Linking Process Engineering to Product Performance

A roll compaction case study

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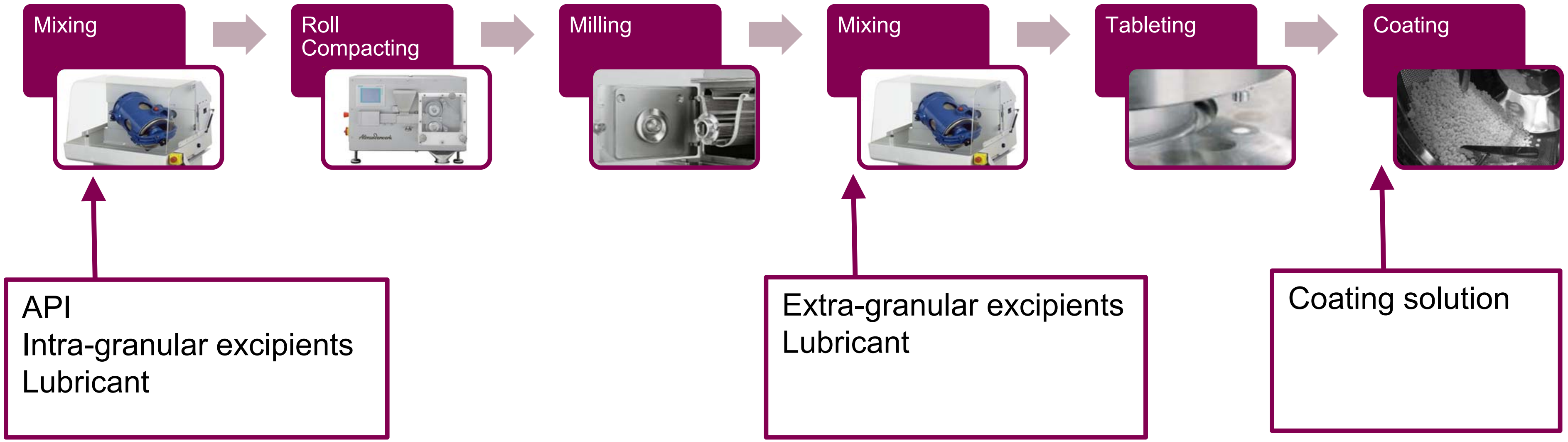
AstraZeneca

(One way) to make a tablet

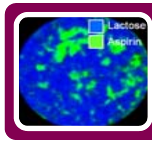


What is important (for a tablet)?
It depends, but often…


Dissolution


Assay


Hardness

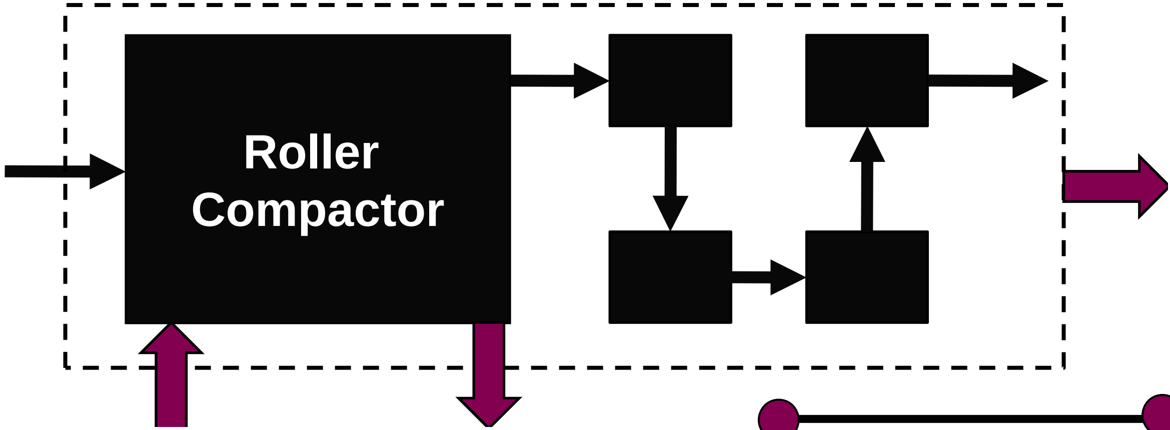


Content Uniformity


Appearance

… and others

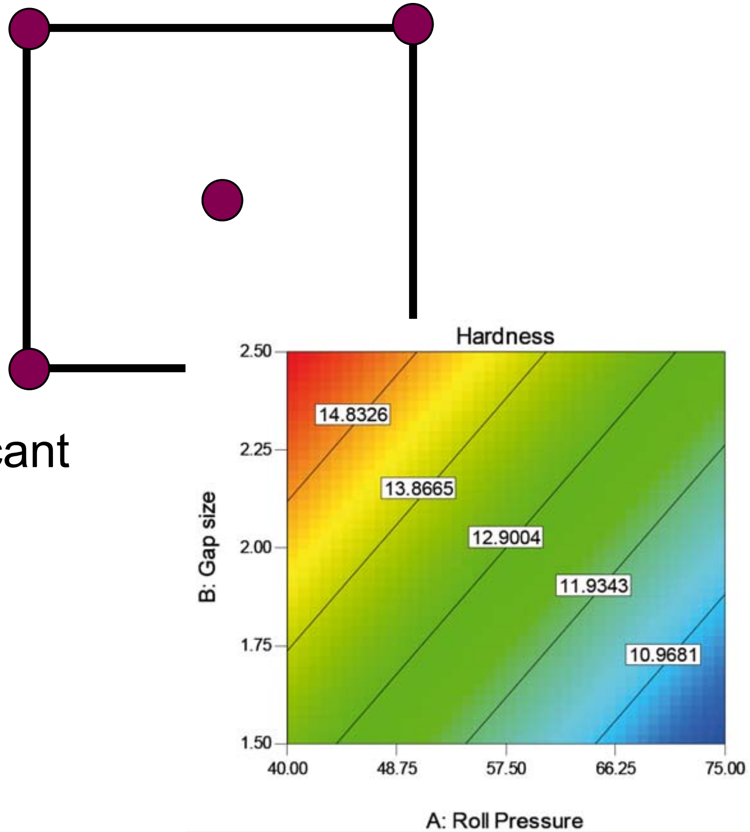
Typical ‘black box’ experimental approach



Response
Hardness
Dissolution

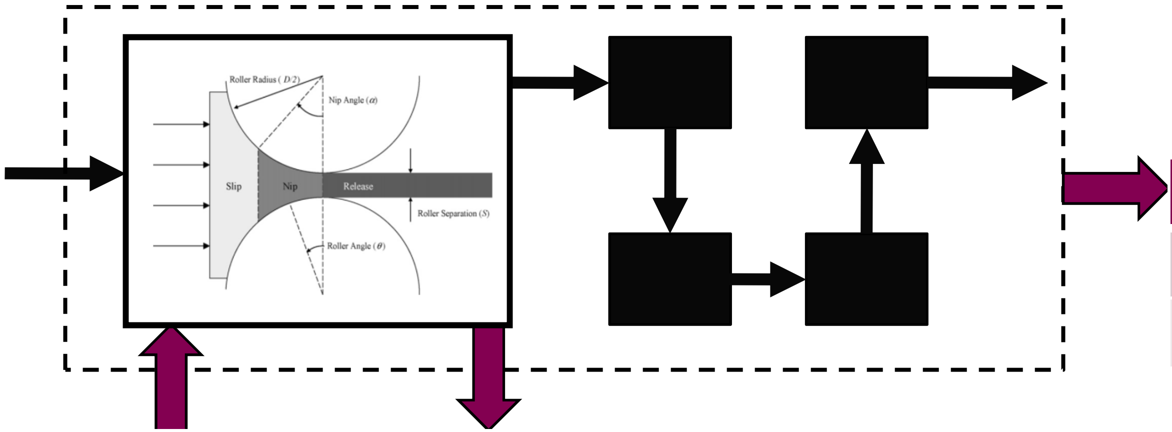
Factor	-	+
Roll Pressure (bar)	20	80
Gap (mm)	1.5	3.0
Roll Speed (rpm)	5	10

Response
Porosity
Tensile strength
Granule size



- Design of Experiments
  - An efficient method to determine significant parameters and interactions
- Develop relationships between factors and responses

What can we model? – unit operations



Response
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Response
Porosity
Tensile strength
Granule size

$$\gamma_R = \gamma_0 \left(\frac{2R_f}{WD\int_{\theta=0}^{\theta=\alpha(\delta_E,\phi_W,K)} [(S/D)/((1+S/D-\cos\theta)\cos\theta)]^K \cos\theta \, d\theta} \right)^{1/K}$$

- We can develop models for individual unit operations, for example RC
- Useful to predict porosity for scale-up and process understanding
- However, what we really want to know is how each process parameter and unit operation impacts on product quality and performance

A systems-based approach

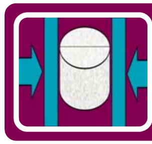
Develop unit operation models and link to product performance

Roll Compacting

Milling

Mixing

Tabletting



Hardness

Dissolution

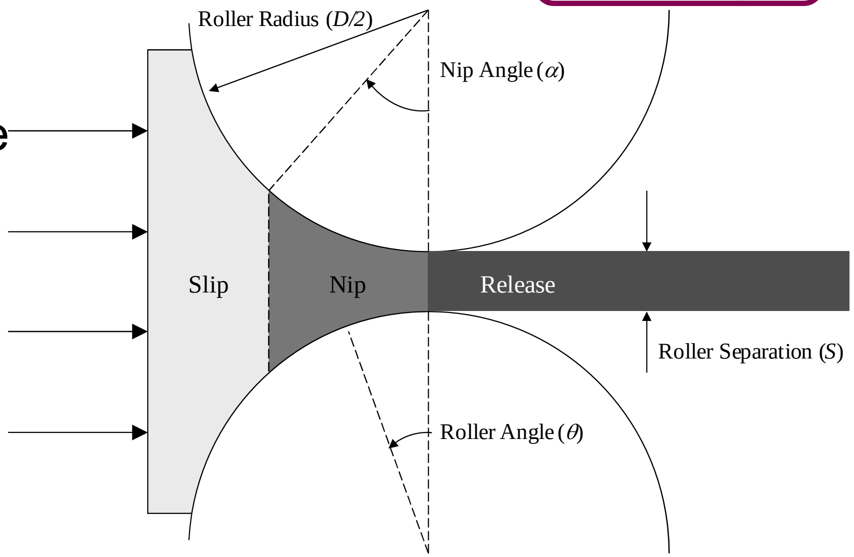
Unit Operation – Roll Compactor

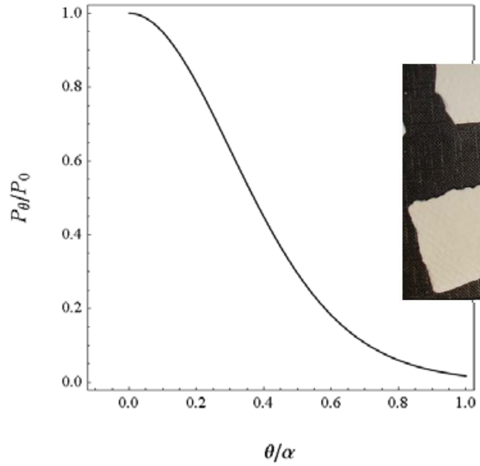
Developing a model

Roll Compacting

- The material properties of the ribbon will be related to the peak pressure exerted within the roll compactor.
- In practise the peak pressure is not known
  - Total pressing force
  - OR hydraulic pressure
- Models can be developed to describe the pressure distribution within the roll compactor and therefore the peak pressure

- Material assumed to be isotropic, frictional, cohesive and compressible, obeying effective yield function of Jenike and Shield (1959).
- Boundary conditions based on determining the nip angle as proposed by Johanson (1965).





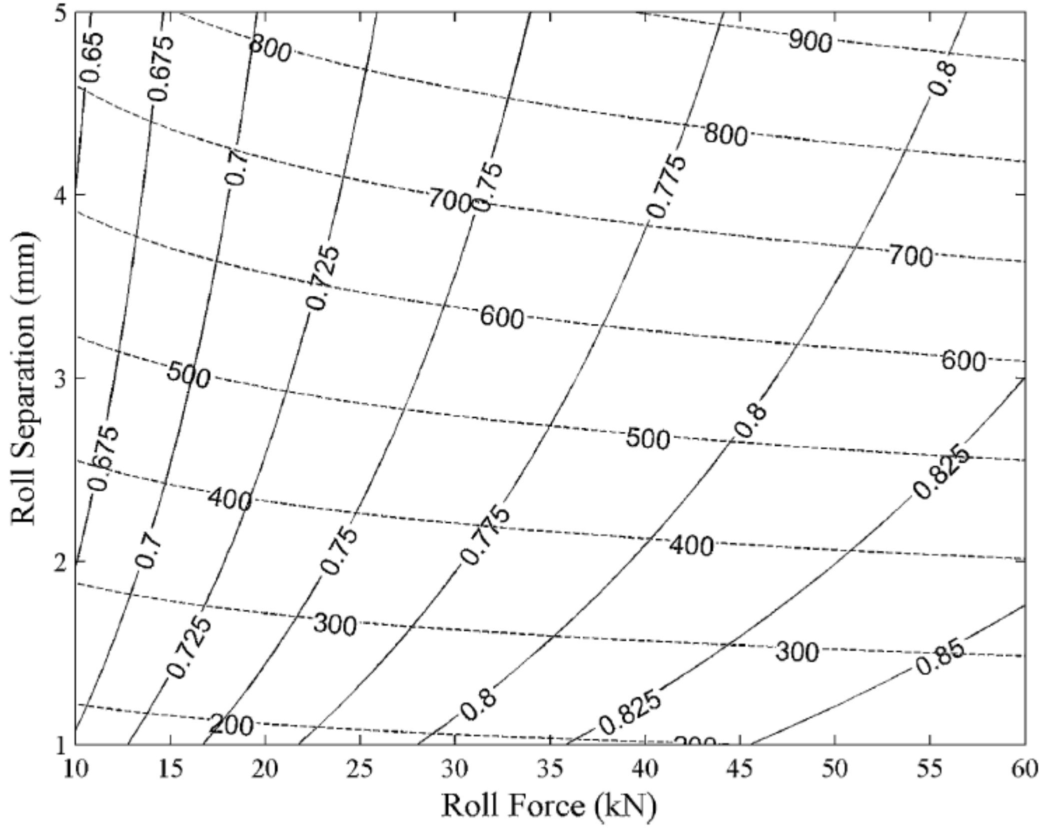
Unit Operation – Roll Compactor

Developing a model

Roll Compacting

$$\gamma_R = \gamma_0 (2R_f)^{1/K} \left(WD \int_{\theta=0}^{\theta=\alpha(\delta_E,\phi_W,K)} \left[\frac{c_S N_S}{\pi \rho_{true} \gamma_R W D^2 N_R (1 + c_S N_S / \pi \rho_{true} \gamma_R W D^2 N_R - \cos\theta)\cos\theta} \right]^K \cos\theta \, d\theta \right)^{-1/K}$$

- Powder mechanics model allows the key intermediate attribute of ribbon relative density or porosity to be related to process parameters (roller pressure, gap size, screw speed) based on material compaction properties (compressibility) and equipment geometry (diameter, width).

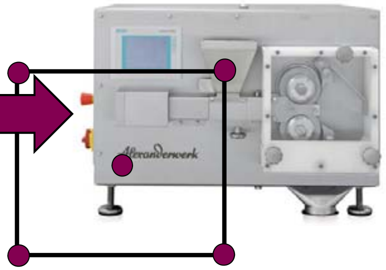


Reynolds (2010), Comp. Chem. Eng. 34, 1049

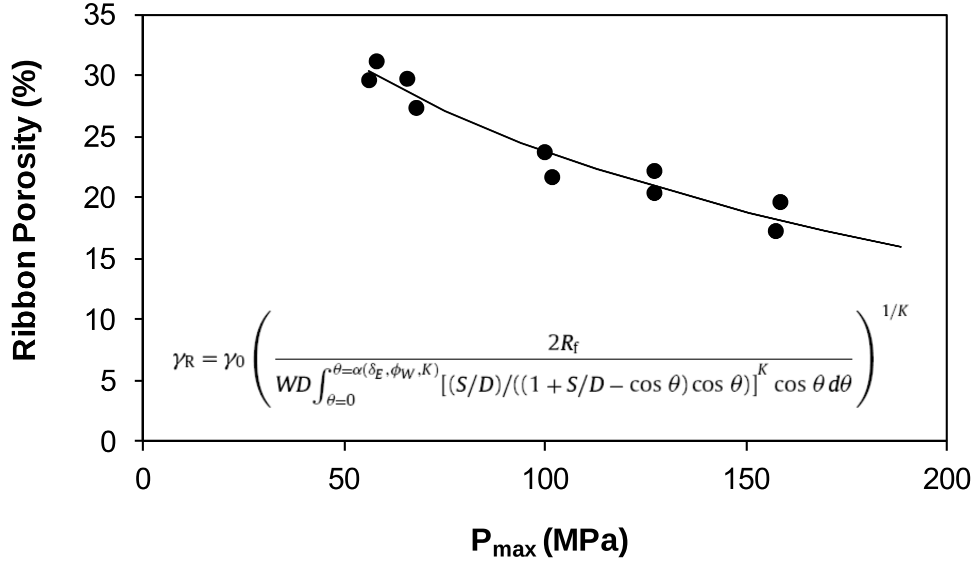
Unit Operation – Roll Compactor

Calibrating a model

Roll
Compacting



- The powder compaction properties are calibrated to RC experimental data.
- P_{max} is dependent on these parameters, so the model needs to be solved iteratively to determine γ_0 and K.



Unit Operation – Milling
Developing a model

Milling

- The roll compactor is followed by a screening mill. This is modelled by coupling a mill model with a classification model.

- The mill model uses the breakage kernel of Vogel and Peukert (2005).
  - Breakage probability

$$P_B = 1 - \exp\{ f_{Mat}\, x k (W_{m,kin} - W_{m,\min}) \}$$

Material strength parameter

Number of impacts

Mass specific impact energy

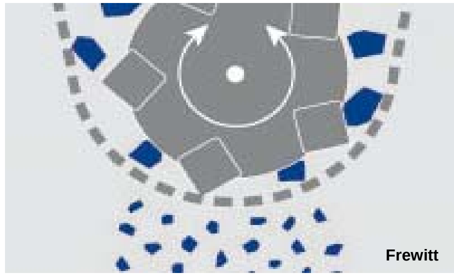
Threshold energy for particle of size x

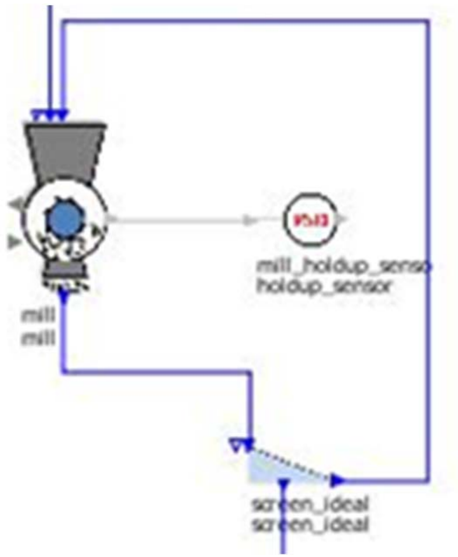
  - Fragment size distribution

$$B = \left(\frac{x}{y}\right)^{q} \frac{1}{2}\left\{ 1 + \tanh\left(\frac{y-y'}{y'}\right)\right\}$$

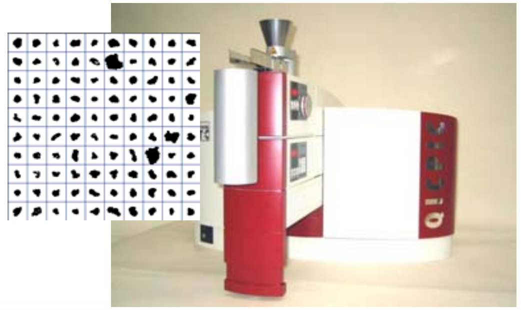
Minimum particle size limit

Power law exponent

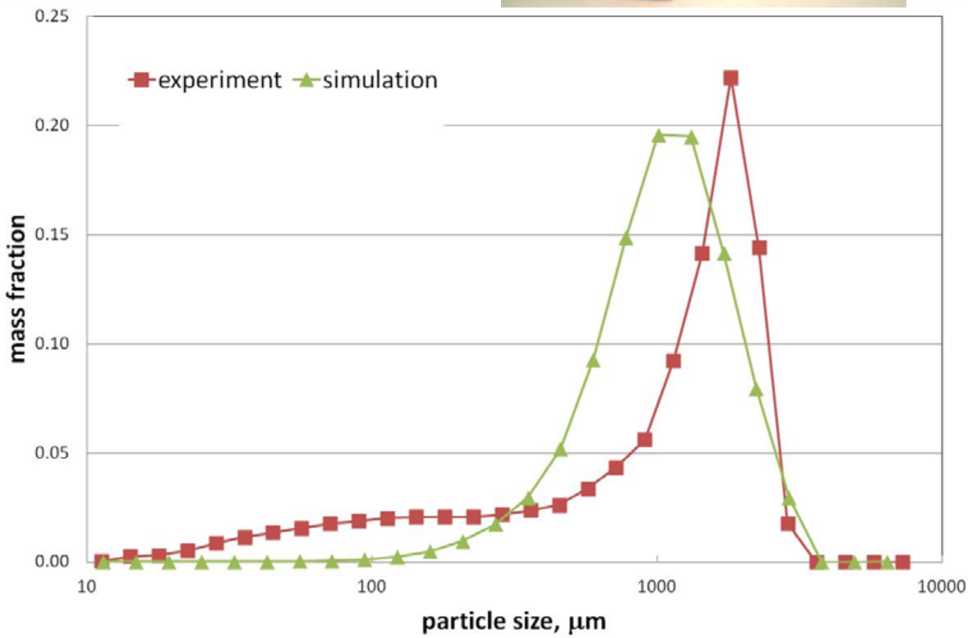




Unit Operation – Milling
Calibrating a model



- The six parameters of the breakage kernel are determined by fitting the predicted granule size distribution to experimental data.
- In this case the mill model was only able to approximate the granule size distribution
  - The sharpness of the large mode is not captured
  - No fines are predicted



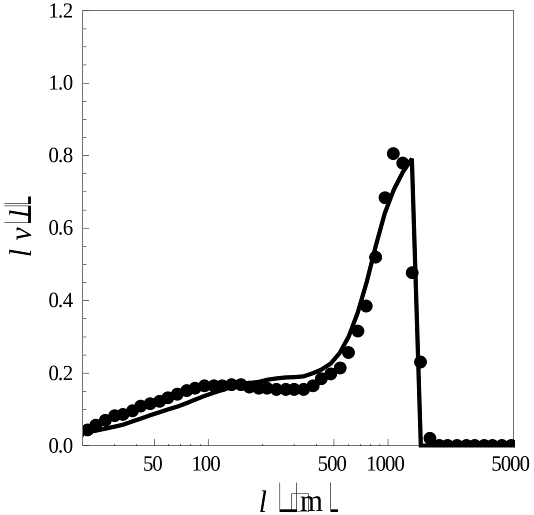
Unit Operation – Milling

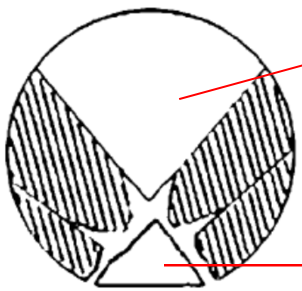
Improving a model

Milling

- Typically granular material exhibits a bimodal breakage mechanism
- The accuracy of the predicted granule size distribution could be improved by incorporating a bimodal fragment size distribution

- However, the approximated distribution was considered sufficient for the initial system model.





Fragmentation

Disintegration

$$b(\upsilon,v)=\frac{u\,z}{3k_v^{1/3}\upsilon^{2/3}}\,\frac{2}{\sqrt{2\pi}\ln\sigma_1}\,\frac{\exp\left[-\left(\frac{\ln\left(\upsilon^{1/3}/k_v^{1/3}\mu_1\right)}{\sqrt{2}\ln\sigma_1}\right)^2\right]}{1+erf\left[\frac{\ln u^{1/3}/k_v^{1/3}\mu_1}{\sqrt{2}\ln\sigma_1}\right]}+(1-z)\frac{p}{u}\,\frac{\left(\frac{\upsilon}{u}\right)^{q-1}\left(1-\left(\frac{\upsilon}{u}\right)\right)^{r-1}}{B(q,r)}$$

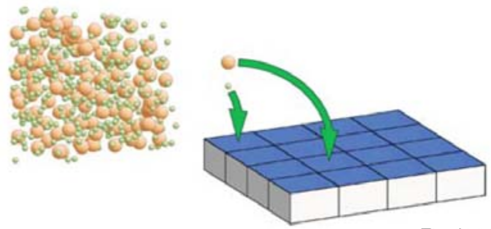
Reynolds (2010), Chem. Eng. J. 164, 383

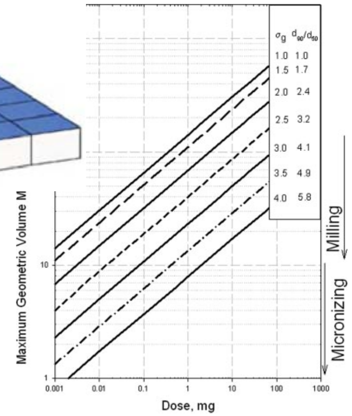
Unit Operation – Mixing
Developing a model

- To simplify the construction of the system model, the mixing unit operation was not modelled (i.e. the stream was considered well-mixed)

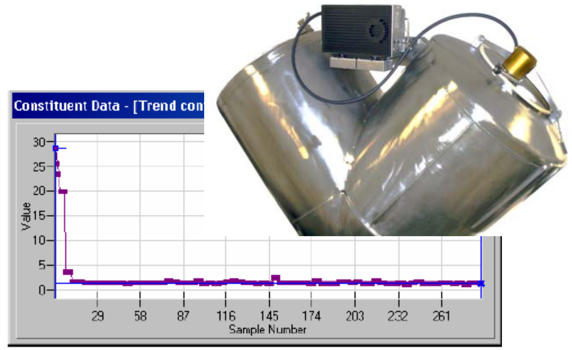
- Various approaches can be envisaged ranging from well-mixed models to empirical exponential decay models.

- One practical challenge would be considering how ‘degree of mixedness’ would propagate downstream to subsequent unit operations and product properties.



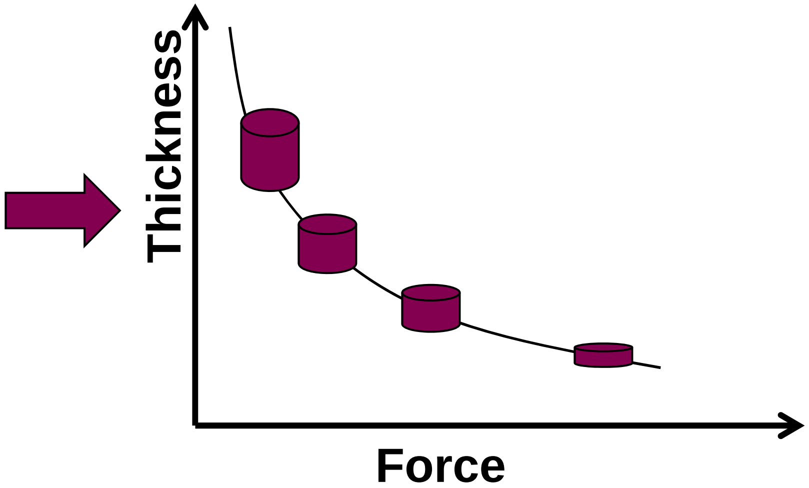


Rohrs, 2006
Hilden, 2012



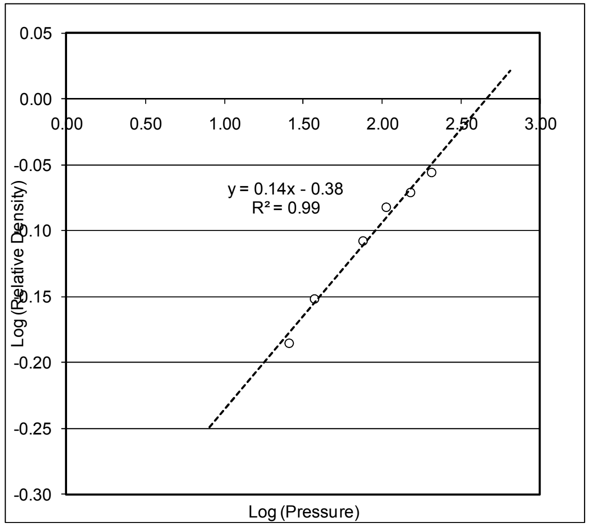
Unit Operation – Tabletting

Developing a model

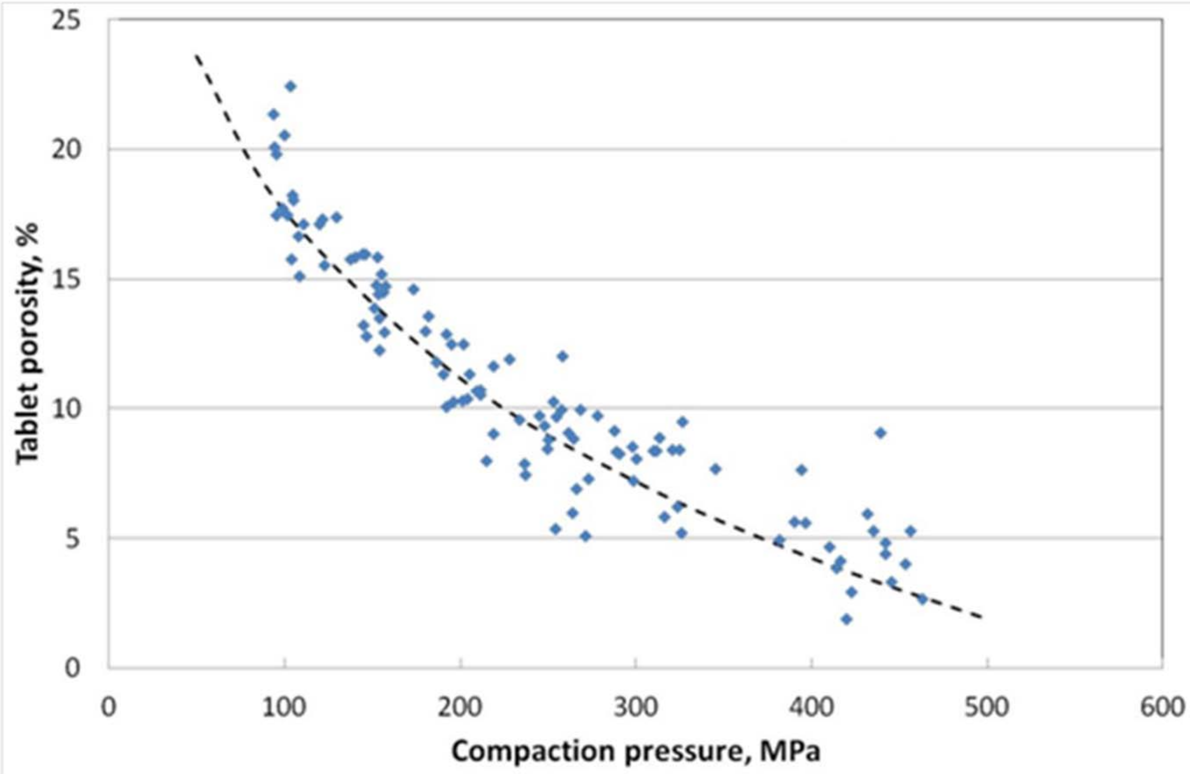


- A simple compaction model is implemented to determine tablet porosity from the tablet dimensions and punch force.

$$P = \frac{F}{A} \qquad \gamma = \gamma_0 P^{1/K}$$



Unit Operation – Tabletting
Calibrating a model



- This simple model assumes that only the formulation composition influences the relationship, and not upstream processes (e.g. roll compaction). In this case, a single relationship across all the experiments seems to be a reasonable approximation.

Performance – Hardness

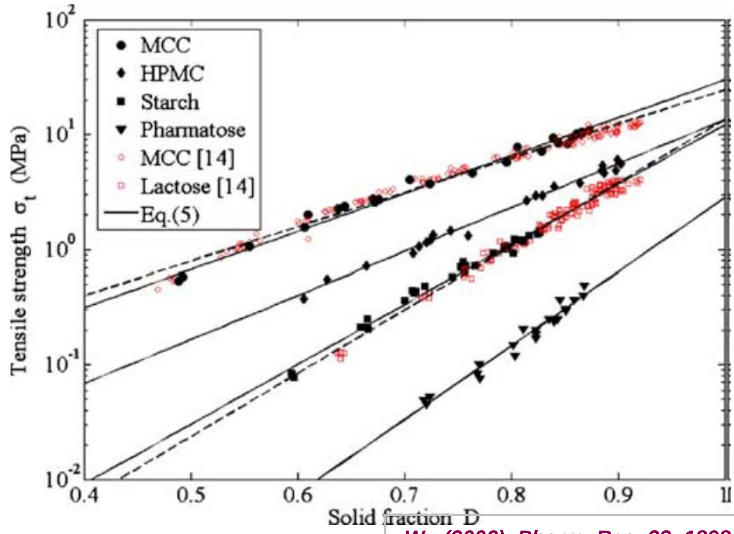
Developing a model

- Tensile strength (hardness) can be related to tablet porosity using the Ryshkewitch-Duckworth equation

$$T = \overline{T}e^{-k_b \varepsilon}$$

Tensile strength at zero porosity

Bonding capacity



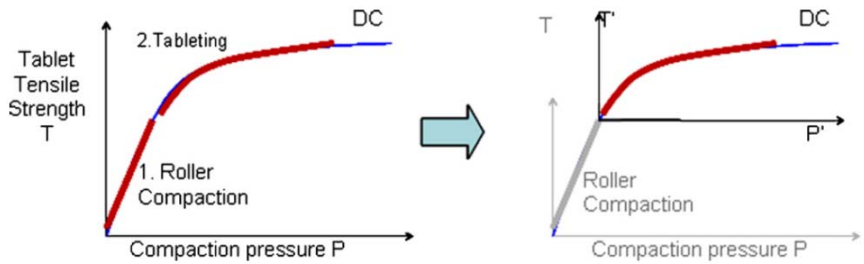
Wu (2006), Pharm. Res. 23, 1898

- In general it is observed that roll compaction typically reduces the apparent tablet tensile strength. This 'loss of compressibility' can be approximated by subtracting the tensile strength generated during roll compaction fro the final tablet tensile strength.

$$T_{tablet} = \overline{T}e^{-k_b \varepsilon_{tablet}} - \overline{T}e^{-k_b \varepsilon_{ribbon}}$$

Tablet porosity

Ribbon porosity

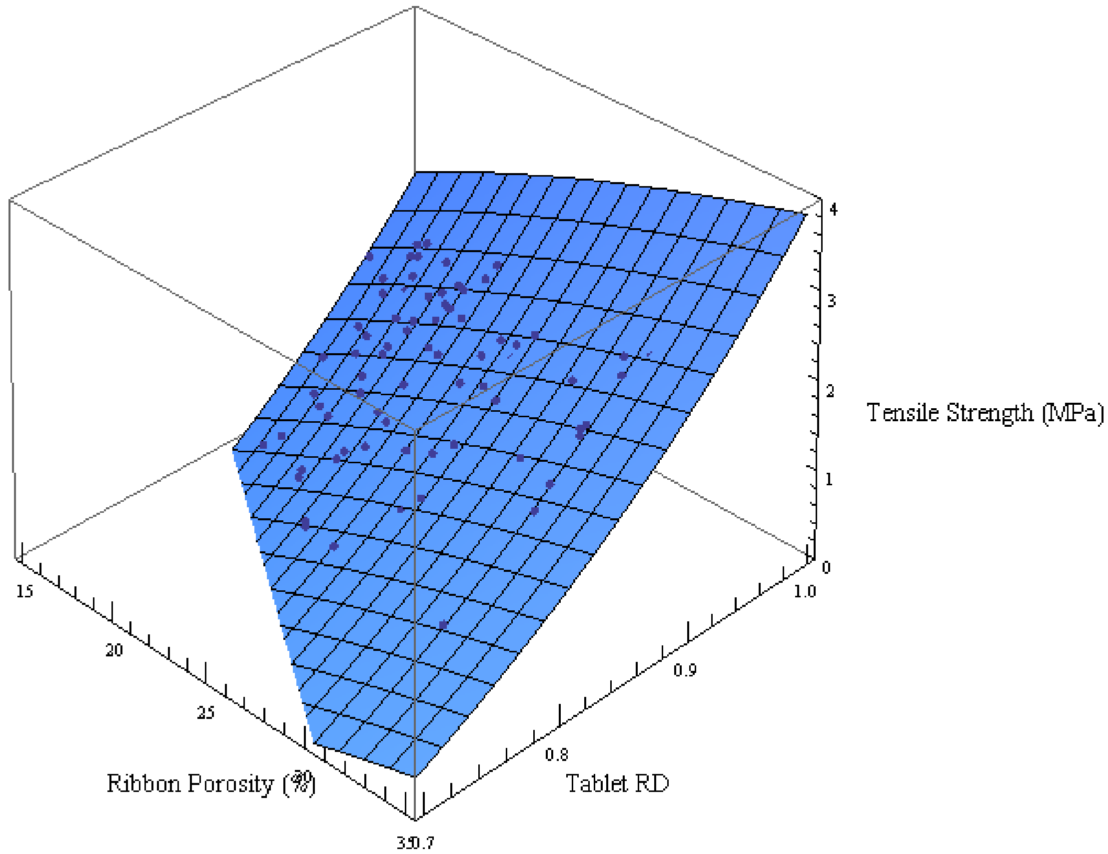


Farber (2008), Int. J. Pharm. 346, 17

Performance – Hardness
Calibrating a model

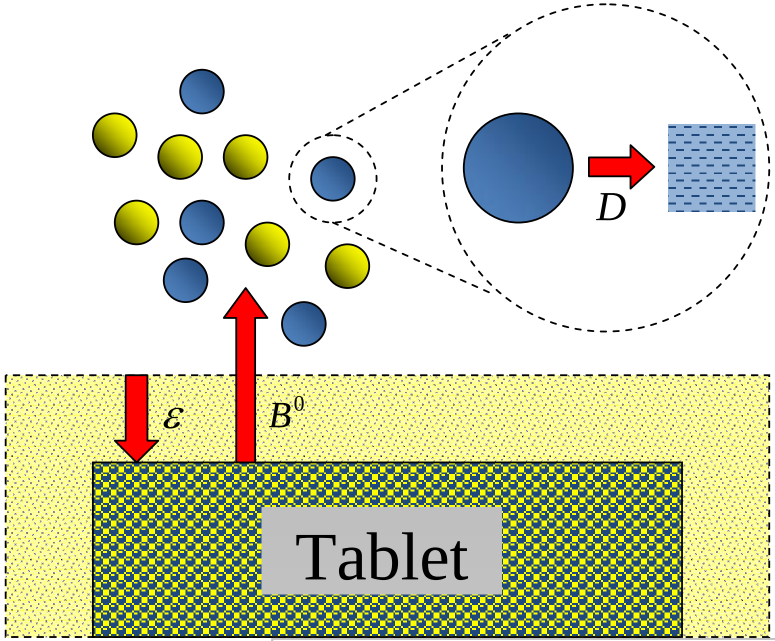
Hardness

- A single set of material parameters was estimated by fitting the compaction model to experimental data.
- This single set of parameters were able to be used across all the process conditions (i.e. related to formulation composition rather than upstream processing such as roller compaction).

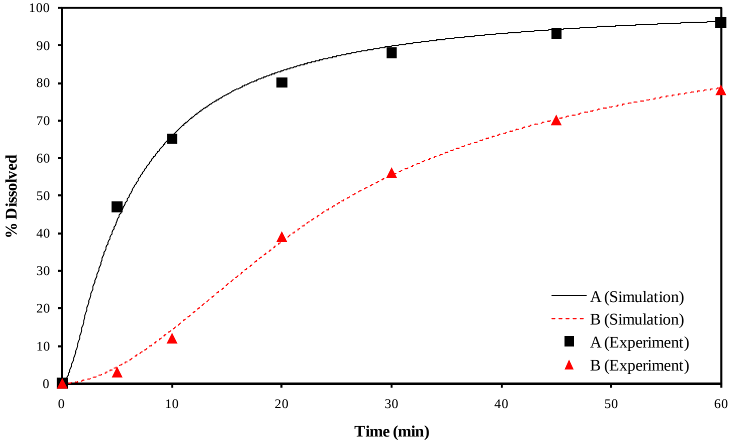


Performance – Dissolution
Developing a model

- A relatively simple model to describe tablet disintegration and dissolution was developed.
- Here, particles are released into suspension as a result of erosion of the tablet. The API is then dissolved into solution by mass transfer from the suspended particles.
- The model is based on that presented by Wilson et al. (2012).

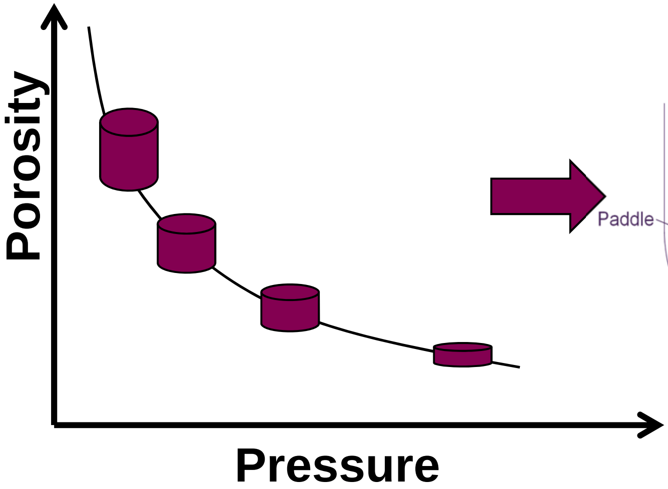


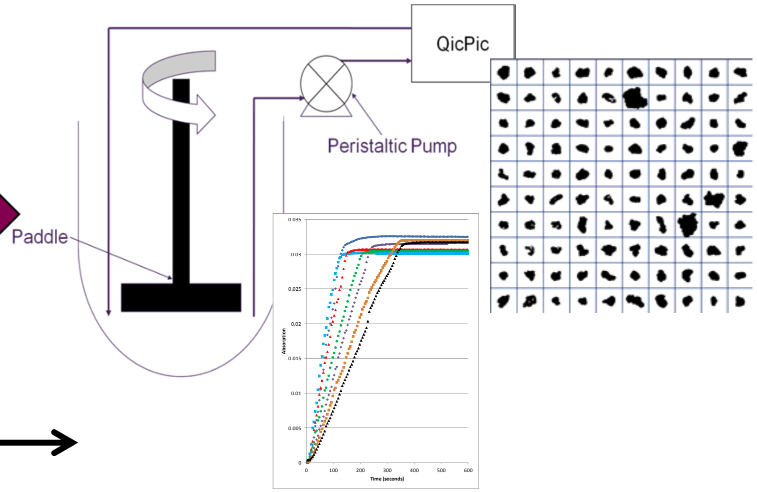
Wilson et al. (2012), Pharm. Res. 29, 198



Performance – Dissolution
Calibrating a model

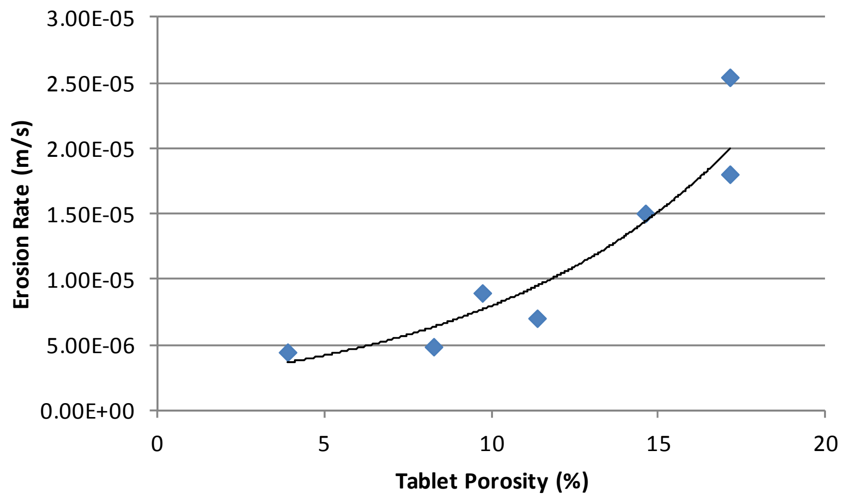
Dissolution





- Experimental data was fitted in order to determine the erosion rate.

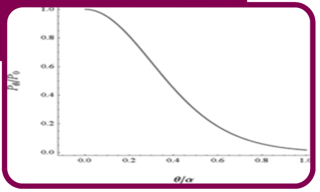
- An exponential relationship was used to describe the link between erosion rate and tablet porosity.



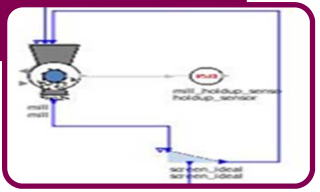
A systems-based approach

Develop unit operation models and link to product performance

Roll Compacting

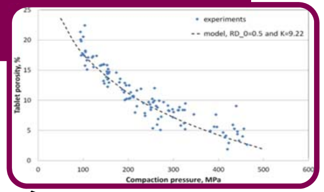


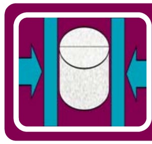
Milling



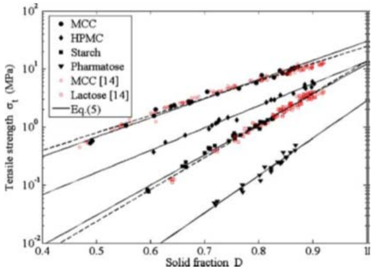
Mixing

Tabletting

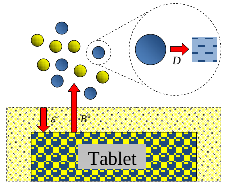




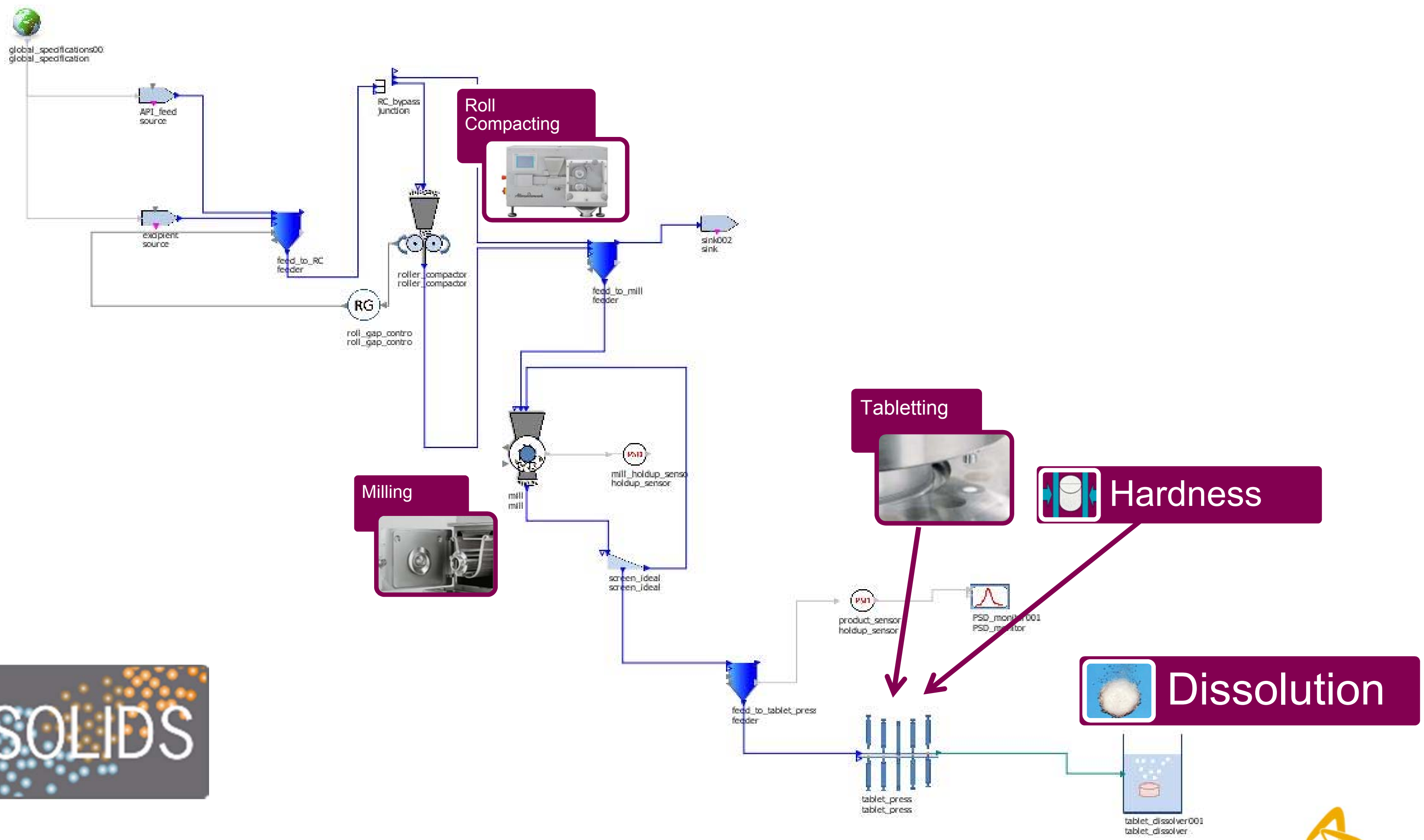
Hardness



Dissolution



Putting it all together
Implementing the system in gSolids



Results

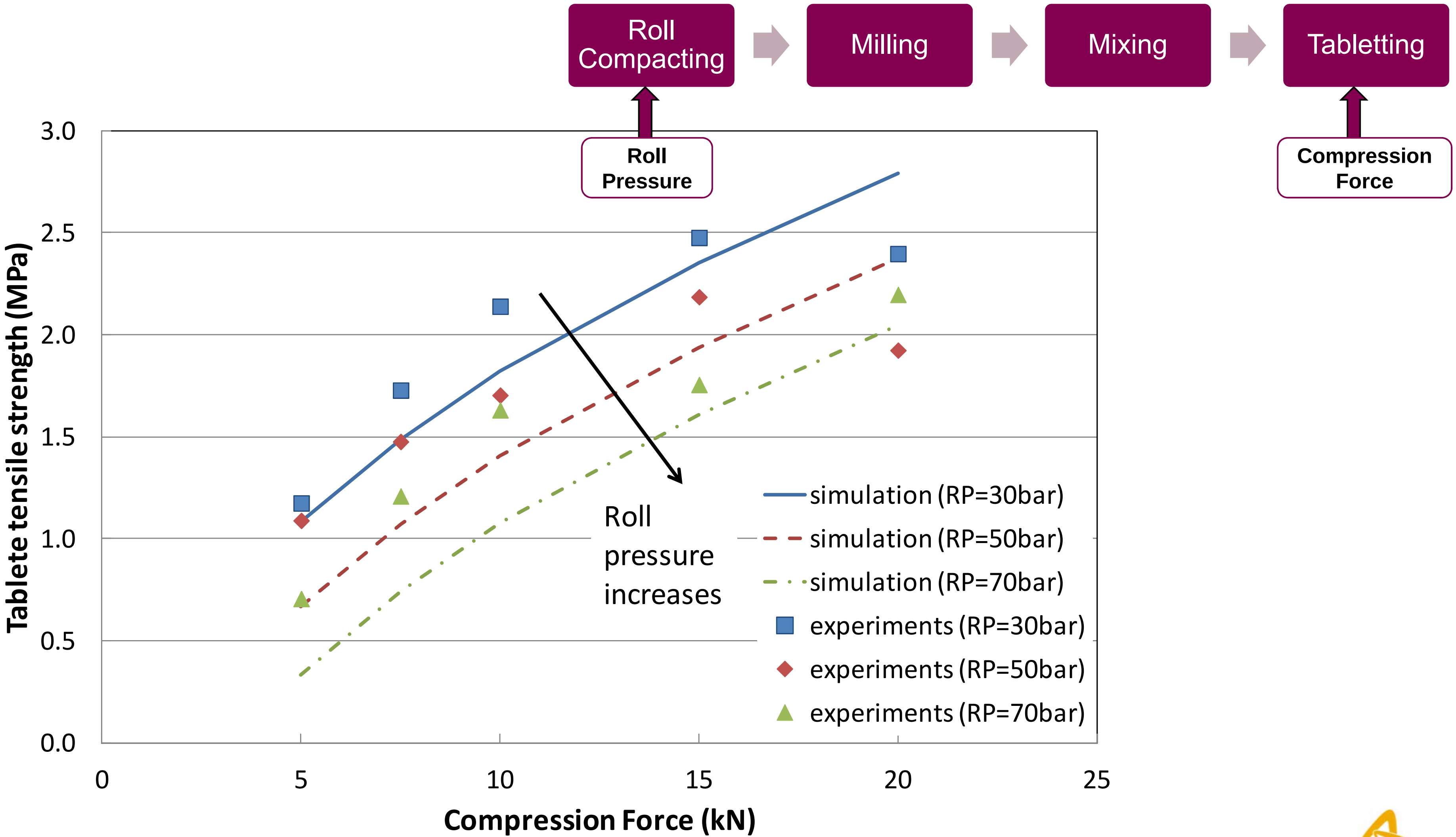
Experimental parameters

- **Typical immediate release tablet formulation**
  - 15% API
  - Mixture of brittle and ductile fillers
  - Lubricant

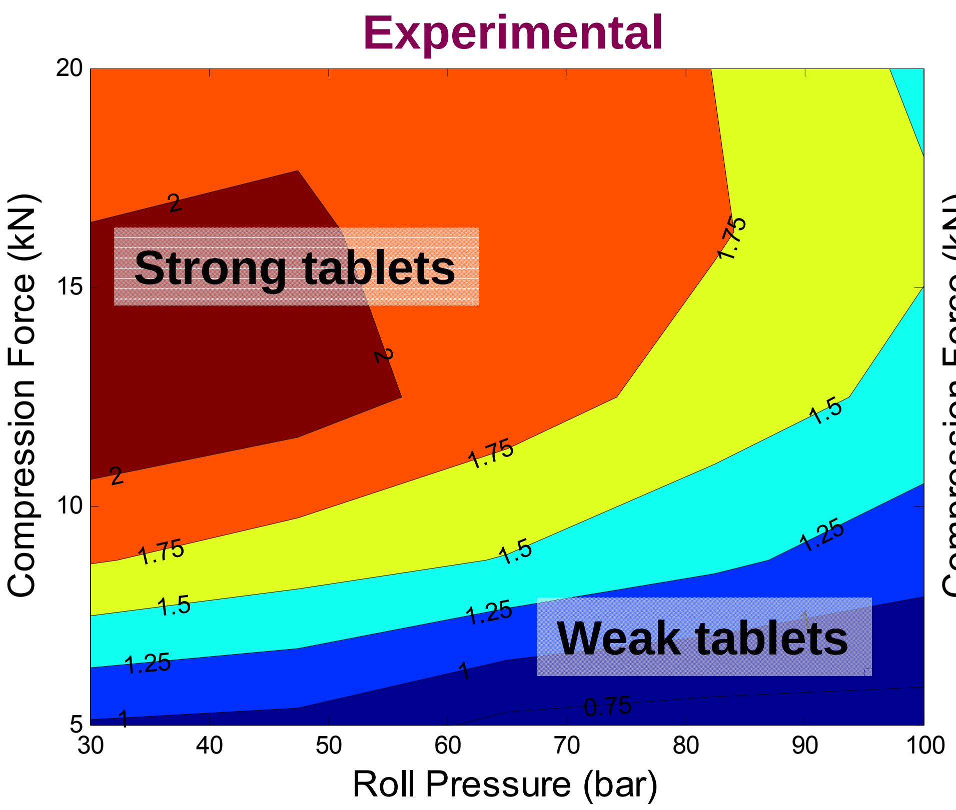
Factor	Range
Roll Pressure	30 – 70 bar
Mill Screen	1.25 – 2.0 mm
Compaction Force	5 – 20 kN
Number of runs	19

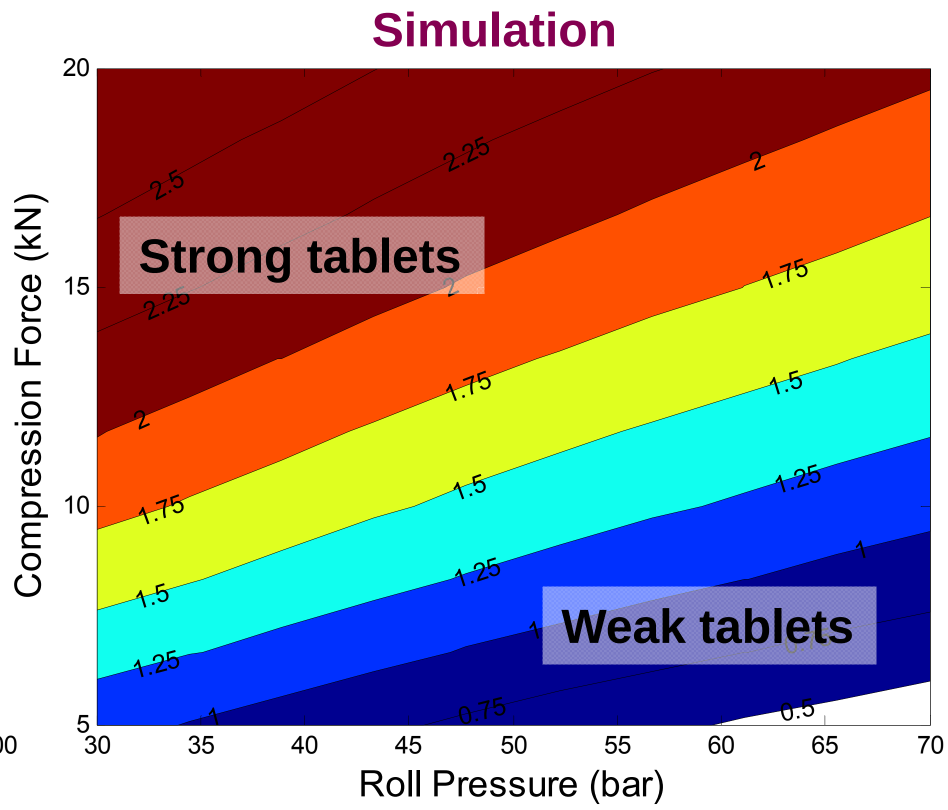
Results

Roller Pressure and Tablet Tensile Strength



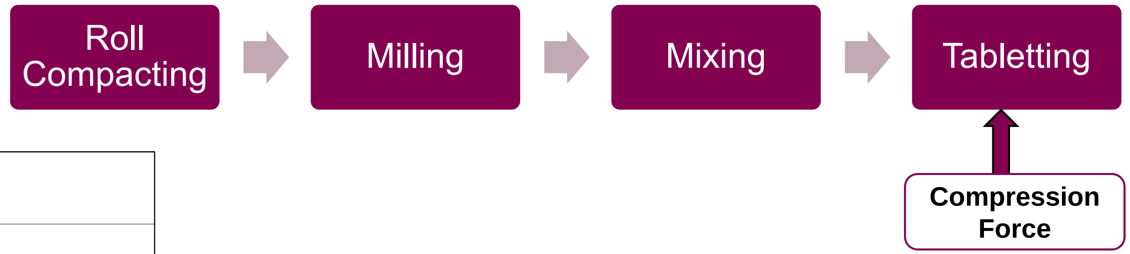
Results
Roller Pressure and Tablet Tensile Strength

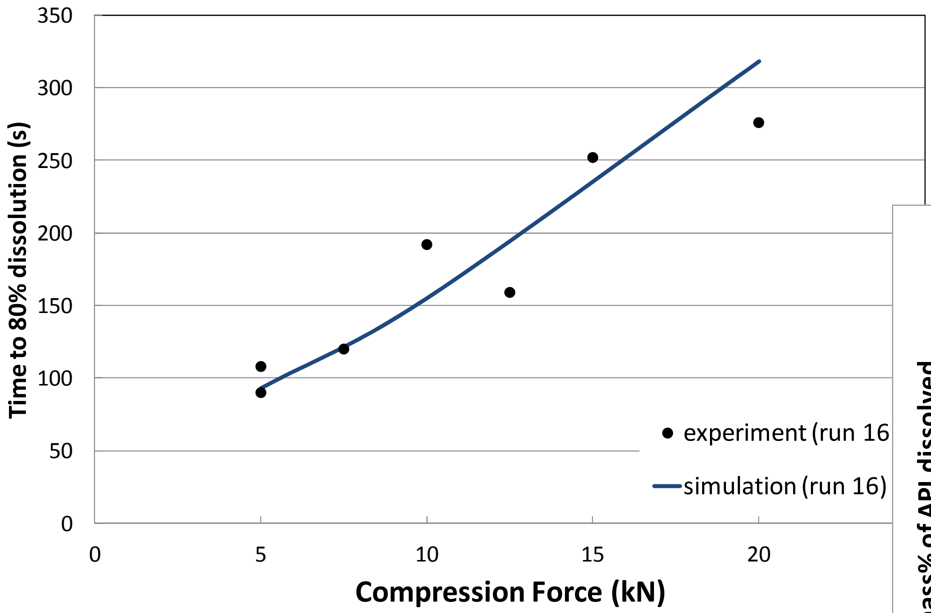


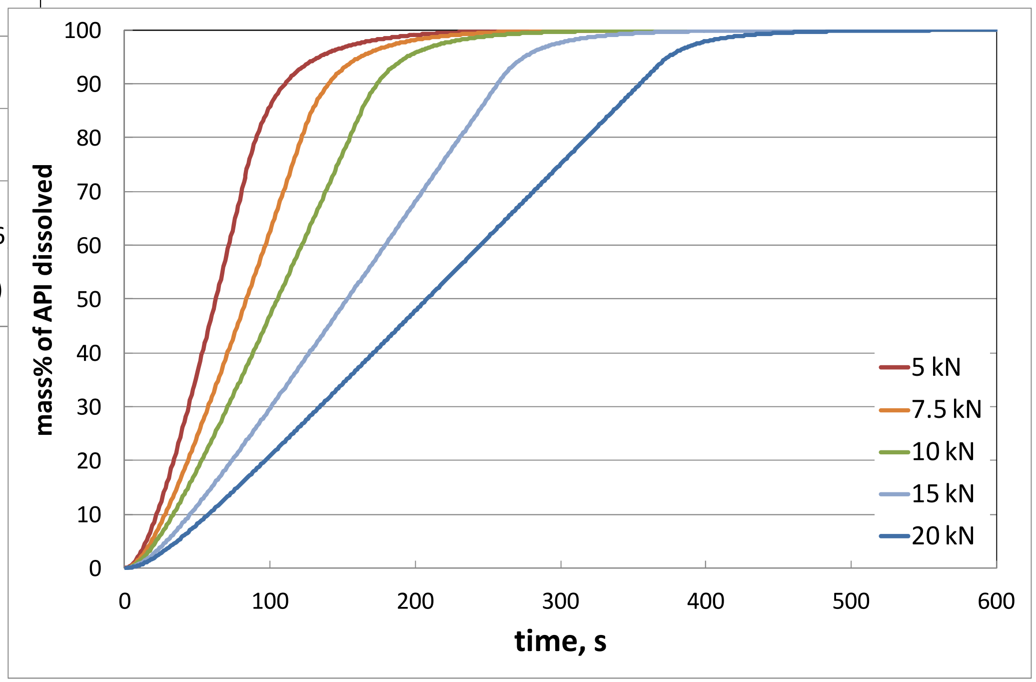


- General qualitative and quantitative trends captured
- Some non-linear behaviour at high compression forces not captured

Experimental Validation
Tablet Compression Force and Dissolution

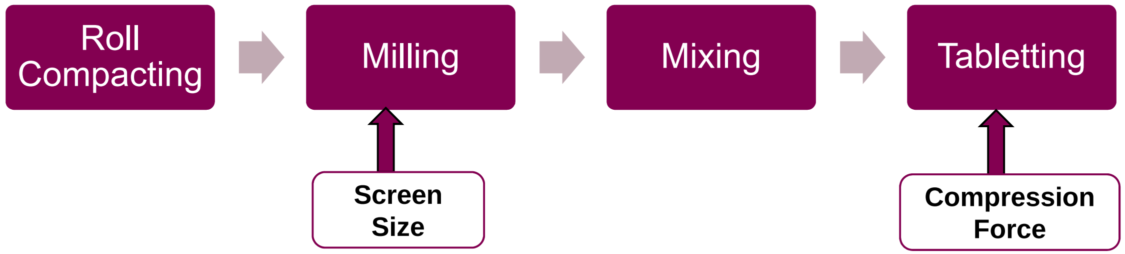


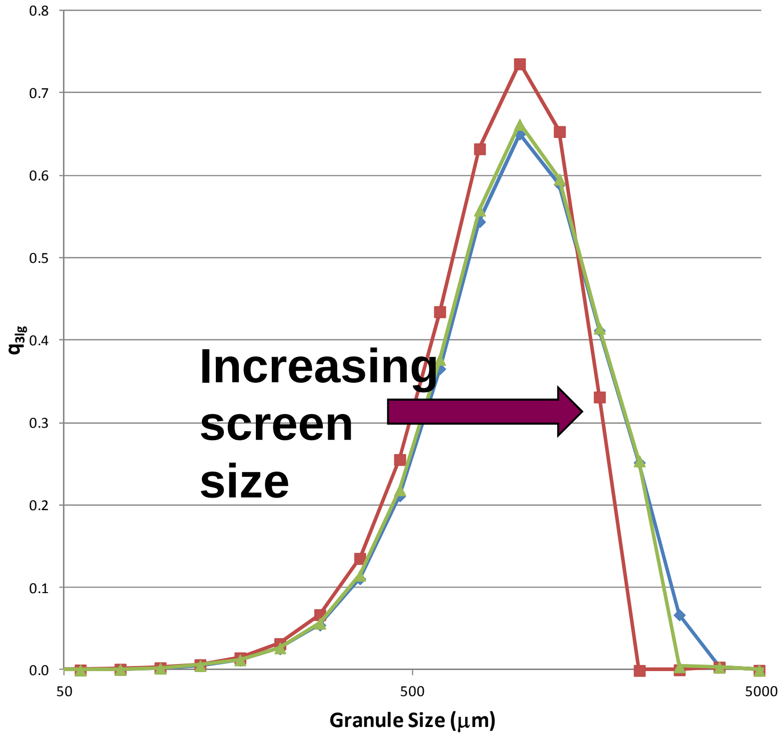


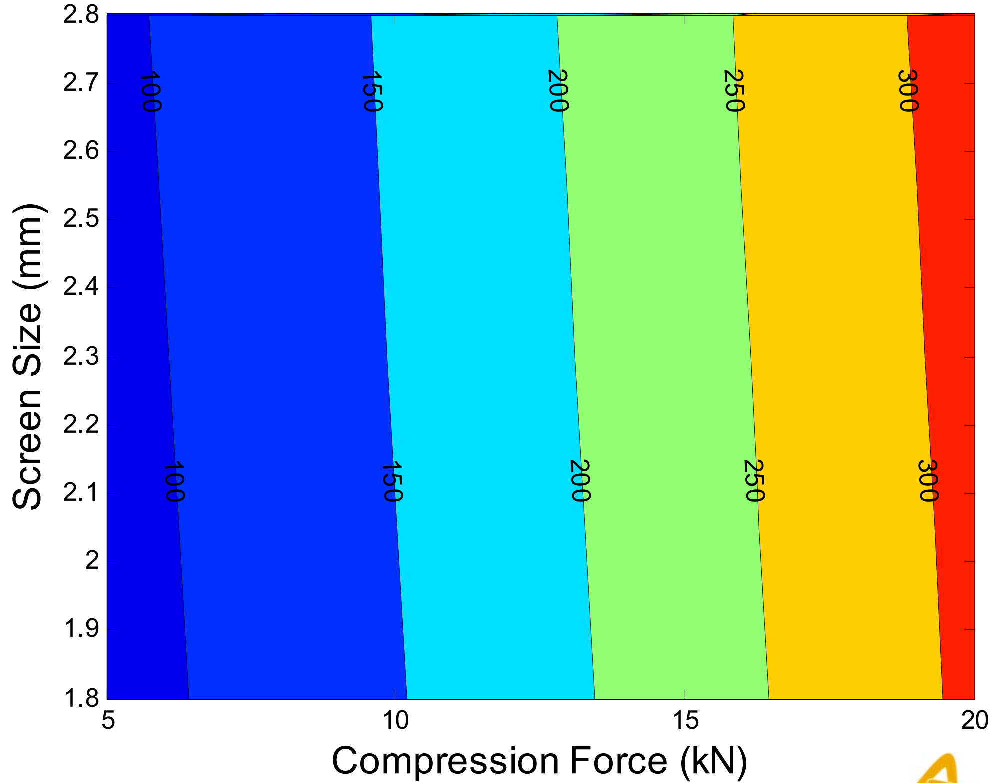


Experimental Validation

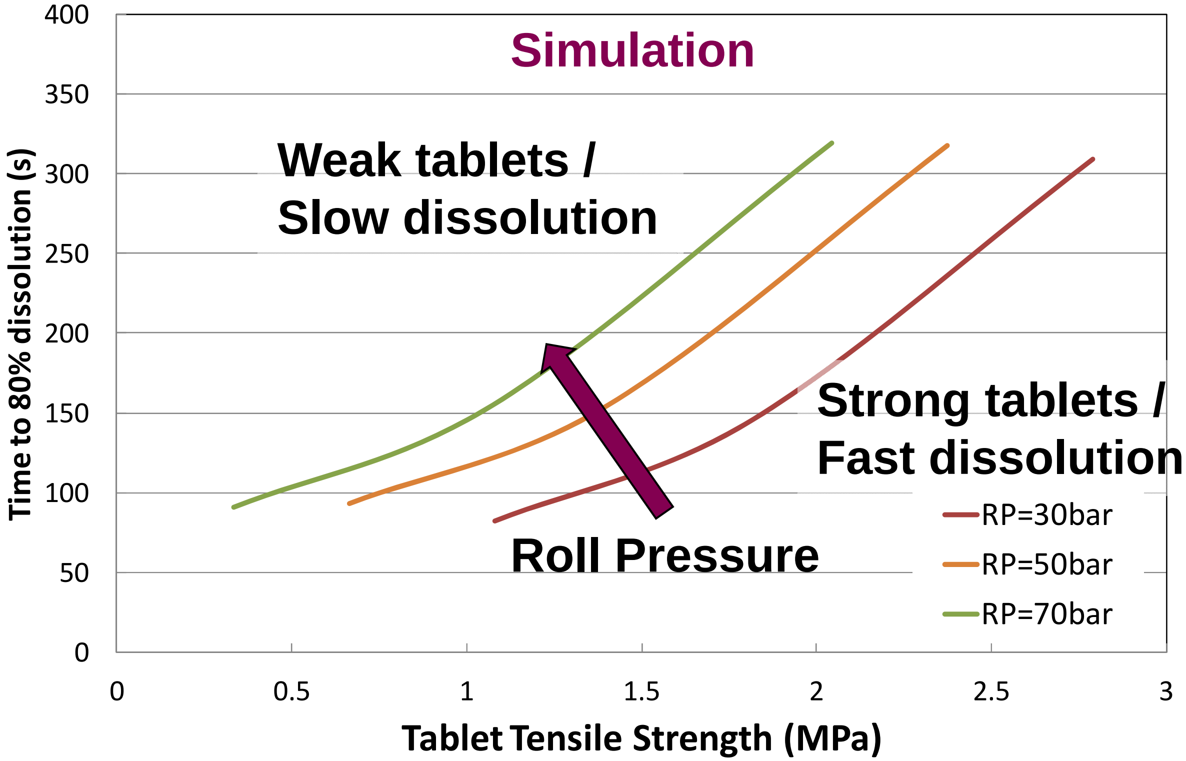
Tablet Compression Force and Dissolution

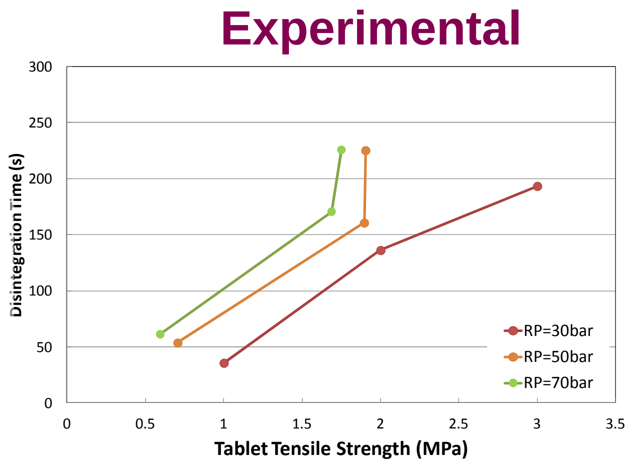






Experimental Validation
Tablet Tensile Strength and Dissolution





- **Predicted dissolution performance in qualitative agreement with experimental disintegration time.**

Conclusions

- **Demonstrated constructing a system model linking tablet manufacture to performance.**
- **Relatively simple unit operation models link together to provide qualitatively and in some cases quantitatively excellent predictions of effects and interactions between process parameters and product quality attributes.**
- **This provides an excellent basis for**
  - Improving product and process understanding
  - Education
  - Supporting process optimisation
  - Building control or RTRT models
  - Implementing improved unit operation or product performance models (e.g. in-vivo absorption)
  - Support a move towards continuous manufacture

Confidentiality Notice