Use of Prediction Engineering Methods in Compression Scale-up

Feng Li

For presentation at
the 51st Annual International Pharmaceutical R&D Conference
Land O'Lakes Conference
June 1-5, 2009
Devil's Head Resort, Merrimac, Wisconsin

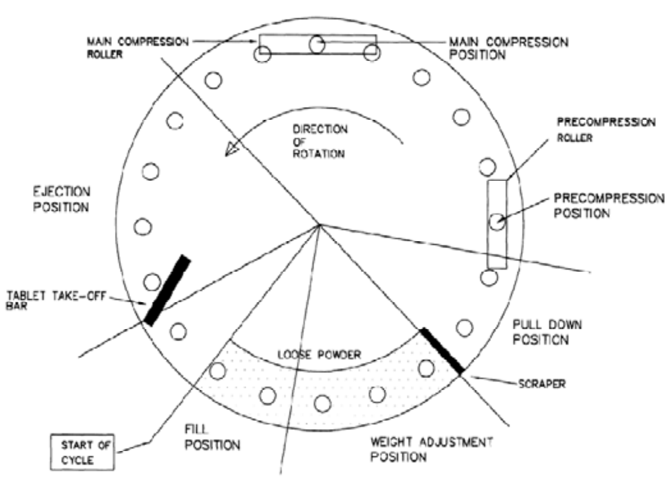
Outline

- The most relevant and important aspects in tablet compression
- Considerations in scale-up and prediction methods
- Case study

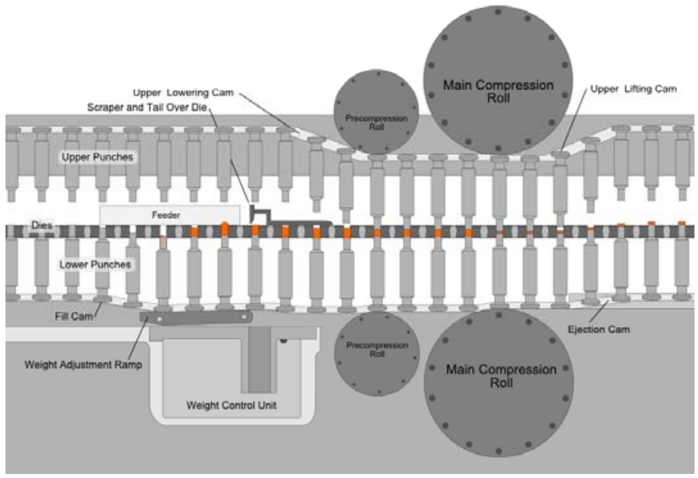
Acknowledgement

- John Cunningham (Johnson & Johnson, US)
- Adam Procopio (Merck & Co., Inc., US)
- Kendal Pitt (GSK, UK)
- Brandon McWilliams (former co-op student)
- Amanda Hunt (former co-op student)
- Angela McIver (former summer intern)
- Adam Chen (Merck & Co., Inc., US)
- Csaba Sinka (University of Leicester, UK)
- Steve Galen (Covance, US)
- Antonios Zavaliangos (Drexel University, US)

Tablet compression process (top view)

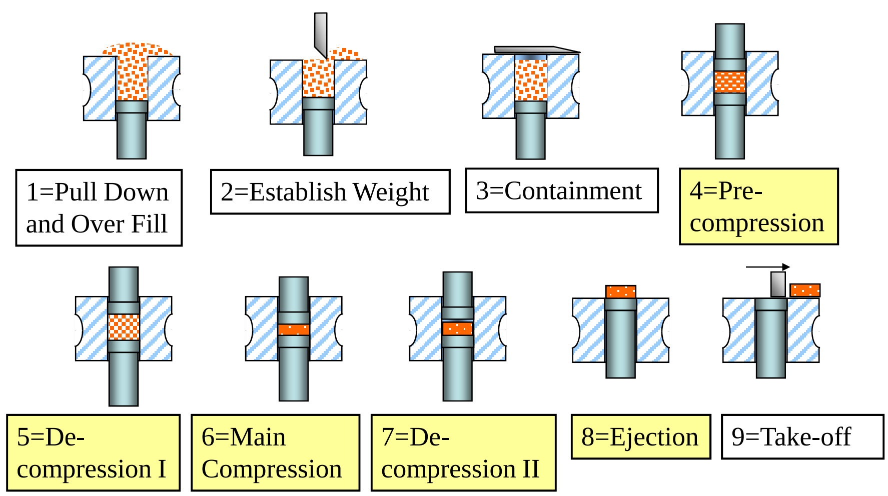


Tablet compression process



Thanks to the good people who made this on Wikipedia!

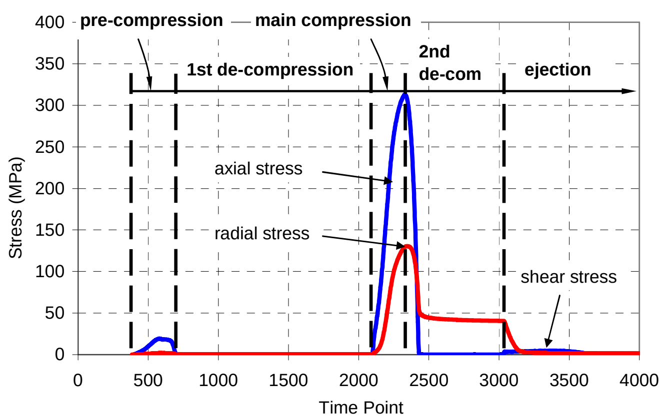
Critical steps in tableting cycle



The most relevant/important aspects in pharmaceutical powder compaction

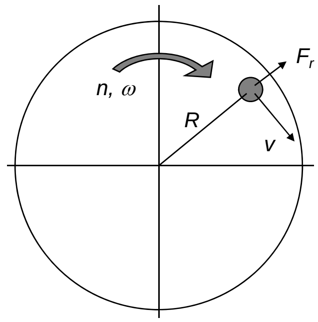
- Stress path of powder/tablet throughout the compaction cycle
- Material properties (e.g., elasticity, plasticity, yield behavior, brittleness)
- Friction (e.g., between powder/tablet and die wall during compaction and ejection)
- Compressibility or densification behavior
- Air entrapment
- Temperature rise in tablet

Stress in powder/tablet as a function of time during die compaction



- ➢ Stress state is similar between small and large tablet press
- ➢ Material properties remain the same

Key changes in the compaction event from small to large rotary tablet press



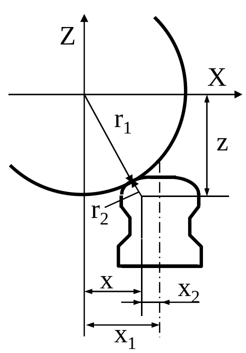
Schematic of a rotary tablet press die table,

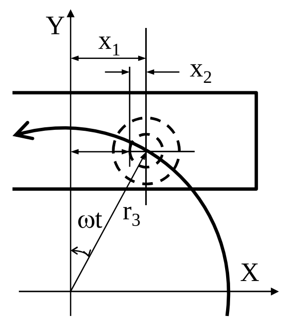
where *n* is the turret speed in RPM, *ω* the angular velocity, *R* the pitch radius and *v* the linear speed

- Linear velocity, i.e., punch horizontal tangential speed *v*
  - $v_2 = v_1 (R_2/R_1)$
- Compression speed, i.e., punch vertical velocity
- Dwell time
- Ejection speed
- Centrifugal force
  - $F_{r2}/R_2 = F_{r1}/R_1 = m \cdot \omega^2$
- Die filling time
- ...

Punch Vertical Velocity - Rippie & Danielson Equation

$$Z = [(r_1 + r_2)^2 - (r_3 \sin\omega t - x_2)^2]^{1/2}$$

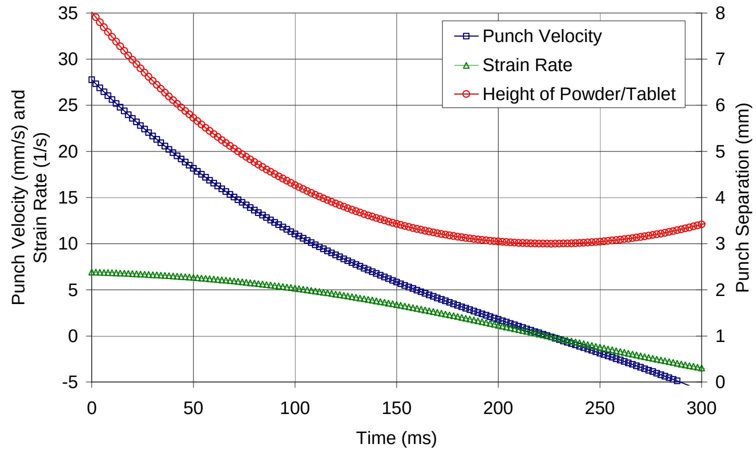




Rippie, E.D. and Danielson, D.W., *J. Pharm. Sci.*, 70 (1981) 476-482.

Punch velocity and strain rate example – a pilot scale rotary press

Small rotary press main-compression at 20 RPM
(Dwell Time = 121.34 ms - for Standard Punch Head)



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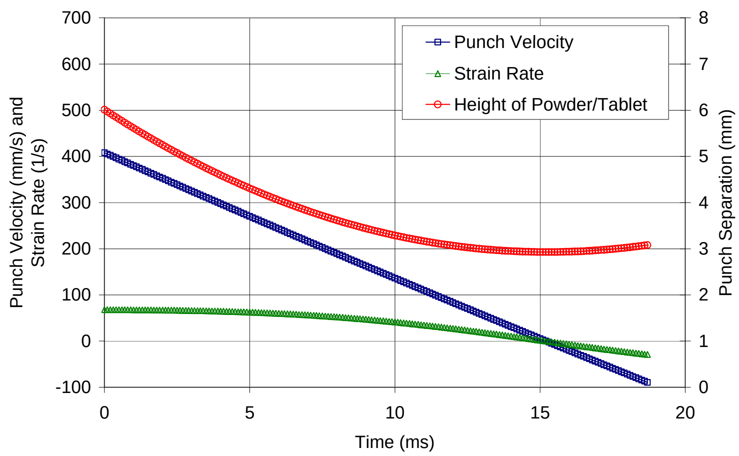
Punch velocity and strain rate example – a production scale rotary press

Production rotary press main-compression at 50 RPM
(Dwell Time = 9.6 ms - for Standard Punch Head)



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Dwell time

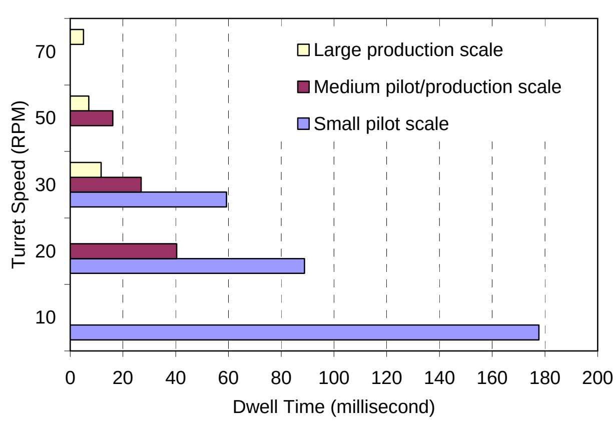
- The period of time in compression during which the punch separation (the height of powder bed or thickness of tablet) remains constant
- Dwell time calculation

$$T_d = 1000 \cdot (60/\pi nD) \cdot d_{hf}$$

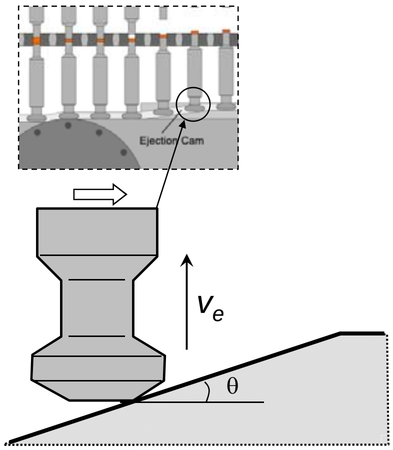
  - T_d is the dwell time in millisecond
  - n is the turret speed in RPM
  - D is the pitch diameter in mm
  - d_{hf} is the diameter of punch head flat in mm

Dwell time example

Dwell time in different scale rotary tablet press



Ejection speed



$$V_e = \pi \cdot D \cdot \tan\theta \cdot (n/60)$$

V_e – ejection speed in mm/s
D – pitch diameter in mm
θ – angle of ejection cam in deg
n – turret speed in RPM

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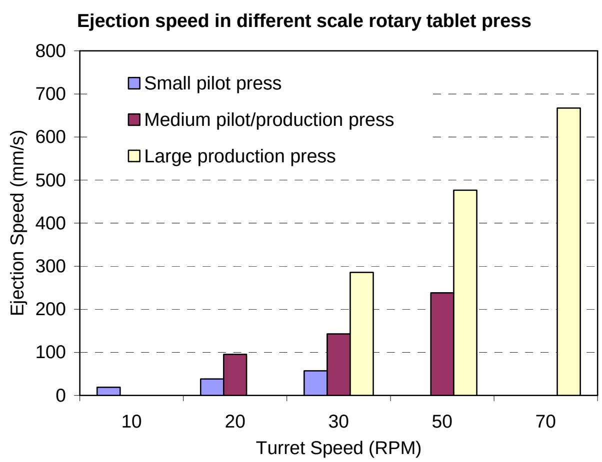
Ejection speed example



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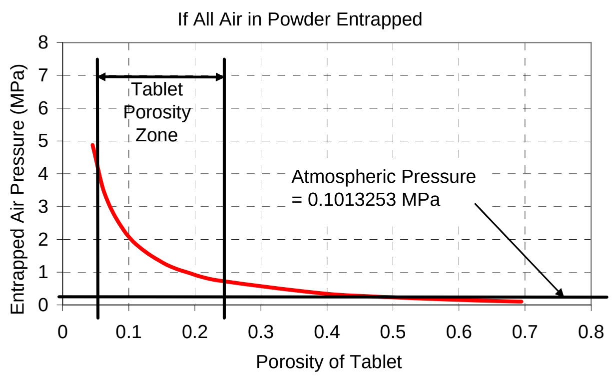
Air entrapment



- **60-80%** volume of powder we process is air!!!
- As compression speed increases, more air will be entrapped

$$P_{air} = P_{atm} \cdot \frac{1 - p_{r0}}{1 - p_r} \cdot \frac{p_r}{p_{r0}}$$

P_{air} = entrapped air pressure
P_{atm} = atmospheric pressure
p_{r0} = initial porosity
p_r = current porosity

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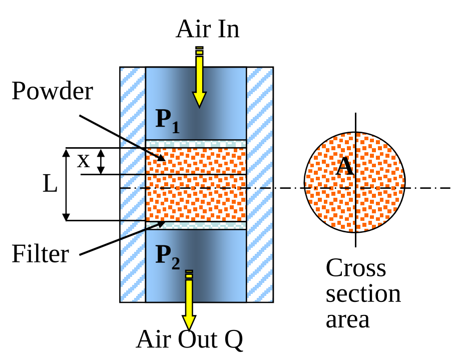
Air permeability

The property which permits the passage of air when a difference in pressure exists across the boundaries of the material

Darcy's Law:

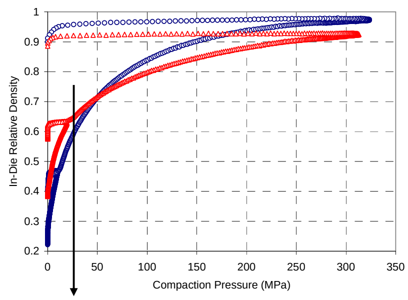
$$\frac{Q}{A} = \frac{k}{\mu}\frac{\Delta P}{L} \quad or \quad V = -\frac{k}{\mu}\nabla P$$



Q = volumetric flow rate
A = cross-sectional area
k = air permeability
μ = air viscosity
P = air pressure
L = length in the flow direction
V= Q/A = apparent velocity

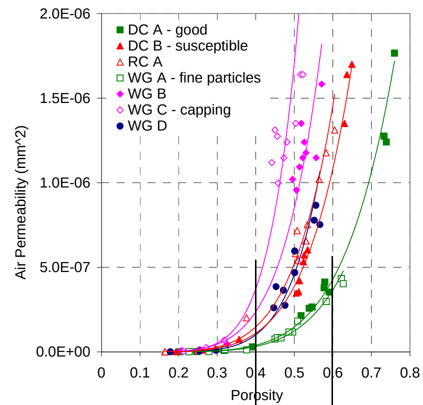
Determining degree of pre-compression based on formulation air permeability

Typical densification profiles



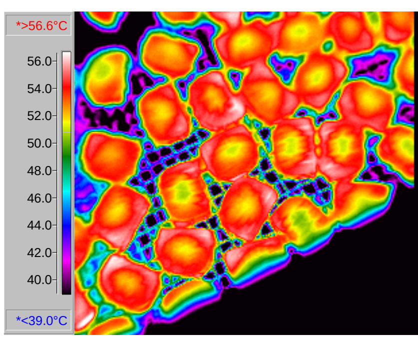
In general, pre-compression force (pressure) should be about 5-15% of the main force. If too low, not effective in air expelling; if too high, air may be trapped during pre-compression.

Air permeability as a function of porosity



Significant reduction in permeability in this region

Temperature rise during compaction



Steven Arrivo, PR&D memo, 26 June, 1998

Tablet Surface Temperature:	52 - 56 °C
Temperature gradient across tablet:	2 - 4 °C
Hottest region of tablet:	Outside Edge
Time for single tablet to cool to room temp:	> 5 minutes
Surface Temperature of tablets in bin after 5 minutes:	> 50 °C

Tablet surface temperature can be 30 ^{0}C or more above room temperature (~ 21 ^{0}C) and internal temperature likely higher (Nurnberg and Hopp, 1981; Arrivo, 1998; Bechard and Down, 1992; Galen, 2002)

Temperature rise – source of the heat

Work input:

$W = W_P + W_F + W_E$

W_P = plastic work (possibly a very small portion may be consumed for surface energy elimination or stored strain energy)

W_F = frictional work

W_E = elastic work

- Work input to the system that causes permanent deformation of powder/tablet and overcomes friction will convert into heat almost entirely:

$$(W_p + W_F) \Rightarrow C_p \cdot m \cdot \Delta T$$

*WARM DIE TABLE AND PUNCH ARE NOT SOURCES BUT RESULTS OF TABLET TEMPERATURE RISE

Temperature rise – energy estimate

Plastic work W_p can be expressed as:

$$W_p = \iiint_{\Omega} \left(\sigma_{ij} \cdot d\varepsilon_{ij}^{p}\right) dv$$

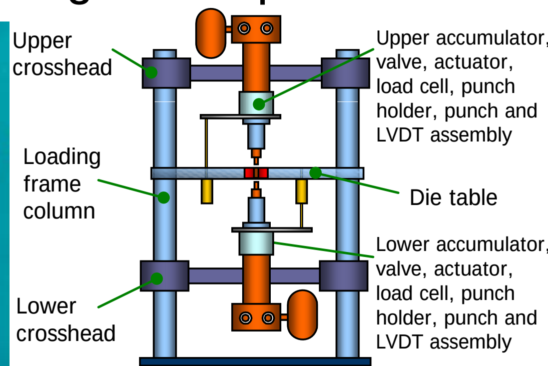
It can be simply obtained from the <u>area under curve in force-displacement plot</u>

Frictional work W_F can be expressed as:

$$W_F = (2\pi r) \cdot \iint \tau v dh dt$$

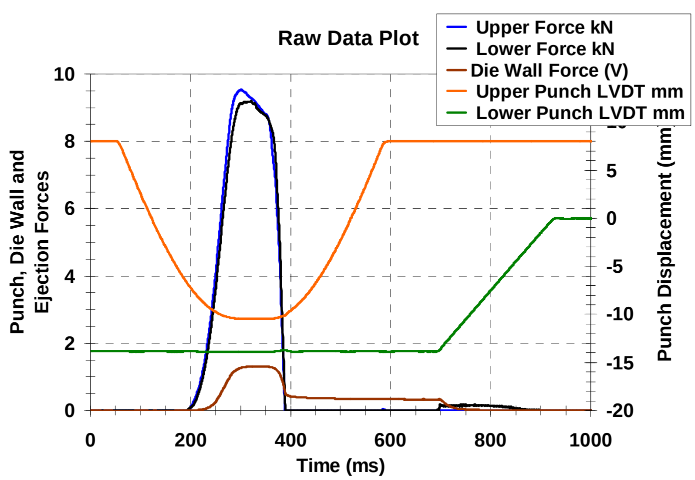
It can be simply obtained from <u>the difference between upper and lower punch force during compression</u> and <u>the force during ejection</u>

Use of compaction simulation to predict tableting scale-up



Mechanical Capability:
Max Force = 50 kN
Max Punch Displacement = 25 mm
Max Punch Velocity = 1400 mm/sec

Raw data from compaction simulator



Considerations in compaction simulation

- Tooling and tablet geometry
  - Type (e.g., F, B, or D)
  - Standard or tapered die
  - Material (e.g., S grades, D grades, A2, 440C)
  - Compliance
  - Surface treatment (e.g., polishing, coating)
  - Tablet design (e.g., round flat-faced or convex tablet, shaped tablet)
  - Size (e.g., 8/32", 12/32", 1/2")
  - Tablet aspect ratio (e.g., 0.3-0.5)
  - Tablet weight (needs to match size and aspect ratio)

Considerations in compaction simulation (cont.)

- Punch displacement profile
  - Artificial profiles (e.g., saw tooth, sine wave)
  - Tablet press profiles
    - By calculation (e.g., Rippie & Danielson equation)
    - By measurement (e.g., SMI instrumented punch, Puuman Oy portable tablet press analyzer)
    - By computer simulation (e.g., rigid body motion simulation)
  - Single action or double action compaction
  - With or without pre-compression and degree of pre-compression
  - Separation (time) between pre and main compression
  - Ejection starting point
  - Compaction position (along die depth)

Considerations in compaction simulation (cont.)

- Compaction force/pressure
  - Limited by tool force rating provided by manufacturers
  - Normally under 700 MPa, much less for deep or extra deep concave, modified ball, double radius or beveled edge tooling
  - Need to factor in compressibility and compaction mechanisms of the material
  - There can be a wide range of force/pressure, select the force / pressure for the intended process

Considerations in compaction simulation (cont.)

- Compaction speed and strain rate
  - Estimate punch vertical velocity from punch displacement profile and turret speed
  - Estimate strain rate (1/sec) from punch vertical velocity and powder fill height
- Dwell time
  - The time period during which the punch separation remains constant
- Ejection speed
  - Important for ejection force measurement

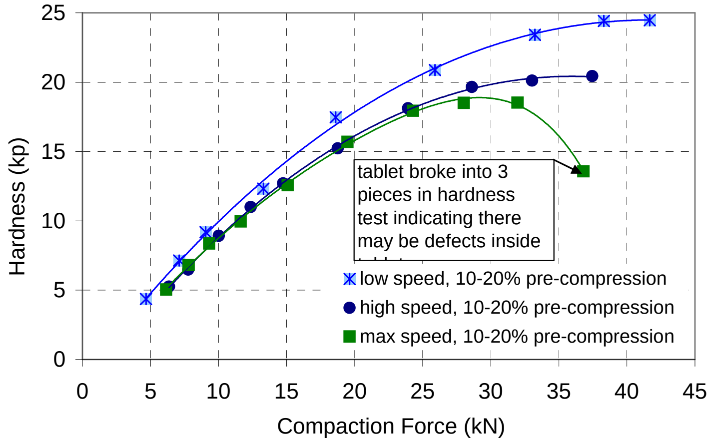
Considerations in compaction simulation (cont.)

- Lubrication
  - Die wall and punch surface lubrication
  - Dry magnesium stearate powder
  - Magnesium stearate suspension
  - Magnesium stearate compression
- Die filling
  - Hopper (gravity feed)
  - Feeder with paddle wheel
  - Manual weighing
  - Manual feed-shoe
- Environment
  - Room conditions
  - Accelerated conditions
  - Conditioning samples or changing lab environment

Analysis that can be performed with the measured parameters

- Compaction force-displacement curve
- Stress-strain curve
- Material densification profile such as density(porosity)-compaction force/stress curve
- Radial stress during compression and de-compression
- Residual radial stress at ejection
- Stress-path
- Compaction and ejection energy (total, net and ejection)
- Tensile strength and hardness (with data from physical testing)
- Ejection force and normalized ejection force
- Friction coefficient
- Pressure transmission ratio
- Tablet elastic recovery (both axial and radial)
- Elastic properties (Young's modulus, Poisson's ratio, shear and bulk modulus)
- Heckel plot, Kawakita plot and other pressure-density plots
- ...

Scale-up prediction by compaction simulation – effect of compression speed



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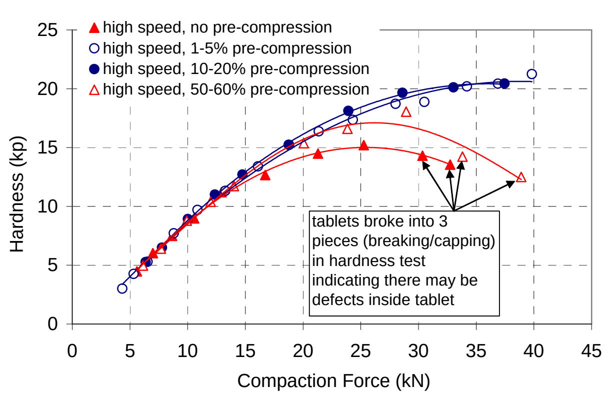
Scale-up prediction by compaction simulation – effect of pre-compression



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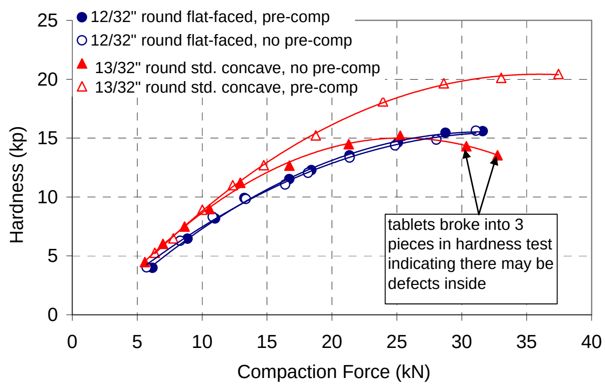
Scale-up prediction by compaction simulation – effect of tablet shape



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Scale-up prediction by compaction simulation – effect of air entrapment

"Bubbling"

Capping

Delamination (cracks along band)

- Capping - capping tendency increases with reduced punch-die clearance and higher speed (also observed by Ritter et al, 1980; Mann et al, 1981).
- Delamination – delamination cracks developed due to entrapped air (also seen by Long and Alderton, 1960; Ritter et al, 1980).
- "Bubbling" - air is largely responsible for it.

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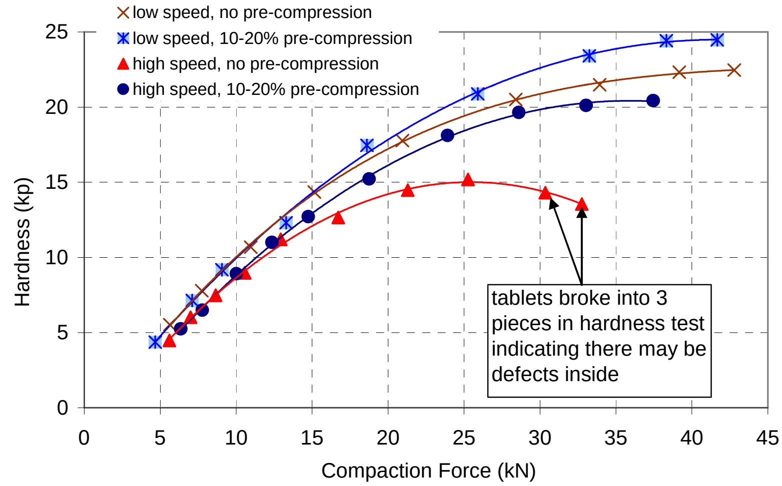
Scale-up prediction by compaction simulation – effect of air entrapment



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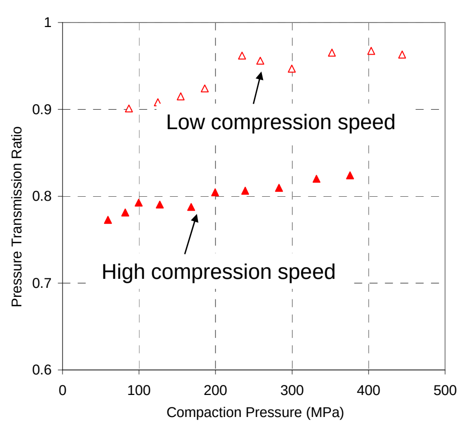
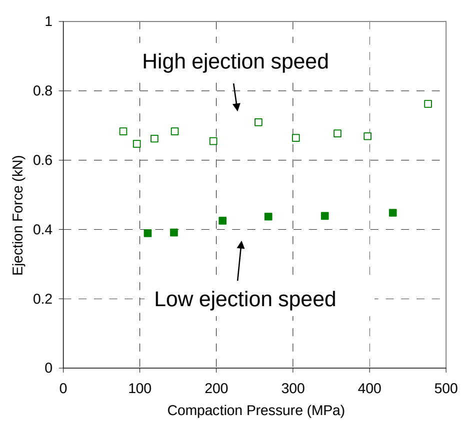
Scale-up prediction by compaction simulation – effect of compression and ejection speed





- pressure gradient increases with compression speed
- ejection force increases with ejection speed

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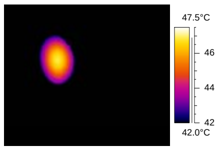
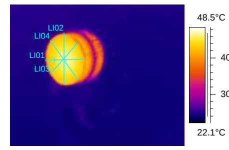
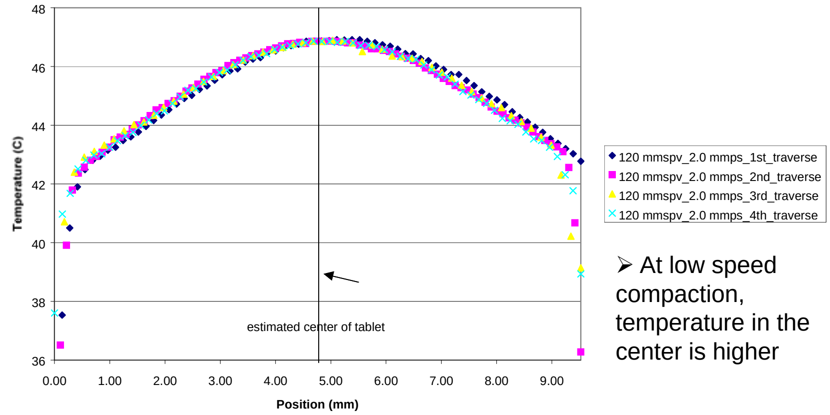
Scale-up prediction by compaction simulation – effect of speed on temperature rise



IR Tablet Imaging Using Compaction Simulator
Temperature vs Position
Corrected emissivity: 0.76
120 mmspv, 2.00 mmps
various traverses





- At low speed compaction, temperature in the center is higher

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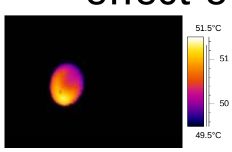
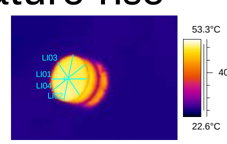
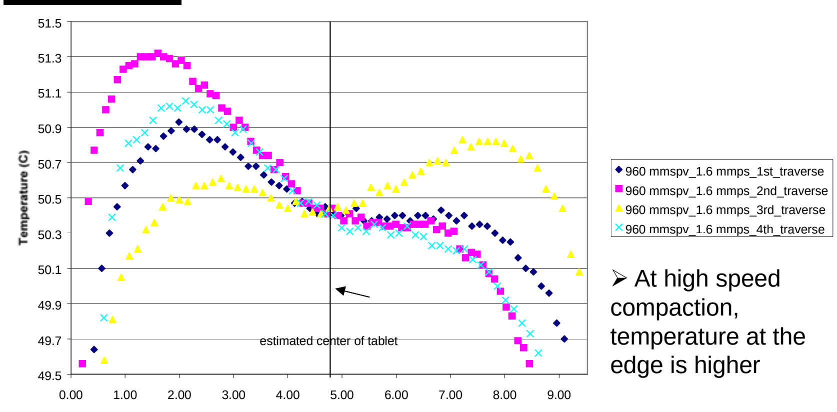
Scale-up prediction by compaction simulation – effect of speed on temperature rise



IR Tablet Imaging Using Compaction Simulator
Temperature vs Position
Corrected emissivity: 0.76
960 mmspv, 1.60 mmps
various traverses





- At high speed compaction, temperature at the edge is higher

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Concluding remarks

- The most important changes from small to large rotary press are the increase in punch vertical velocity (strain rate), dwell time, ejection speed, air entrapment, and temperature rise
- These changes can be estimated and predicted by simple engineering analysis
- The impact of these changes can be assessed by compaction simulation to predict the performance of a formulation at large scale and do this at earlier stage at much smaller scale
- Understanding the material properties of our formulations, the processes, and their relationships to quality attributes ENABLES a true QbD
- More understanding ➔ better quality with lower cost