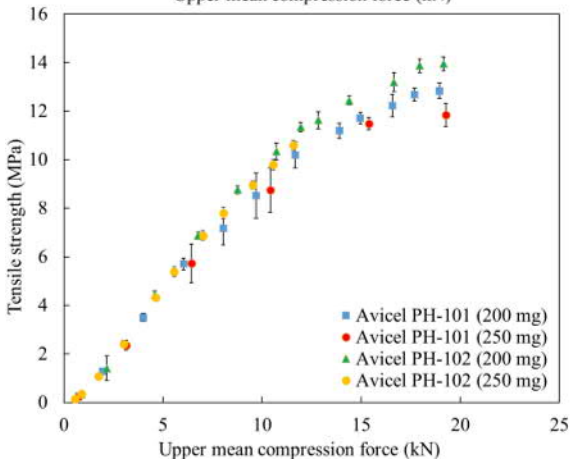
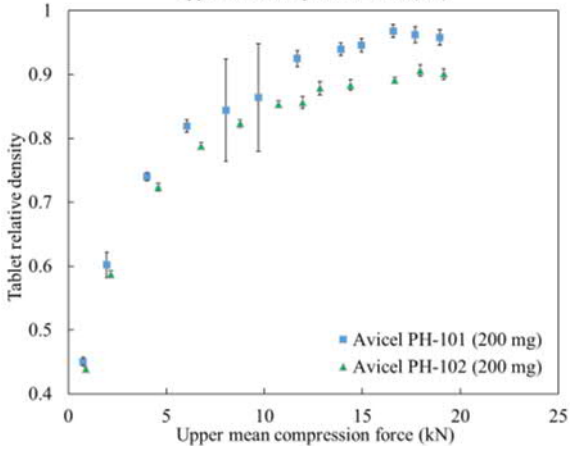

Avicel PH-101 (200 mg)
Avicel PH-101 (250 mg)
Avicel PH-102 (200 mg)
Avicel PH-102 (250 mg)
Tensile strength (MPa)
Upper mean compression force (kN)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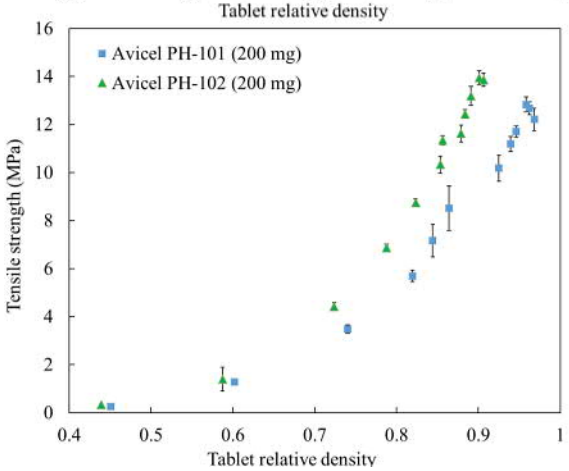
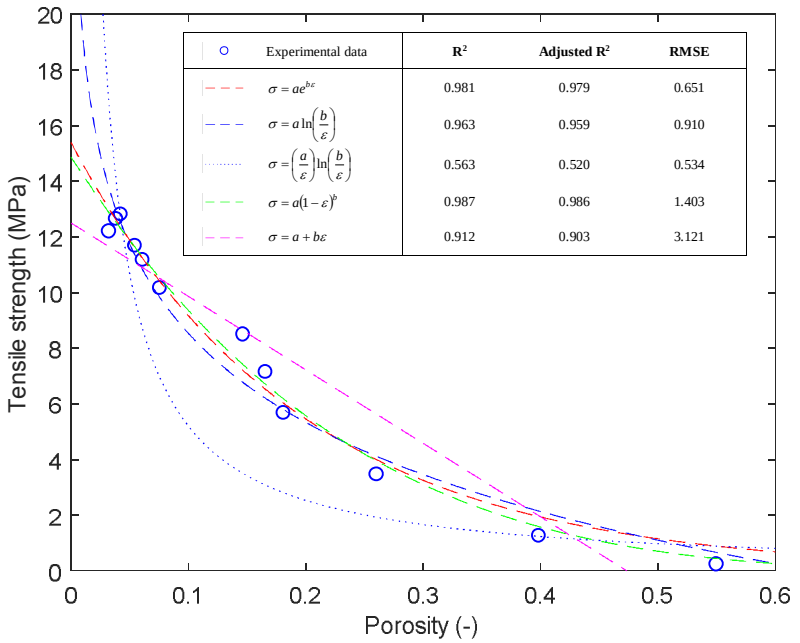
Tablet relative density
Upper mean compression force (kN)


Avicel PH-101 (200 mg)
Avicel PH-102 (200 mg)
Tensile strength (MPa)
Tablet relative density

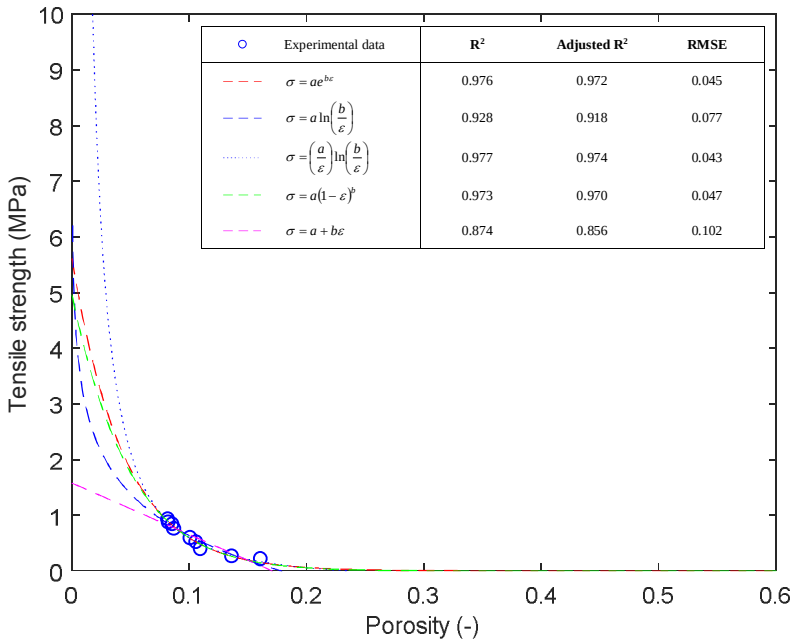
Parameter estimation: initial guess for σ_{T0}

Tensile strength at zero porosity
Fit curves to find value at $\varepsilon = 0$

Avicel PH-101 (cellulose)



Pharmatose 50M (lactose)



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Parameter estimation: results for pure cellulose and lactose tablets

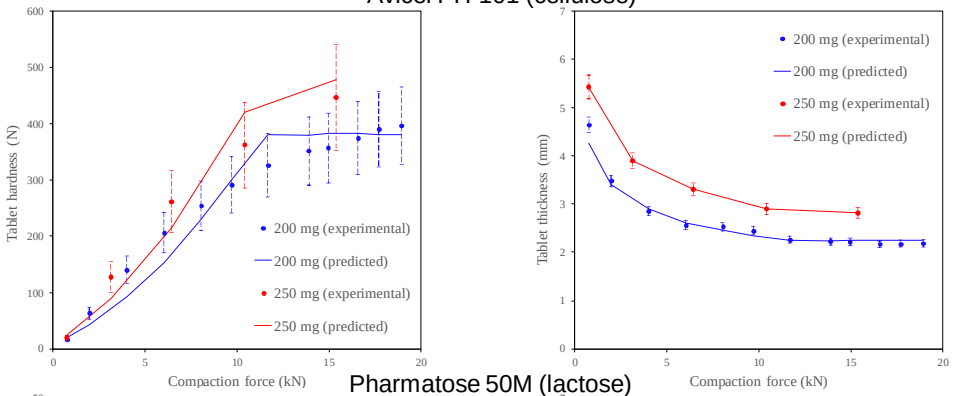
Key compression data for Avicel PH-101 tablets (200 mg target mass)

Compression force (kN)	Tablet mass (mg)	Tablet thickness (mm)	Tablet hardness (N)
0.76	197.32	4.647	16.9
1.97	197.44	3.481	63.4
4.01	198.72	2.850	140.6
6.04	197.79	2.562	206.4
8.04	199.05	2.531	254.0
9.70	197.13	2.450	291.4
11.68	197.37	2.265	326.1
13.90	196.81	2.224	351.8
14.96	197.47	2.216	366.8
16.57	197.72	2.168	374.7
17.70	197.34	2.177	390.0
18.95	197.32	2.186	396.6

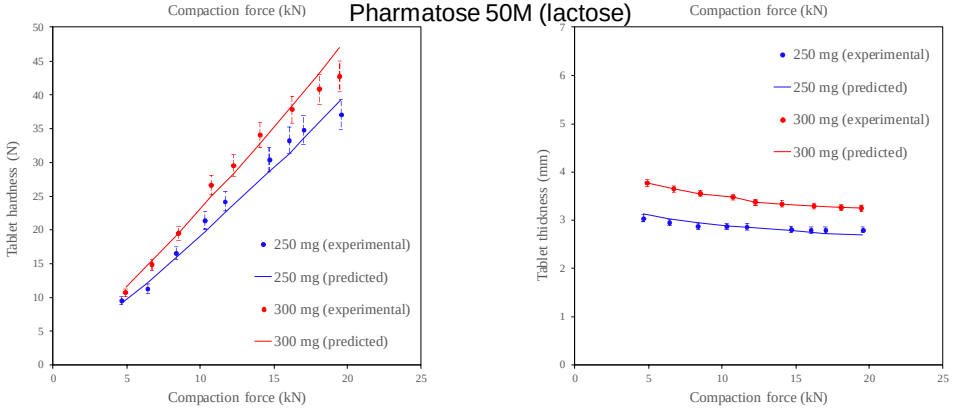
Optimal pure component parameters for Avicel PH-101 and Pharmatose 50M.

Component	Tensile strength at zero porosity		Bonding capacity		Compressibility constant	
	σ_0 (MPa)	99% CI	k_b (-)	99% CI	K_T (-)	99% CI
Avicel PH-101						
Pharmatose 50M						

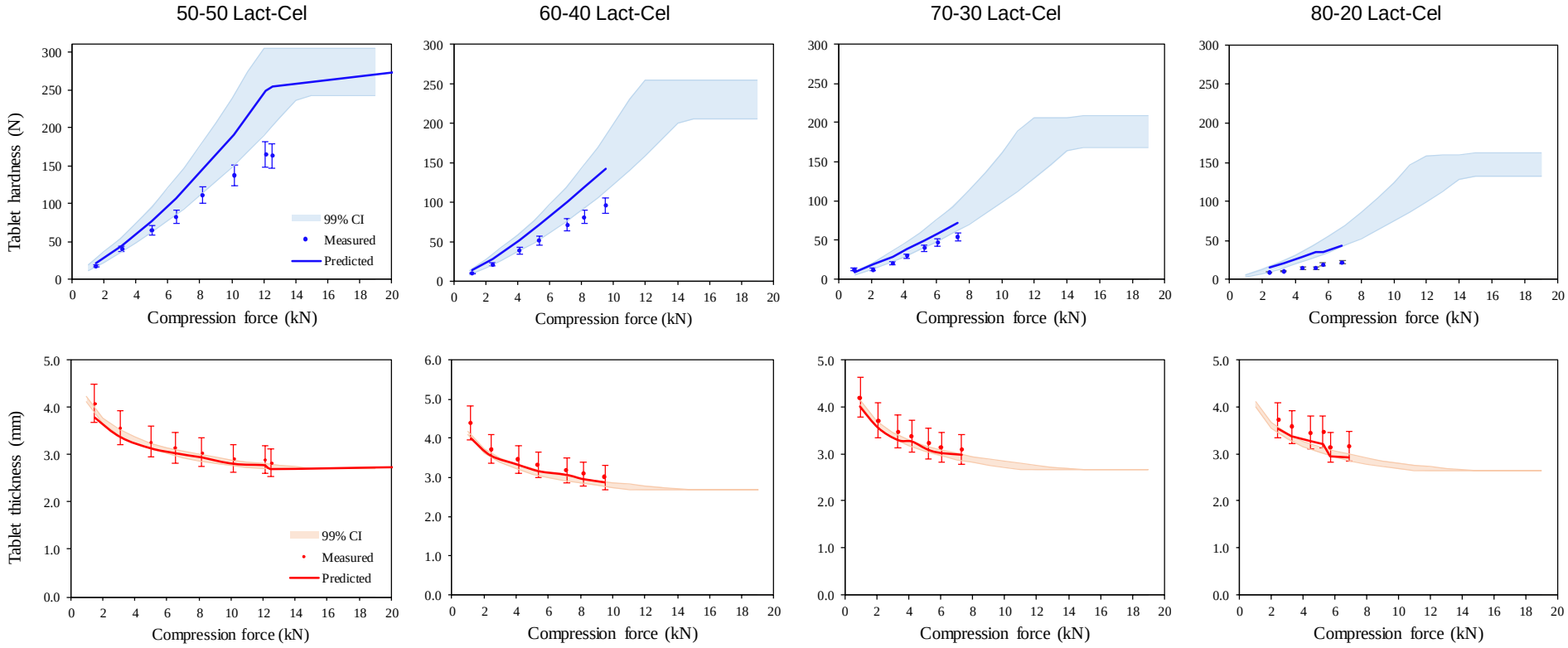
Avicel PH-101 (cellulose)



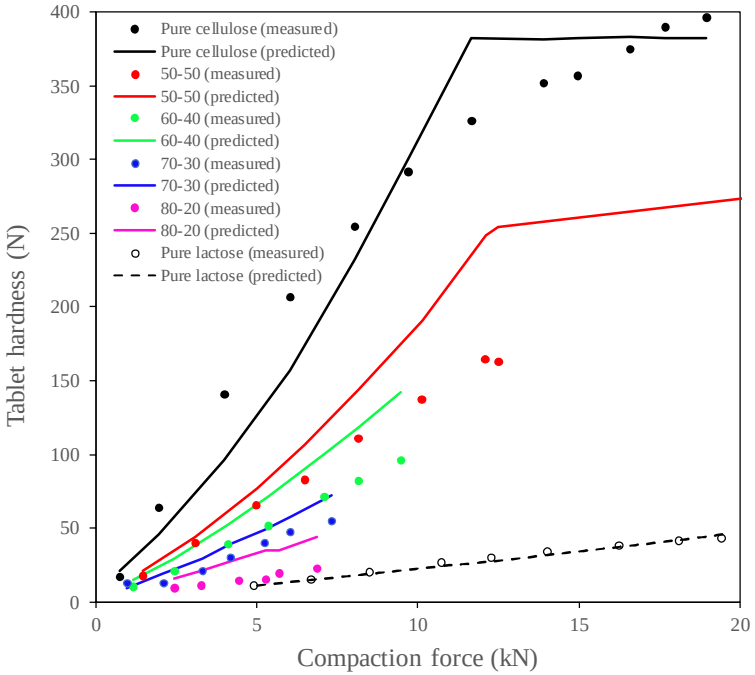
Pharmatose 50M (lactose)

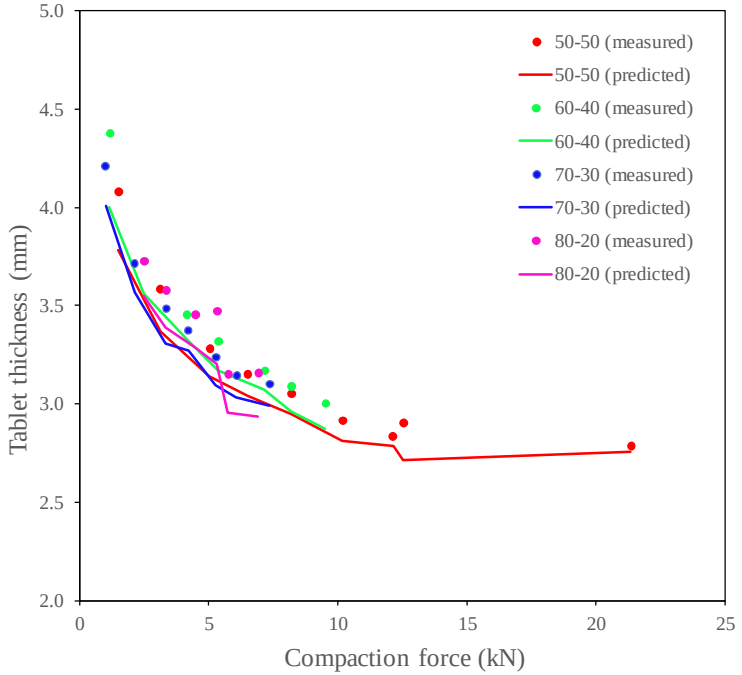


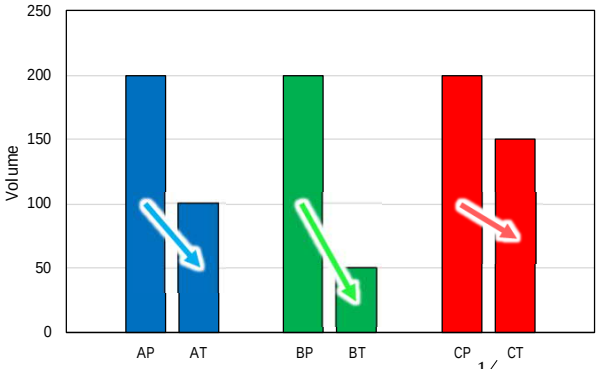
Parameter estimation: results for binary cellulose and lactose tablets

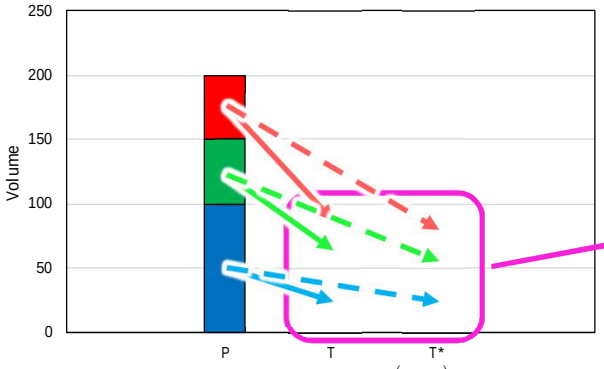


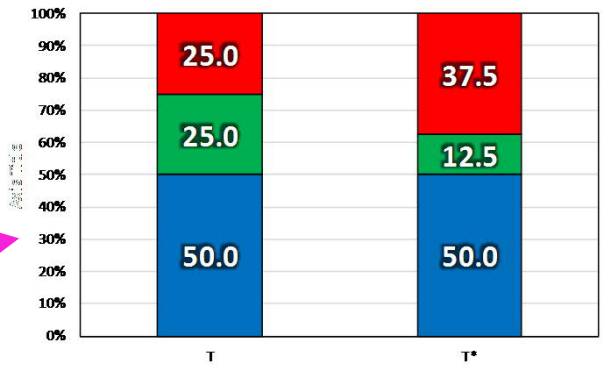
Parameter estimation: results for binary cellulose and lactose tablets









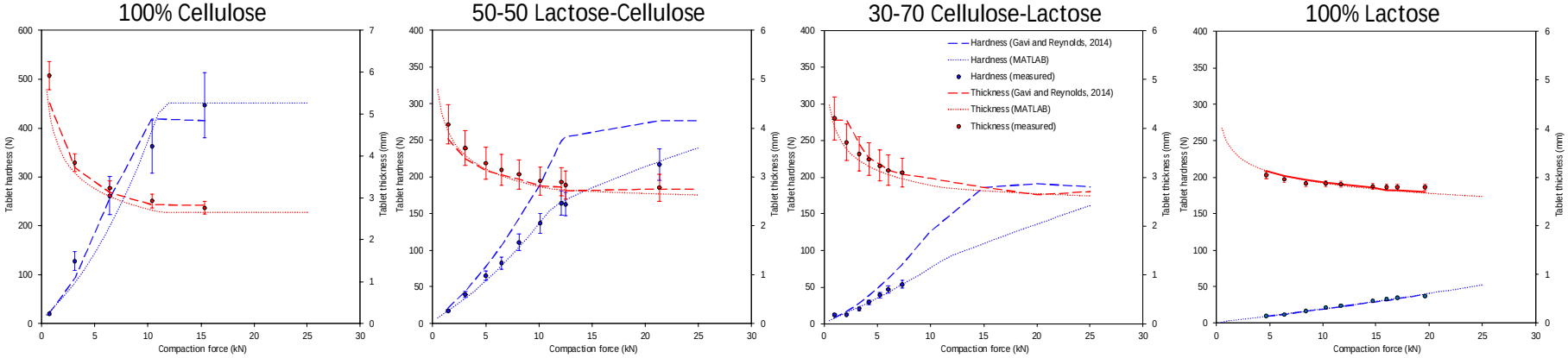


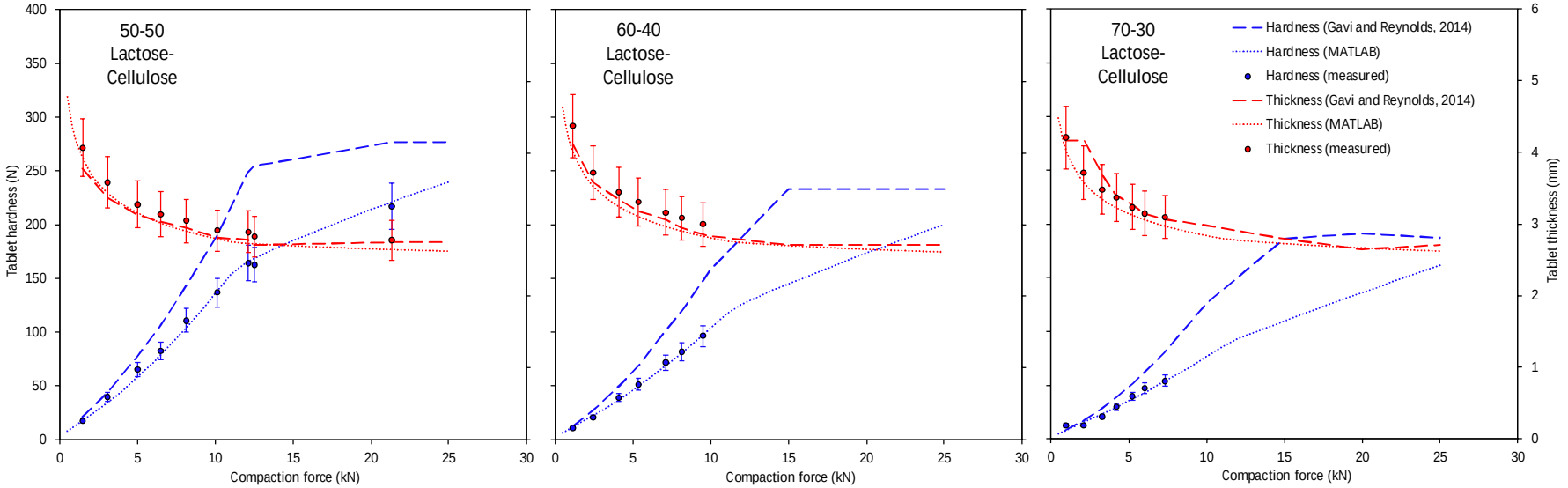
$$\rho^*_{tab} = \rho^*_{0,mix} P^{1/K_{T,mix}}$$

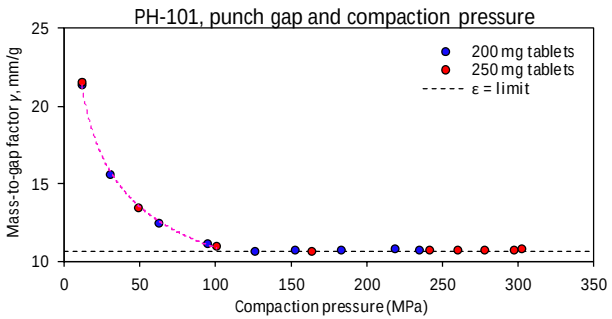
$$\sigma_{T,tab} = \sigma_{T0,tab} e^{-k_{b,tab}\left(1-\rho^*\right)}$$

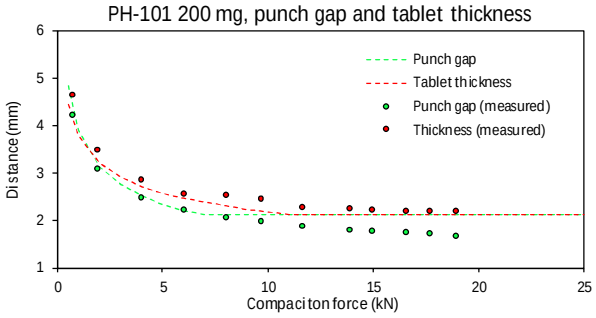
$$p_{tab} = \sum_i \phi_i p_i \,, \qquad p = \left\{K_T, \sigma_{T0}, k_b\right\}$$

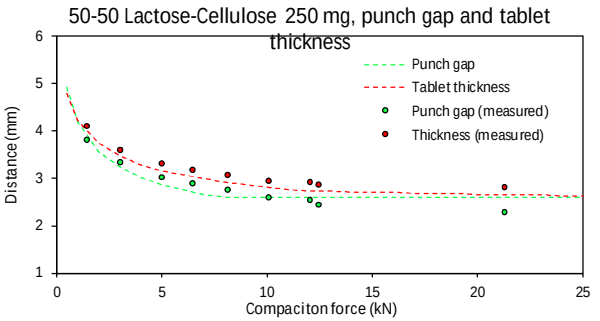
250 mg, 9 mm diameter tablets:

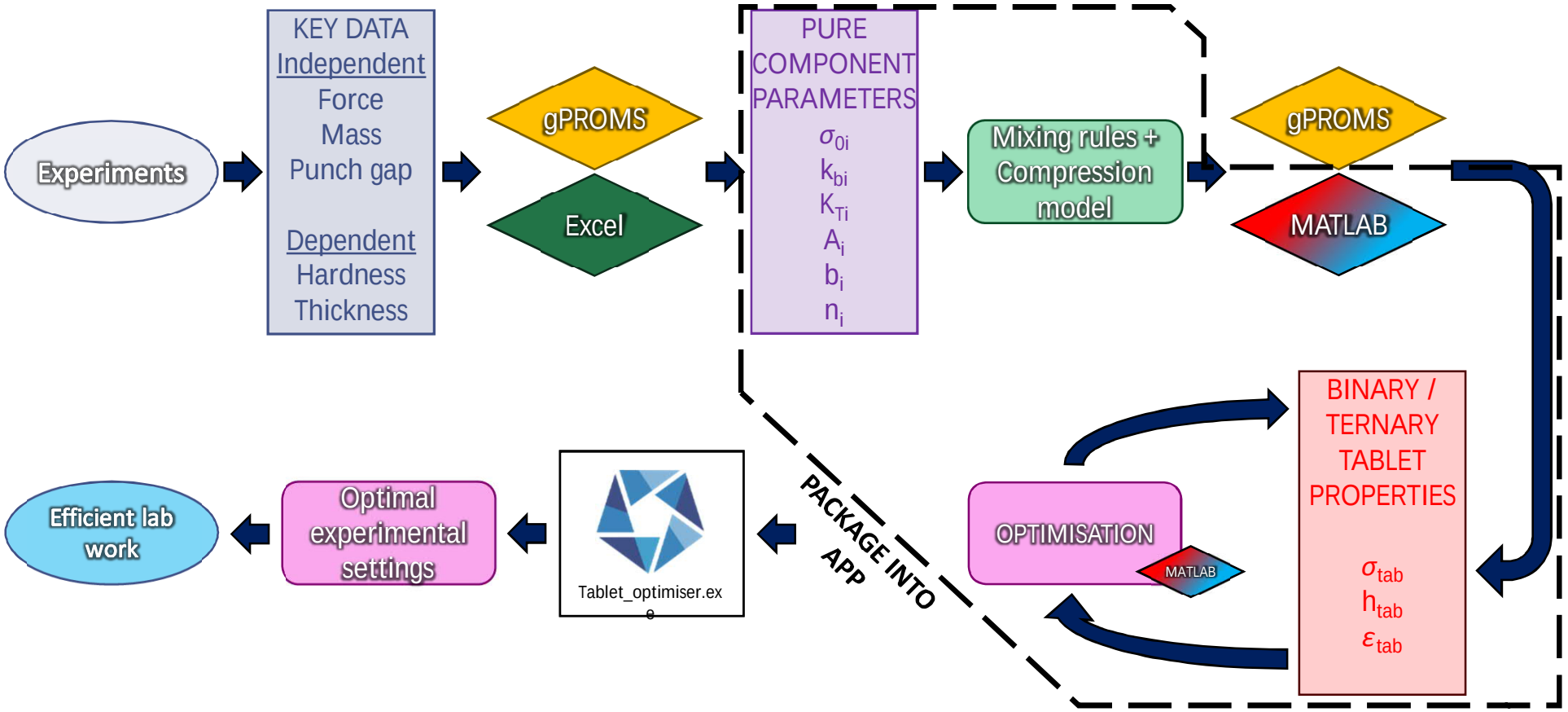


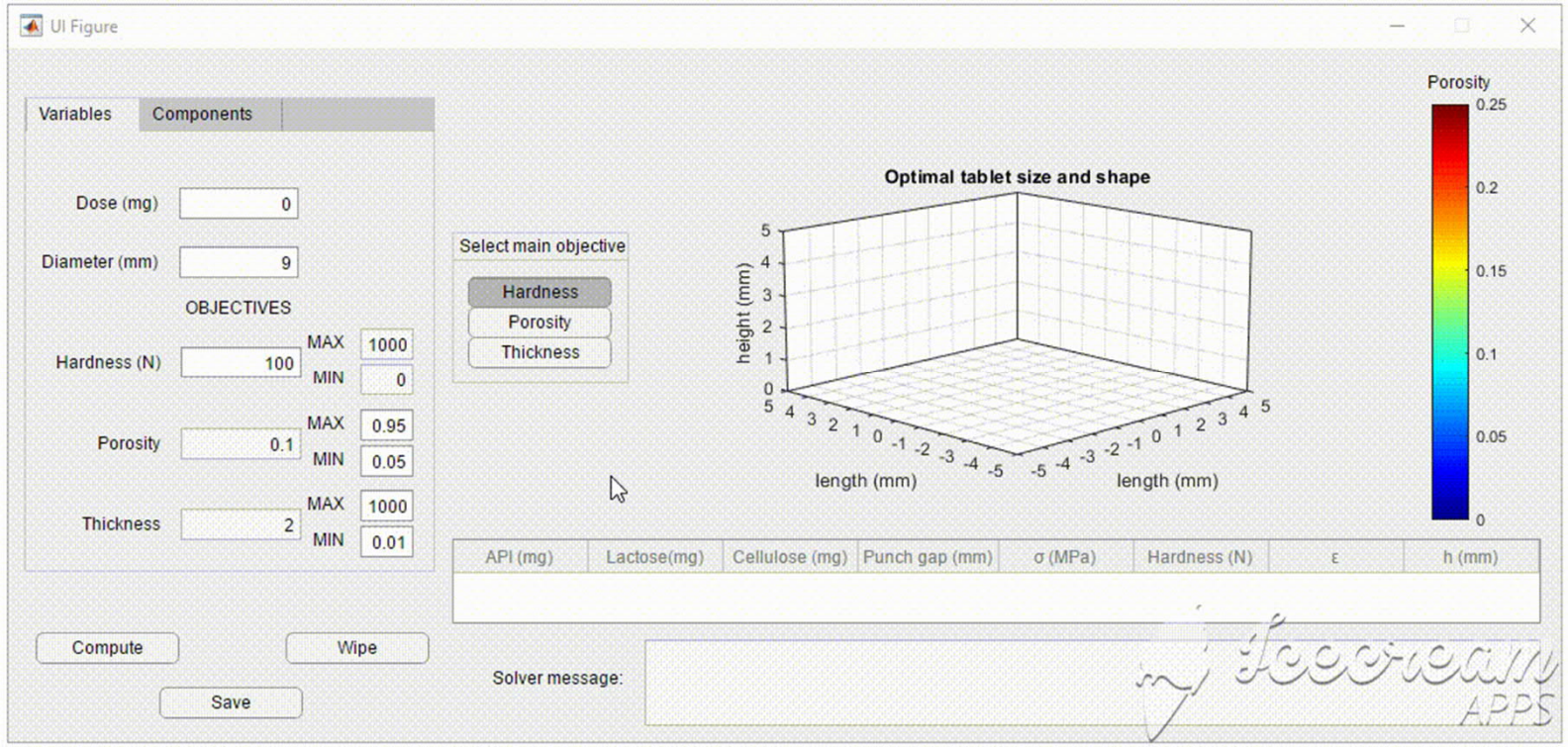

50-50 Lactose-Cellulose
60-40 Lactose-Cellulose
70-30 Lactose-Cellulose
Tablet hardness (N)
Tablet thickness (mm)
Compaction force (kN)
Hardness (Gavi and Reynolds, 2014)
Hardness (MATLAB)
Hardness (measured)
Thickness (Gavi and Reynolds, 2014)
Thickness (MATLAB)
Thickness (measured)


PH-101, punch gap and compaction pressure
Mass-to-gap factor γ, mm/g
Compaction pressure (MPa)
200 mg tablets
250 mg tablets
ε = limit


PH-101 200 mg, punch gap and tablet thickness
Distance (mm)
Compaciton force (kN)
Punch gap
Tablet thickness
Punch gap (measured)
Thickness (measured)


50-50 Lactose-Cellulose 250 mg, punch gap and tablet thickness
Distance (mm)
Compaciton force (kN)
Punch gap
Tablet thickness
Punch gap (measured)
Thickness (measured)


Experiments
KEY DATA
Independent
Force
Mass
Punch gap
Dependent
Hardness
Thickness
gPROMS
Excel
PURE COMPONENT PARAMETERS
σ_{0i}
k_{bi}
K_{Ti}
A_i
b_i
n_i
Mixing rules + Compression model
gPROMS
MATLAB
BINARY / TERNARY TABLET PROPERTIES
σ_{tab}
h_{tab}
ε_{tab}
OPTIMISATION
MATLAB
PACKAGE INTO APP
Tablet_optimiser.exe
Optimal experimental settings
Efficient lab work


UI Figure
Variables
Components
Dose (mg)
0
Diameter (mm)
9
OBJECTIVES
Hardness (N)
100
MAX
1000
MIN
0
Porosity
0.1
MAX
0.95
MIN
0.05
Thickness
2
MAX
1000
MIN
0.01
Compute
Wipe
Save
Select main objective
Hardness
Porosity
Thickness
Optimal tablet size and shape
height (mm)
length (mm)
length (mm)
Porosity
0.25
0.2
0.15
0.1
0.05
0
API (mg)
Lactose(mg)
Cellulose (mg)
Punch gap (mm)
σ (MPa)
Hardness (N)
ε
h (mm)
Solver message:
Icecream APPS

Conclusions & Final Remarks

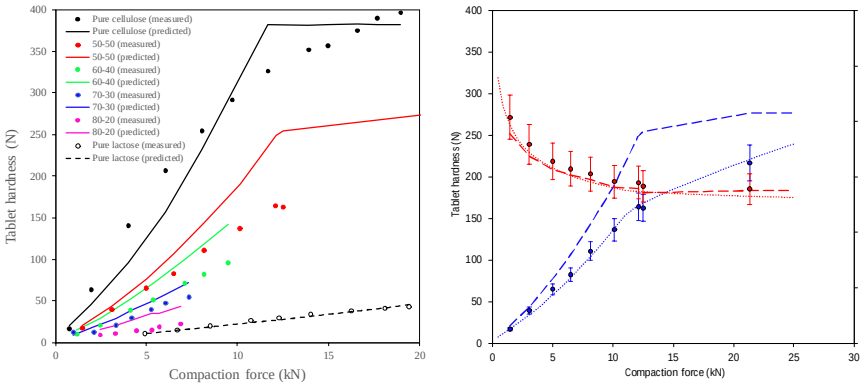
Extensive compression data generated for a variety of materials and material grades

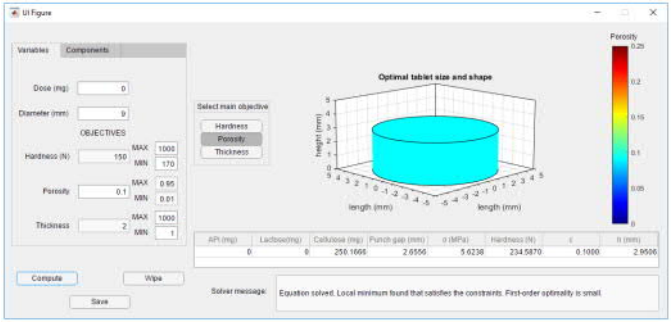
Optimal values for key parameters (K_T, k_b, σ_{T0}) found
- For pure components
- Good fits to experimental data

Binary tablet properties predicted using pure parameters
- Various tablet compositions
- Predictions improved with modified parameter weighting.

Optimising tablet design
- Nonlinear optimisation of tablet compaction
- User-friendly MATLAB app.

Ongoing work
- More components, additional validation
- Lubrication effects





Acknowledgements

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