Understanding, predicting and mitigating air entrapment defects in pharmaceutical tablet manufacturing

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OUTLINE

- **About the team**
- **Pharmaceutical Manufacturing in PA**
- **Introduction to the problem**
- **Basic understanding developed and first order results**
- **Experimental work**
- **Modeling**
- **Conclusions**
- **Work forward**

THE TEAM

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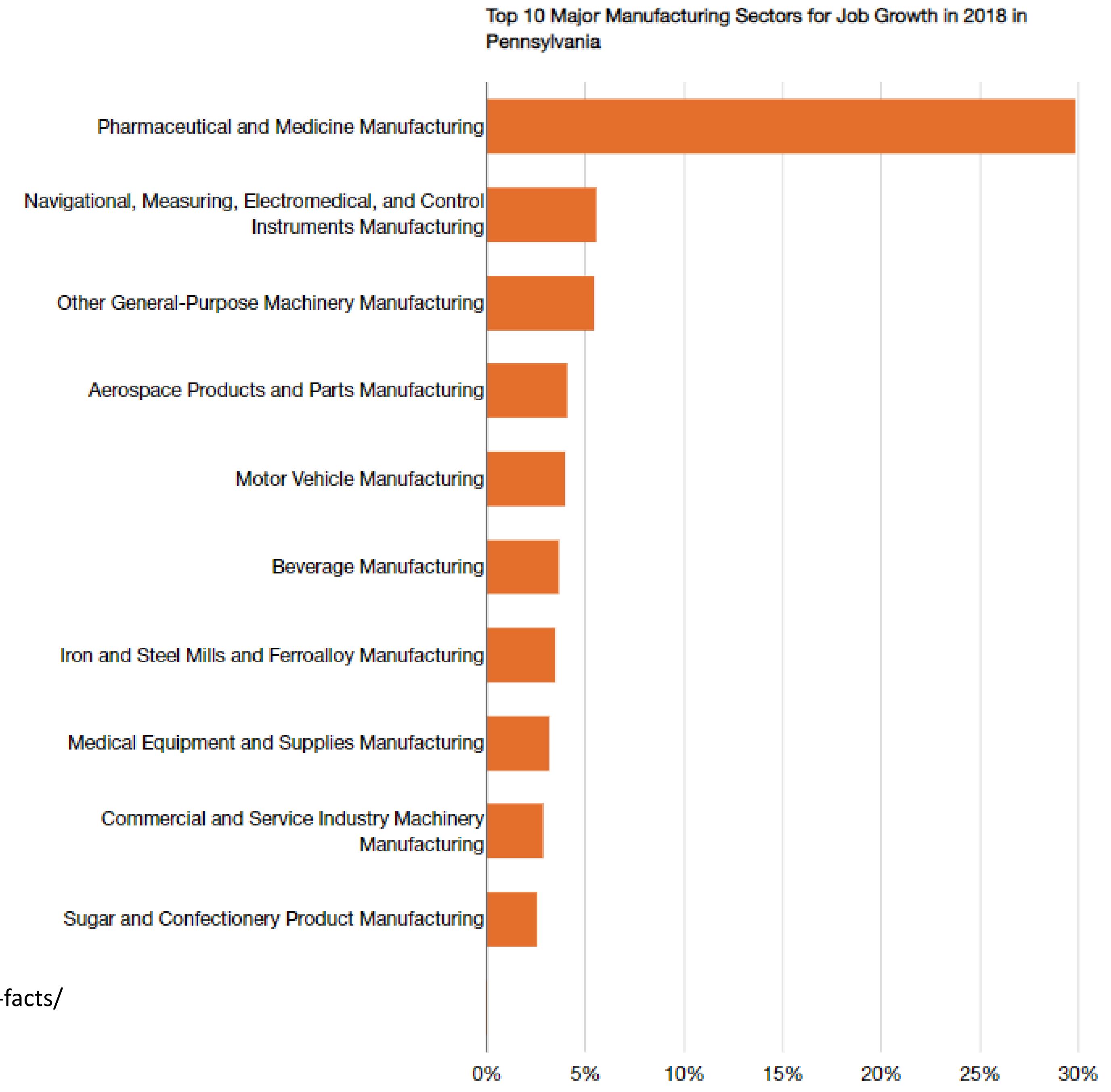
2019 Pennsylvania Manufacturing Facts

Manufacturing in PA (*):

- **11.89% of the total output in PA**
- **Total output is $94 billion**
- **Employing 9.47% of the workforce**
- **~569,000 manufacturing employees in PA**
- **Average annual compensation of $73,730**

Pharmaceutical and Medicine Manufacturing is the highest growth sector

(*) Data source:
NATIONAL MANUFACTURERS ASSOCIATION
https://www.nam.org/state-manufacturing-data/2019-pennsylvania-manufacturing-facts/

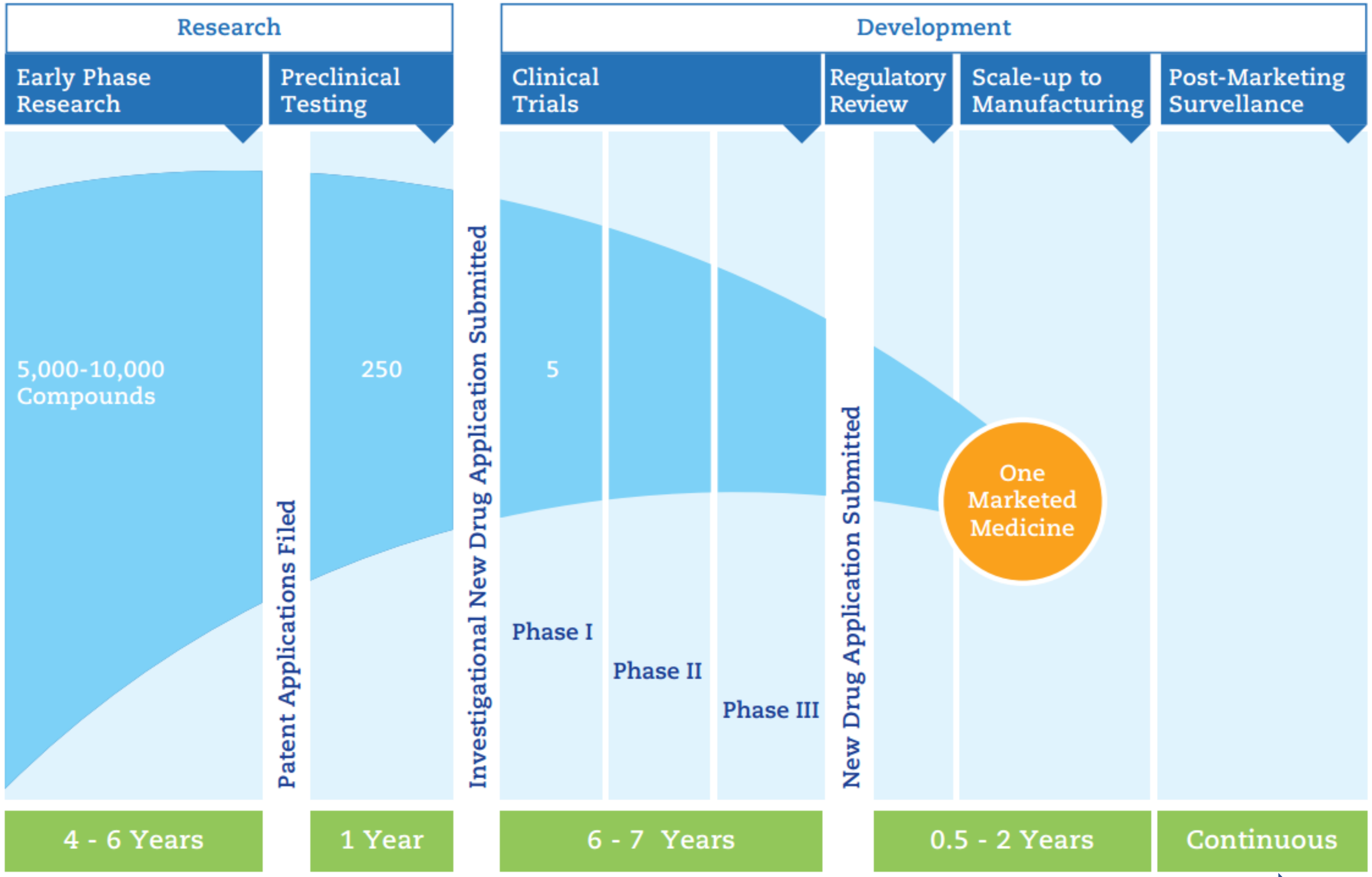


PHARMACEUTICALS

SOLID DOSAGE (**tablets,** capsules)
LIQUIDS (suspensions, solutions, syrups)
CREAMS
INHALERS/SPRAYS
PATCHES
INJECTIBLES
SUPPOSITORIES

TABLETS = 60-80% OF PHARMACEUTICALS $

Figure 1: The research and development process[4]



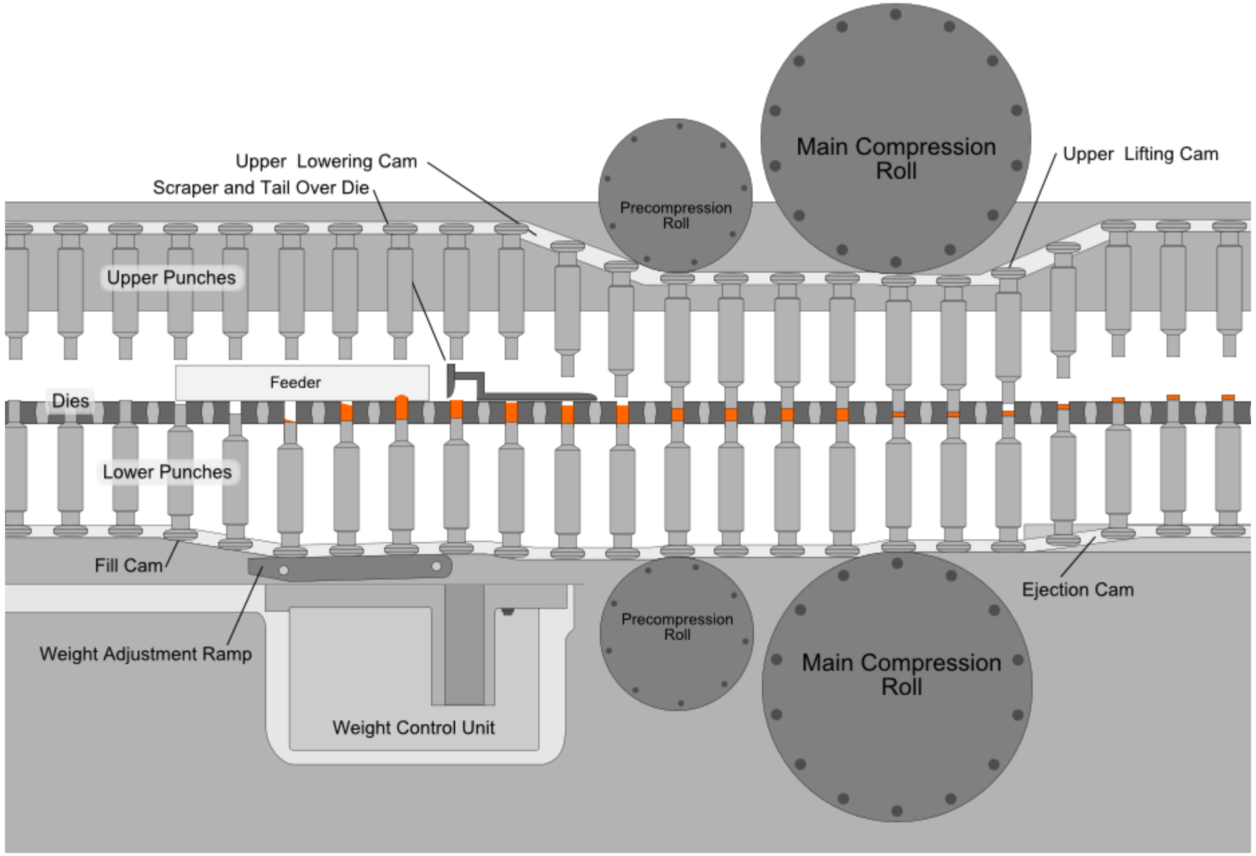
<1lb few tool set — O[100lb]50 tool set — tons thousands tool sets

MANUFACTURING PROBLEMS BECOME EXPENSIVE

MATERIAL SPARING TECHNIQUES NEEDED

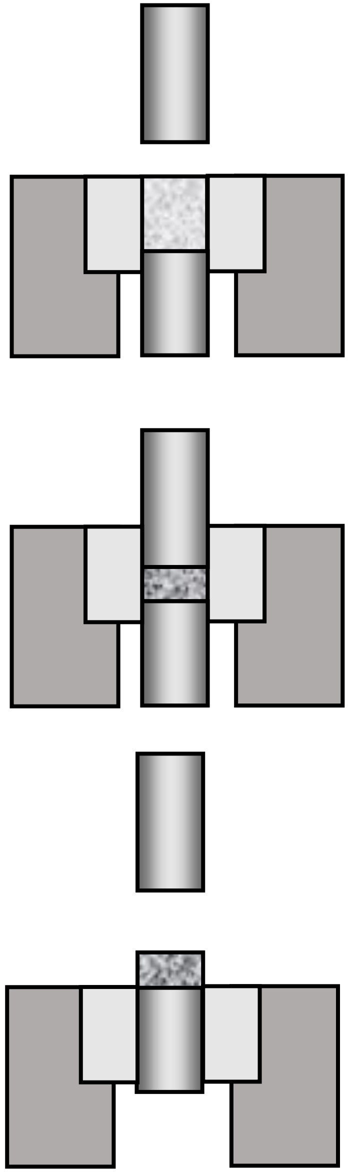
BACKGROUND – COMPACTION

- Active Pharmaceutical Ingredients (APIs) and Bulk Excipients constitute volume of pills and compacts.
- Powder compacted within a die to form solid product as shown:
  - Lower punch moves down to make room for powder to feed into die. Excess powder is leveled by scraper.
  - Upper punch is moved to the top of the powder in precompression.
  - Upper punch is moved downward to desired compression depth.
  - The upper punch and then the lower punch are raised to eject the compacted tablet.



[1]Dahl, J. (2008). "Tablet_Press_Animation.gif" Wikimedia Commons. https://www.wikiwand.com/en/Tableting.

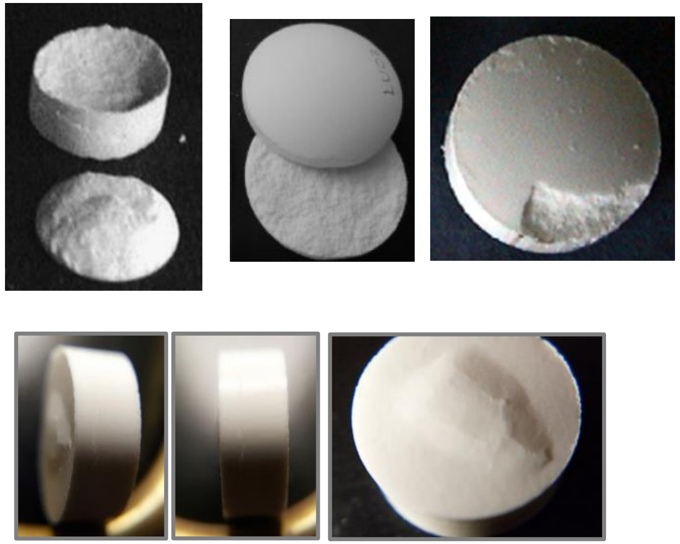
DEFECT FORMATION IN TABLETING



EJECTION → CAPPING, LAMINATION, MICRO-DEFECTS

STORAGE

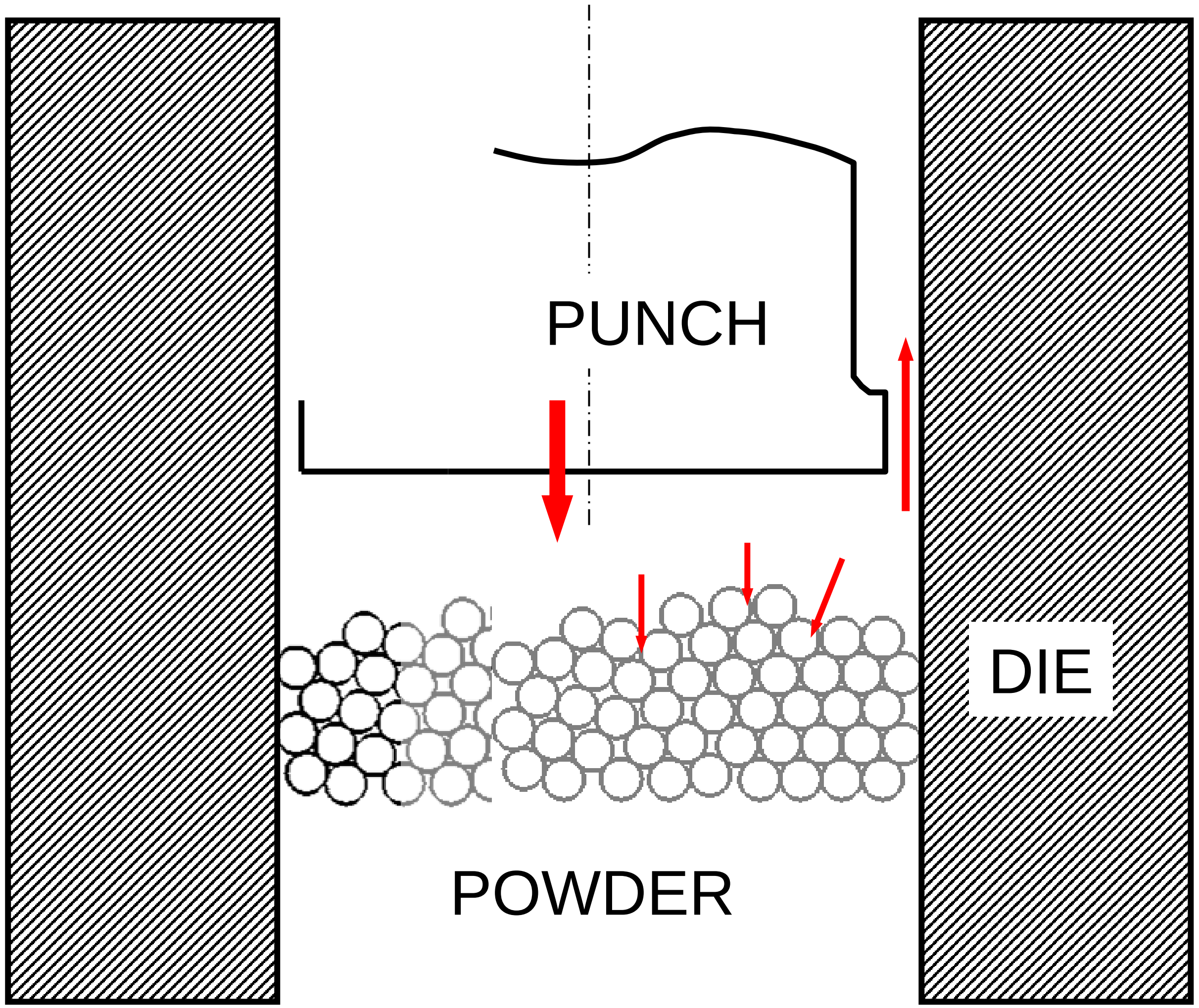
HANDLING



CLASSIFICATION IS UNCLEAR
MULTIPLE DEFECTS ARE OFTEN PRESENT
CAUSE AND EFFECT ARE NOT ESTABLISHED

THIS LEADS TO THE NEED OF EXTENSIVE
(NEAR BLIND EXPERIMENTATION)

FOCUS ON AIR ENTAPMENT



- How much air is in there begin with?
- What determines the ease of air escaping?
- How quickly are we forcing the air out?
- How far do we compress the entrapped air

A roadmap towards a predictive capability

- **Understand the fundamental phenomenon**
- **Measure the important properties of the material involved**
- **Develop preliminary models that will guide the experiments**
- **Controlled experiment to identify parameters involved**
- **Develop models that describe all aspects of the problem**
- **Develop failure criteria**
- **Validate models and criteria**

Worst case scenario: Full entrapment

- **If all air is trapped**

$$p_{air} = p_{atm} \frac{1-D_0}{1-D} \frac{D}{D_0}$$

- **If ∃ air above the compact that is 'pushed' into the powder**

$$\frac{p_{air}}{p_{atm}} = \frac{D}{D_0} \frac{1-D_0+\beta}{1-D}$$

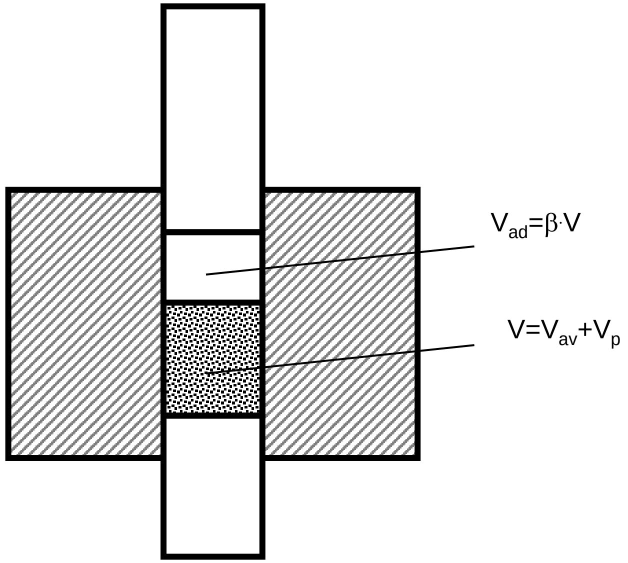
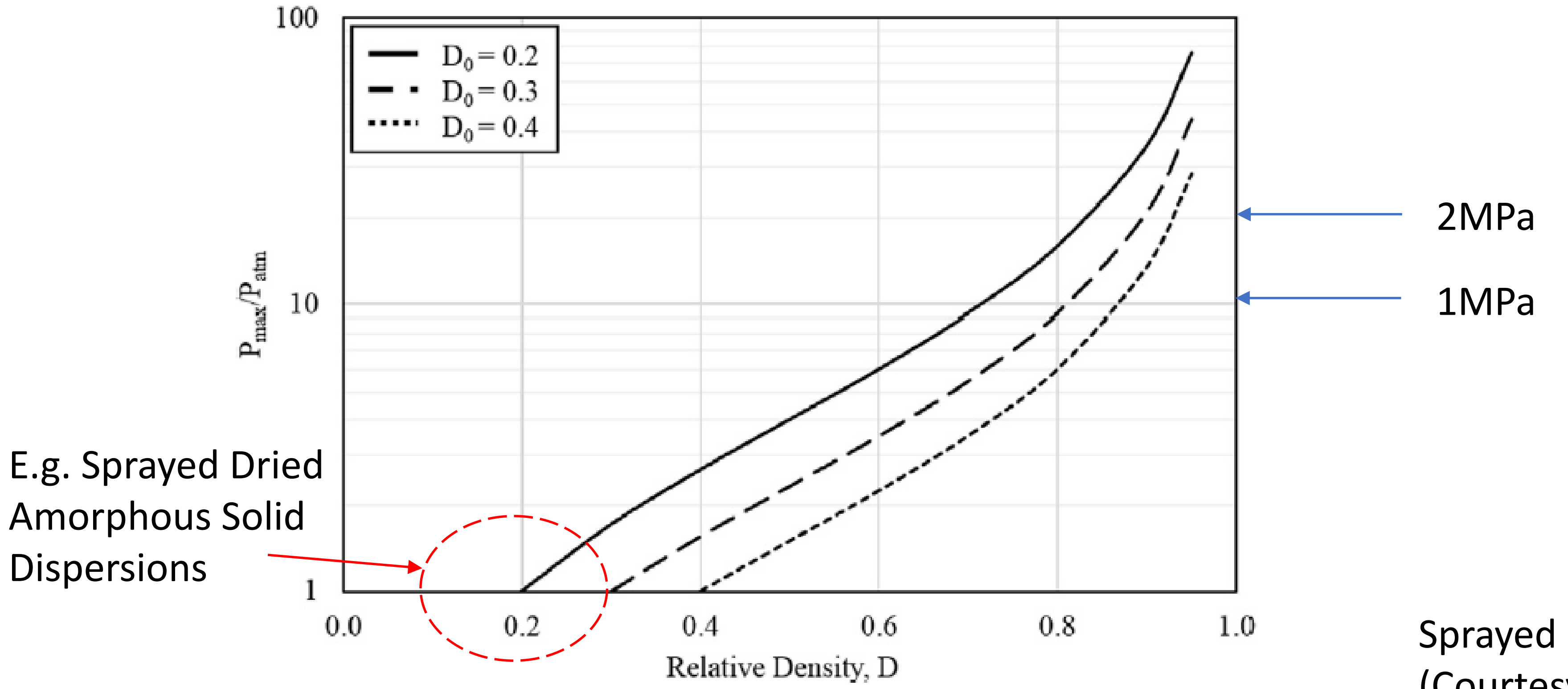
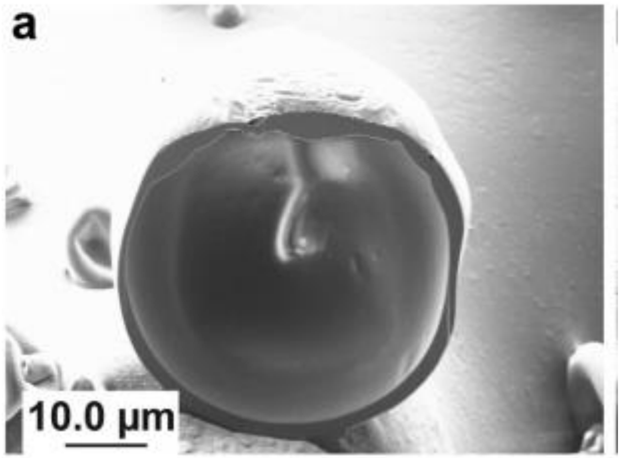
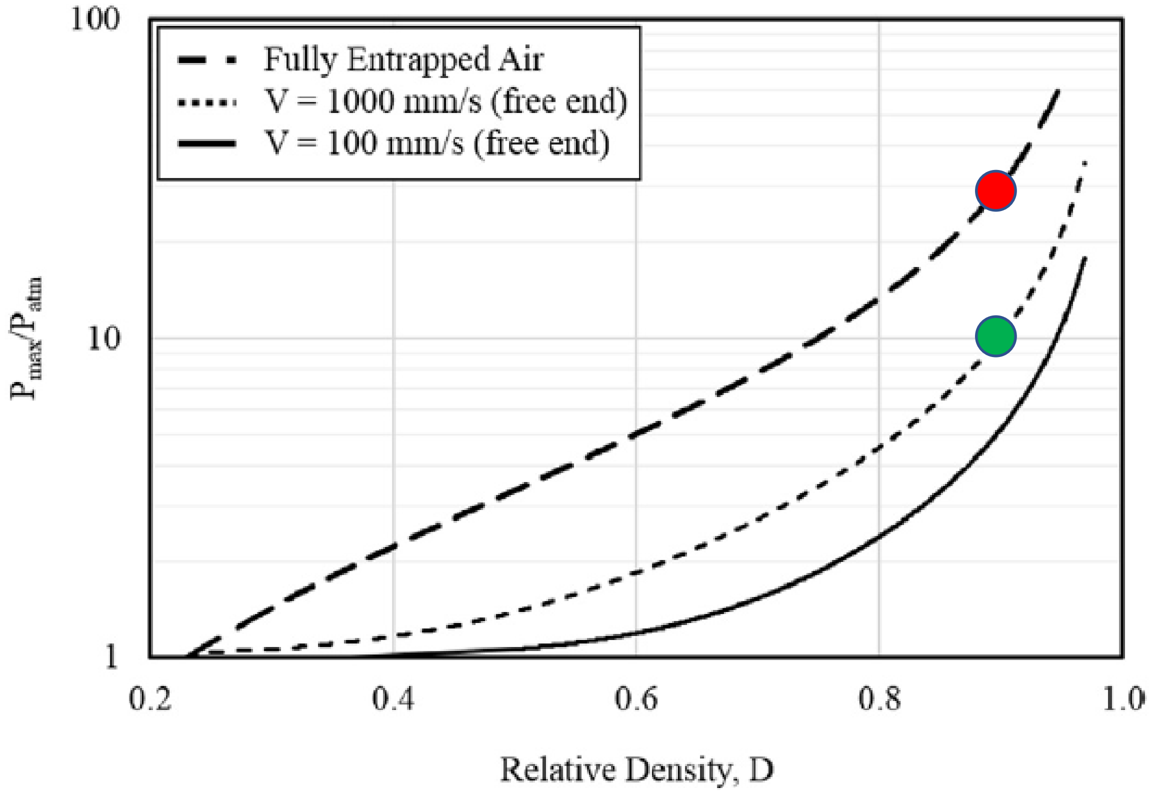


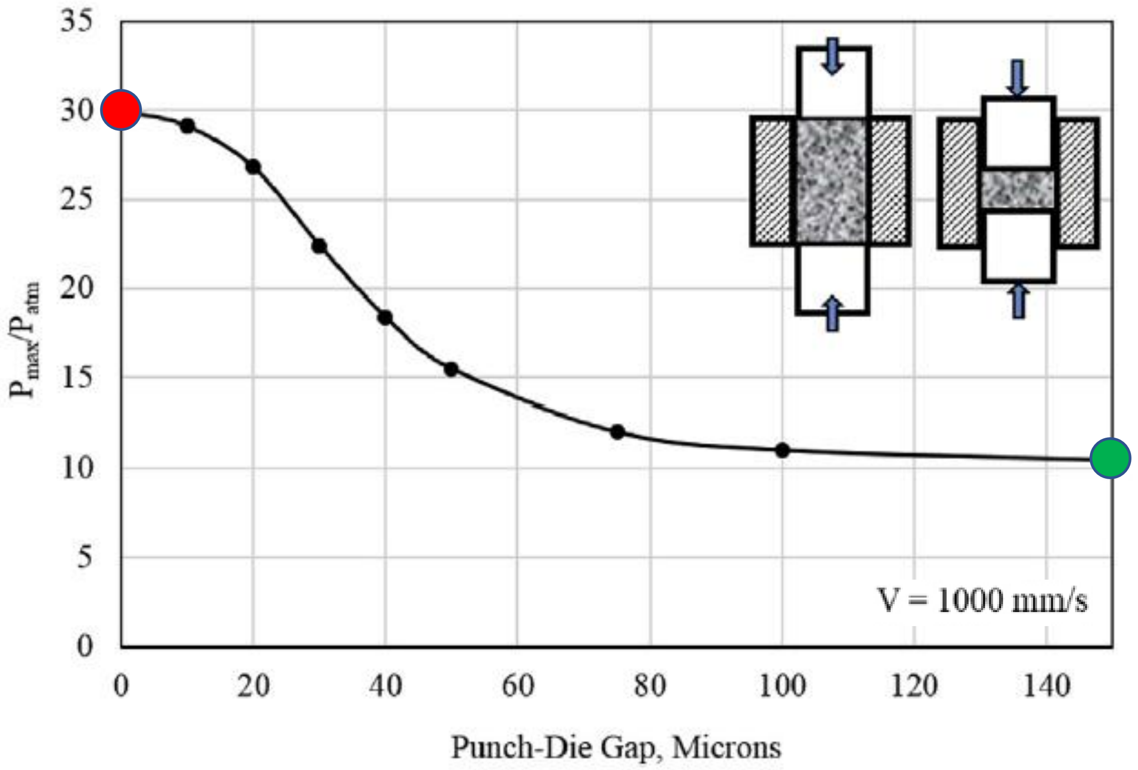
Figure 3. Air pocket above compact in die compaction.





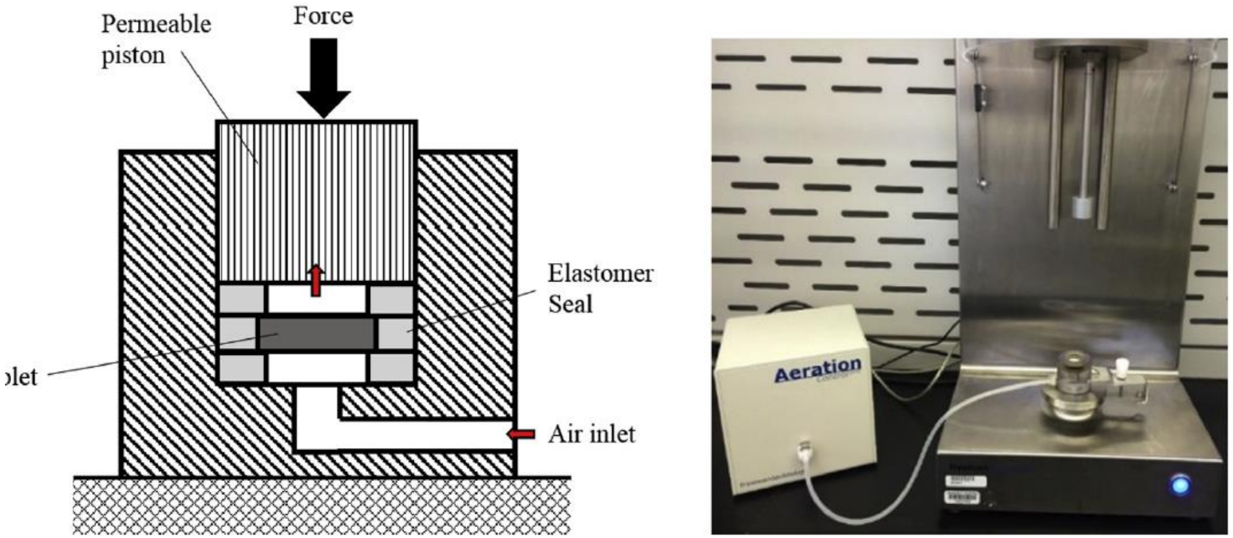
Sprayed Dried Amorphous Solid Dispersions (Courtesy of Merck – Dr. Klinzing)





- **High compaction speed pushes towards the full entrapment limit**
- **The punch-die tolerance is a key parameter that determines how restricted is the flow of air out of the die**

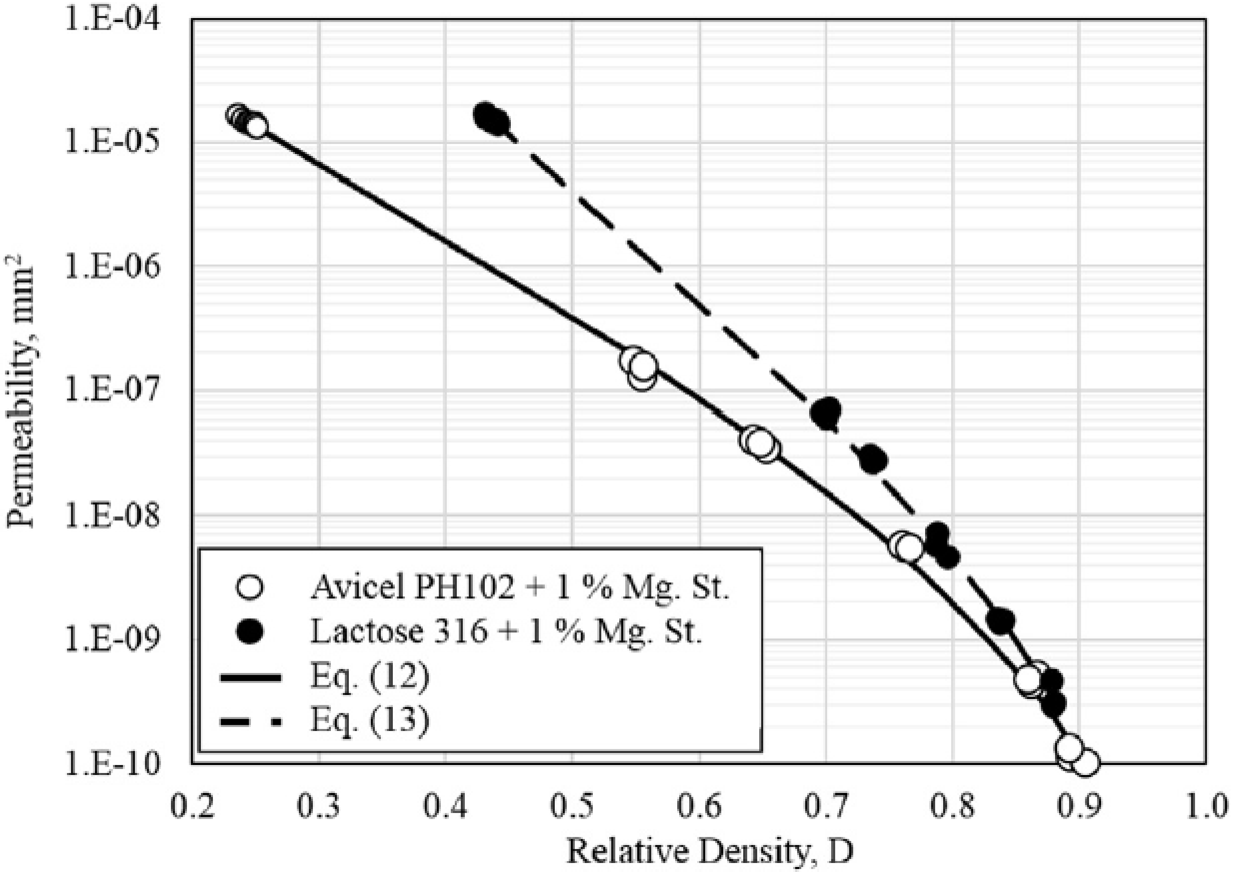
Measurement of permeability, K



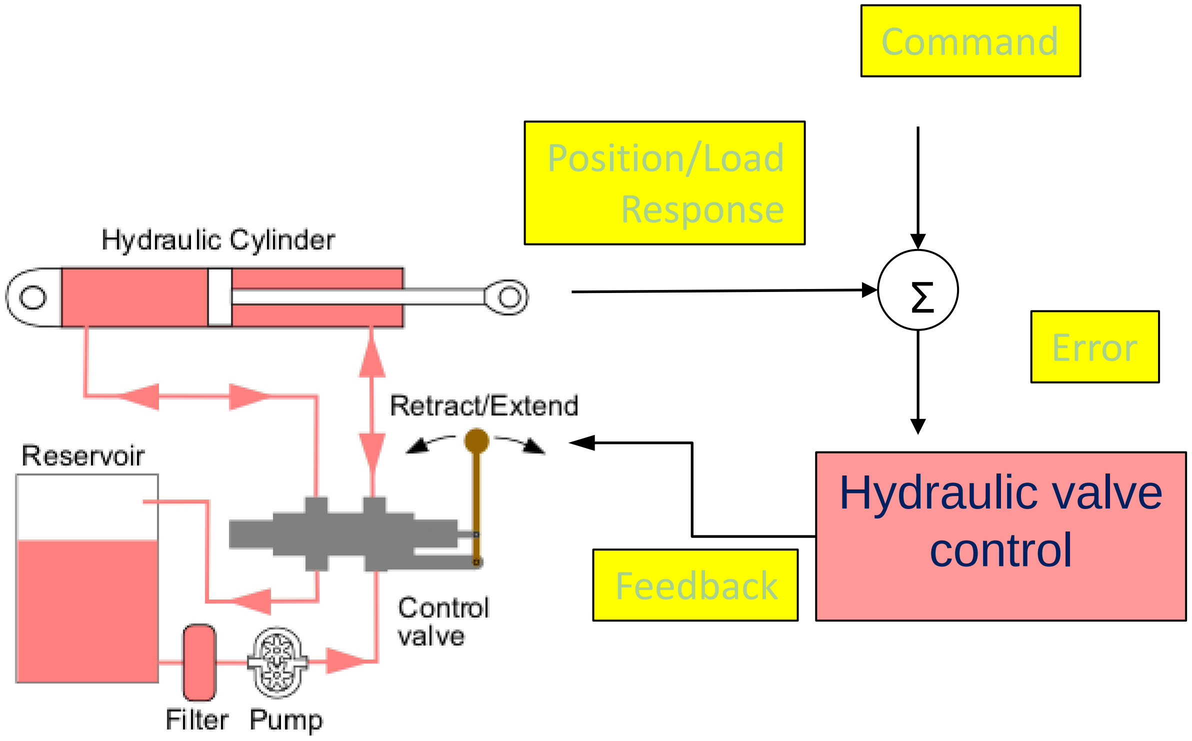
Monolithic 3D printed test cell (left) and Freeman FT4 experimental set-up (right).

$$\varphi \overrightarrow{v} = -\frac{K}{\mu}\nabla P$$

- φ = porosity
- v = air velocity
- μ = air viscosity
- P = air pressure
- ∇ = spatial gradient



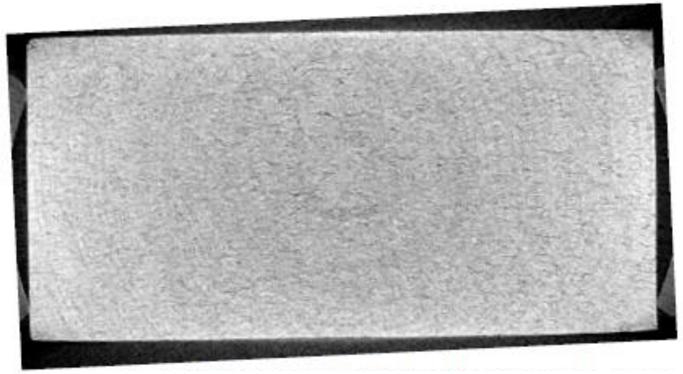
Compaction Simulator work at Merck



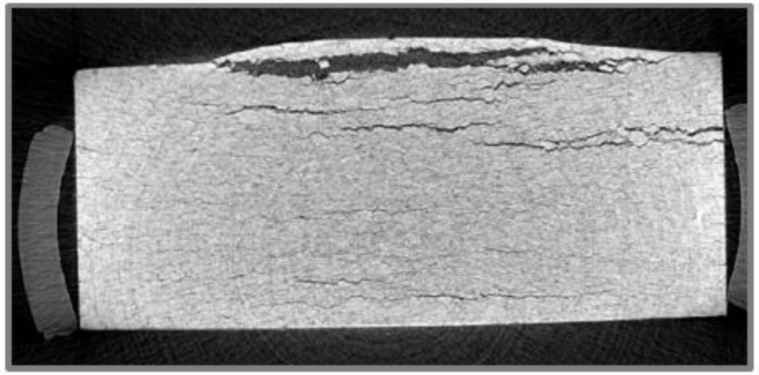
- Hexley&Bertram
- A well-designed hydraulic servo-valve forces the response to agree with the command
  Works great unless BOTH load and speed are very high - Transient error
- Very high versatility/flexibility in displacement or load profiles
- There is a small transient error that can be evaluated post mortem

COMPACTION SPEED

- Compaction speed study
- Vivapur 200 + 2%MgSt
- Triangular profile with a varying total time of 30sec, 3sec, and .3 sec from beginning of descent to ejection.
- Defects (bubble and/or lamination) appear to present around .3sec compaction duration, with .15sec compaction defects occur regularly.



Compaction time=0.6 s

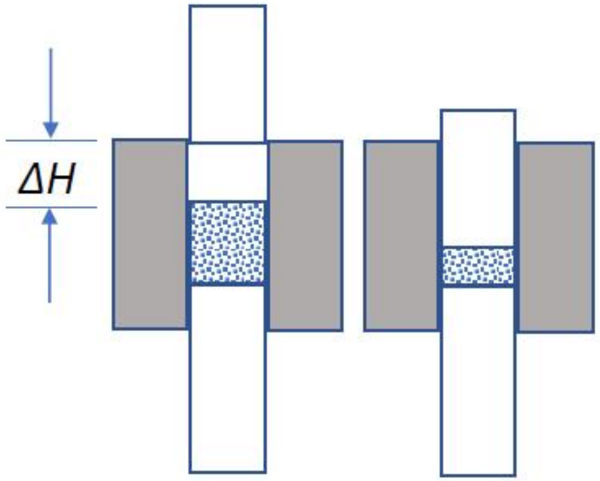


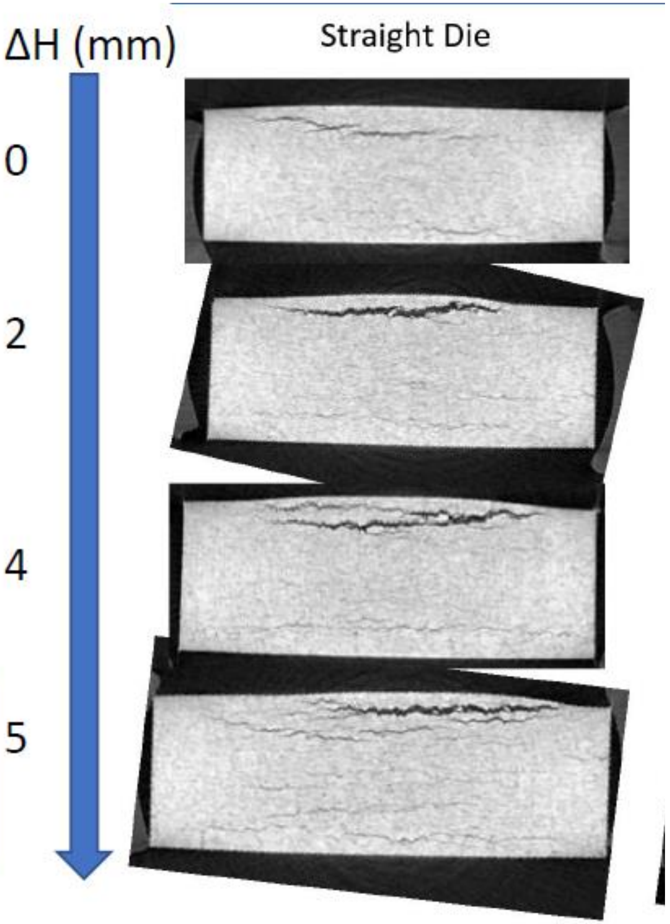
Compaction Time=0.15 sec

TABLET PLACEMENT-EXIT EFFECTS

- Bubbles appear larger (crack opening and length under the surface), as ΔH increases

prevent defects

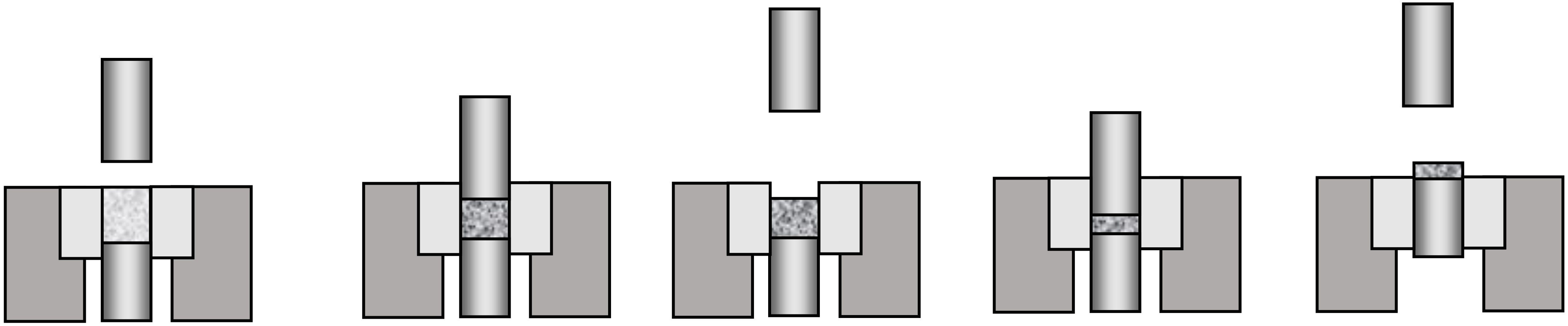




Operators often pull down the bottom punch to facilitate flow of materials that are difficult to fee

The result is positive for feeding but it increases the amount of air into the tablet

Precompation: Induce "enough" pressure by partially densifying the tablet followed by unloading and reloading to final shape



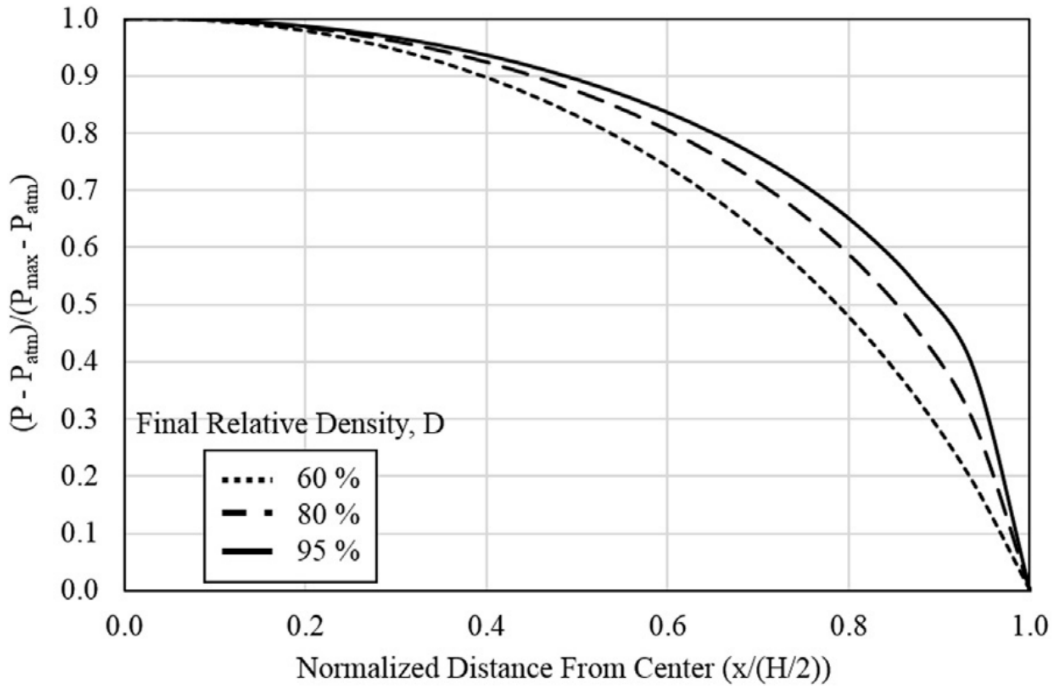
Precompaction

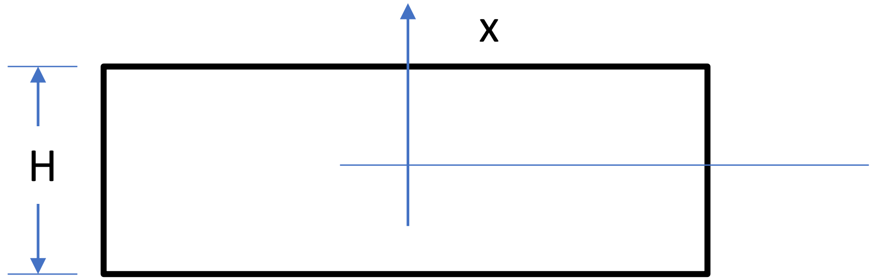
Main Compaction

Complex effects

ENTRAPPED AIR

- **Estimated air pressure (double compaction)**
  - **Maximum pressure found to be in the center (vertically)**
  - **Location of maximum pressure not the location where bubbles form / air entrapped**
  - **The need for a local criterion**

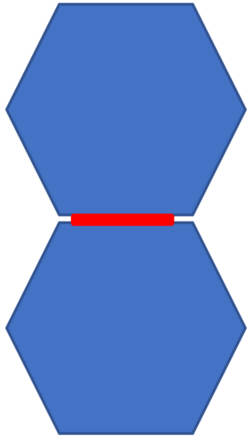


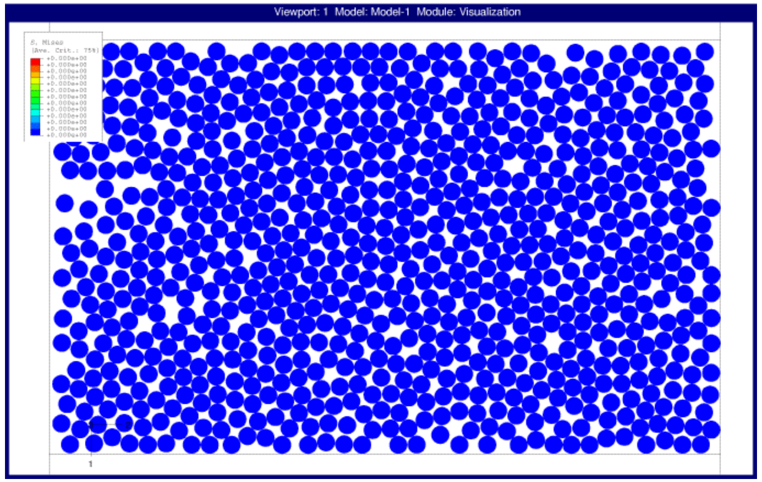


[1]Zavaliangos, A., Katz, J., Daurio, D., Johnson, M., Pirjanian, A., Alvarez-Nunez, F. (2017) Prediction of Air Entrapment in Tableting: An Approximate Solution. Journal of Pharmaceutical Sciences 106 3604-3612

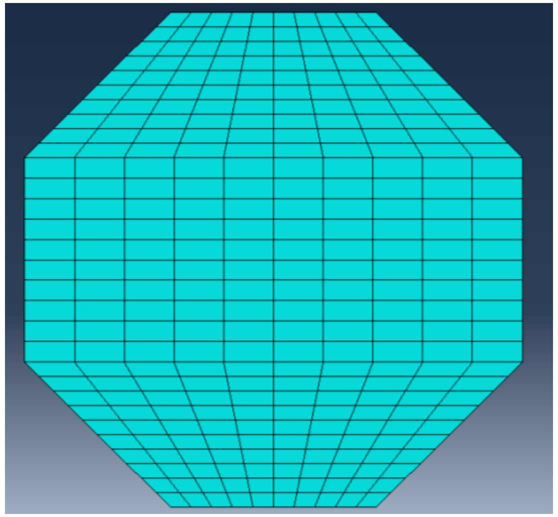
The role of weakened contacts & the need for a local criterion

- Modern evaluation of mechanical properties requires the consideration of cracks
- Cracks = weakened contacts due to
    - Concentrated lubricant
    - Non uniform local contact stress
- Even if the microstructure of the tablet was same from point to point (it is not) the local strength is NOT the same

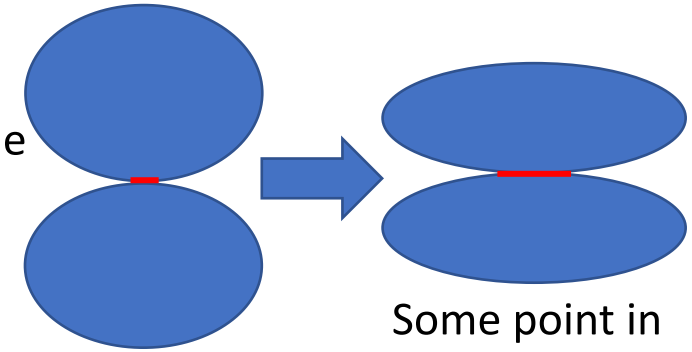




- **“Octagonal particle” approximation**
  - **Circular particles would have increasing interparticle contacts as material is compressed but this leads to some ambiguity in pressure application (currently explored)**
  - **Interparticle contacts “preformed”**
  - **Air pressure pressure applied easily on octagon side**

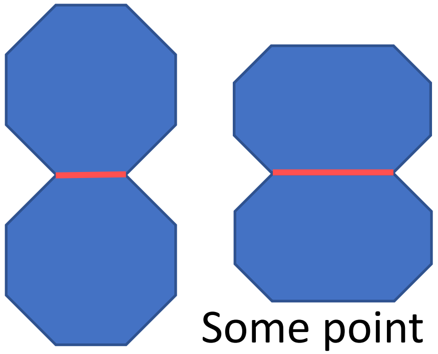


Interparticle Contact



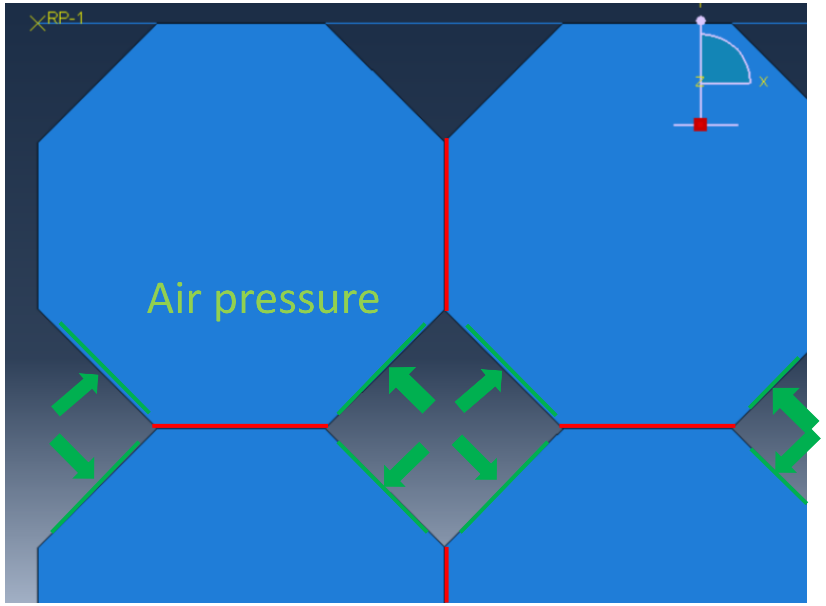
Start of Compaction

Some point in compaction

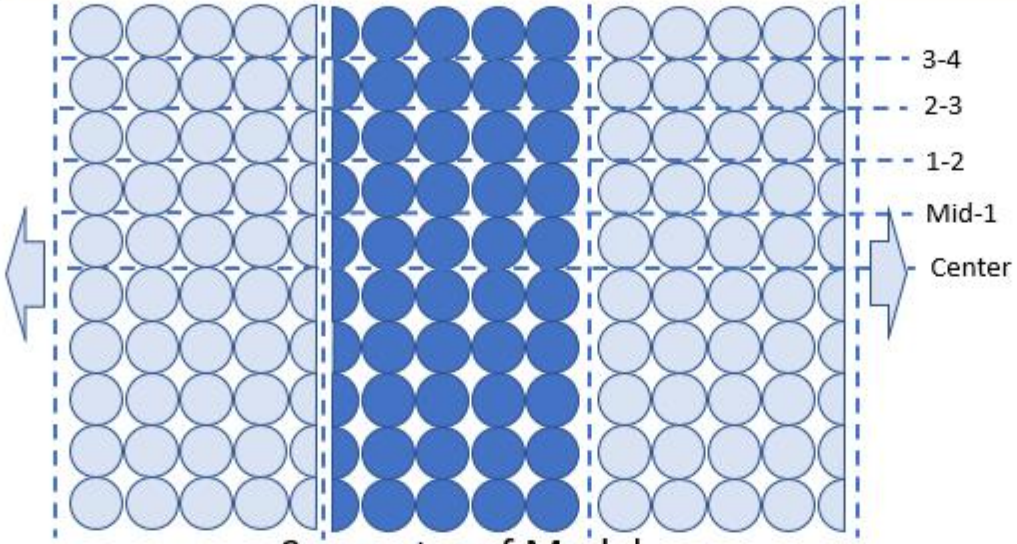


Start of Compaction

Some point in Compaction

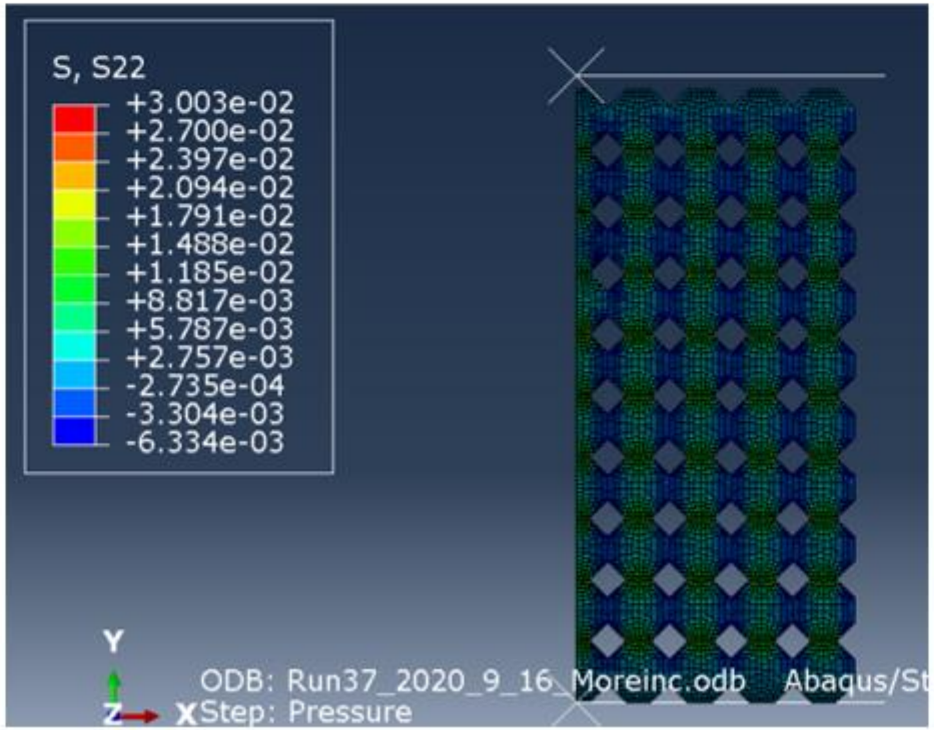


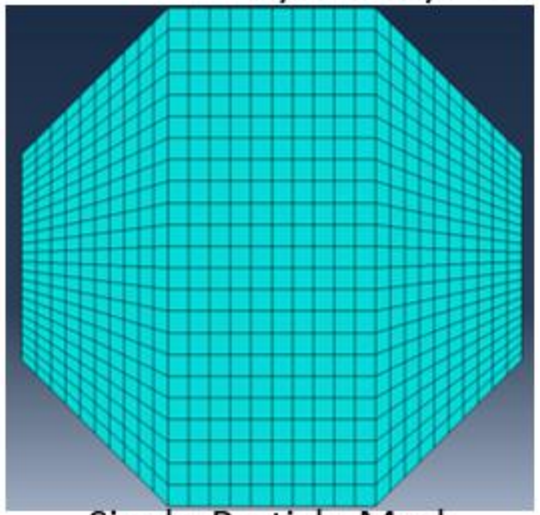
MODEL CONSTRUCTION



Symmetry of Model

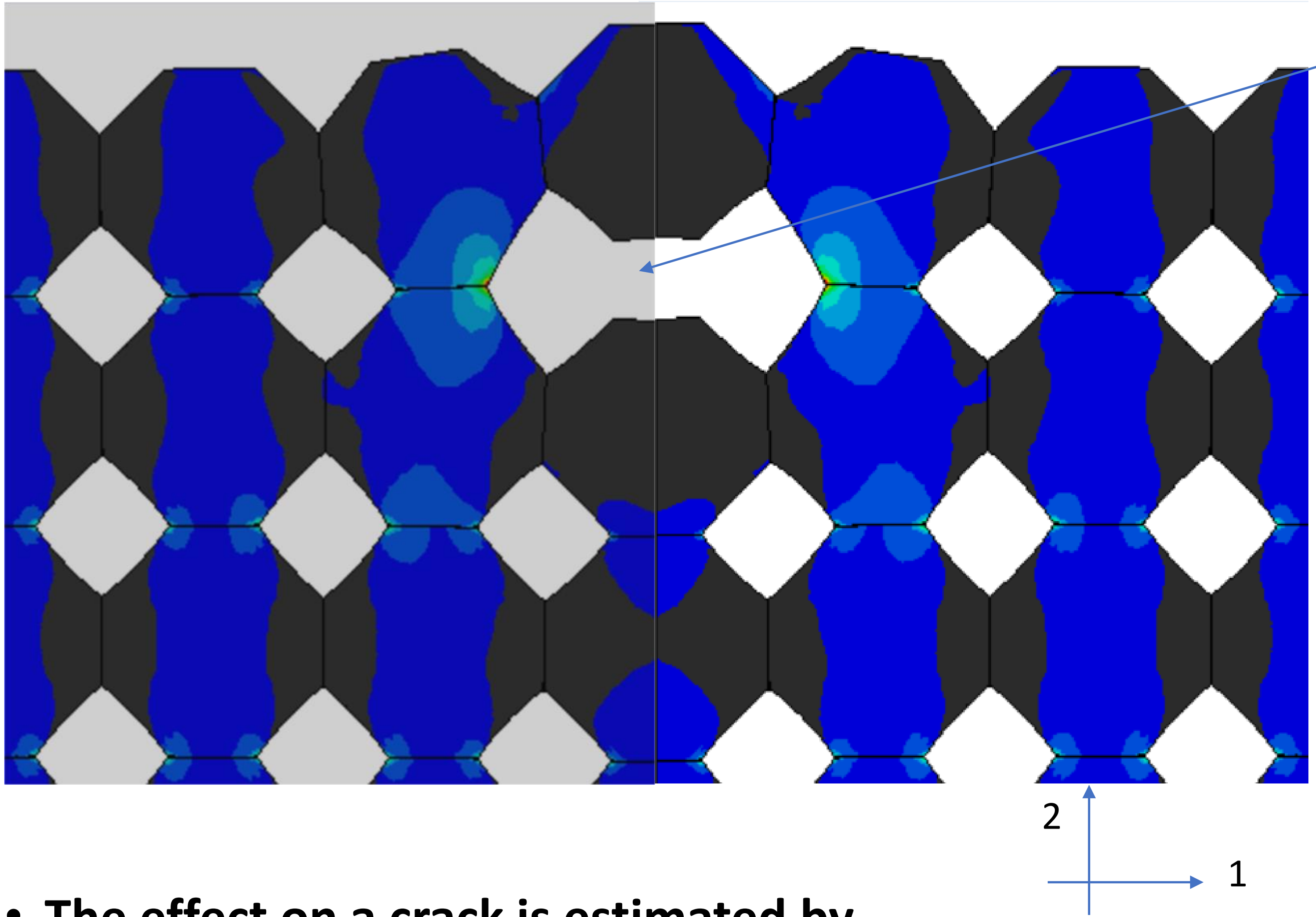
Abaqus Model



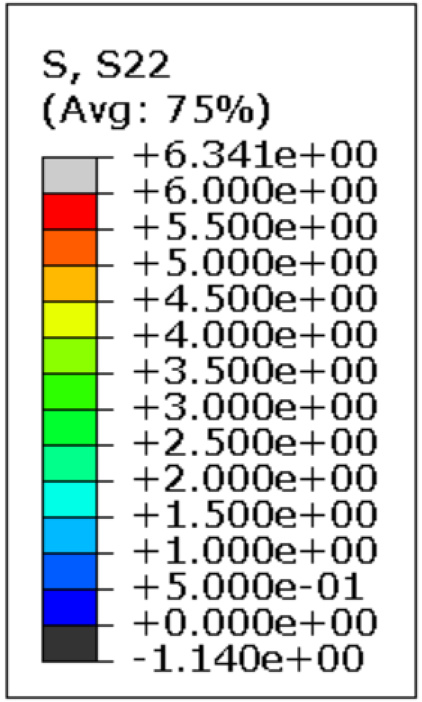


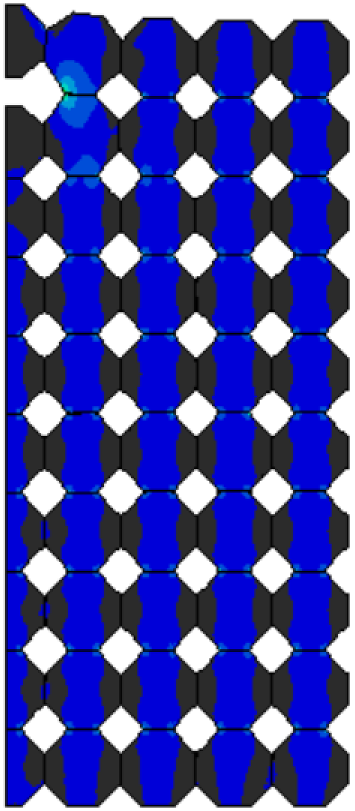
Single-Particle Mesh

- **Periodic structure**
- **Uniform pressure approximation**
- **One or more contacts are considered weakened to the point that air is applied on the previously compacted contact face**



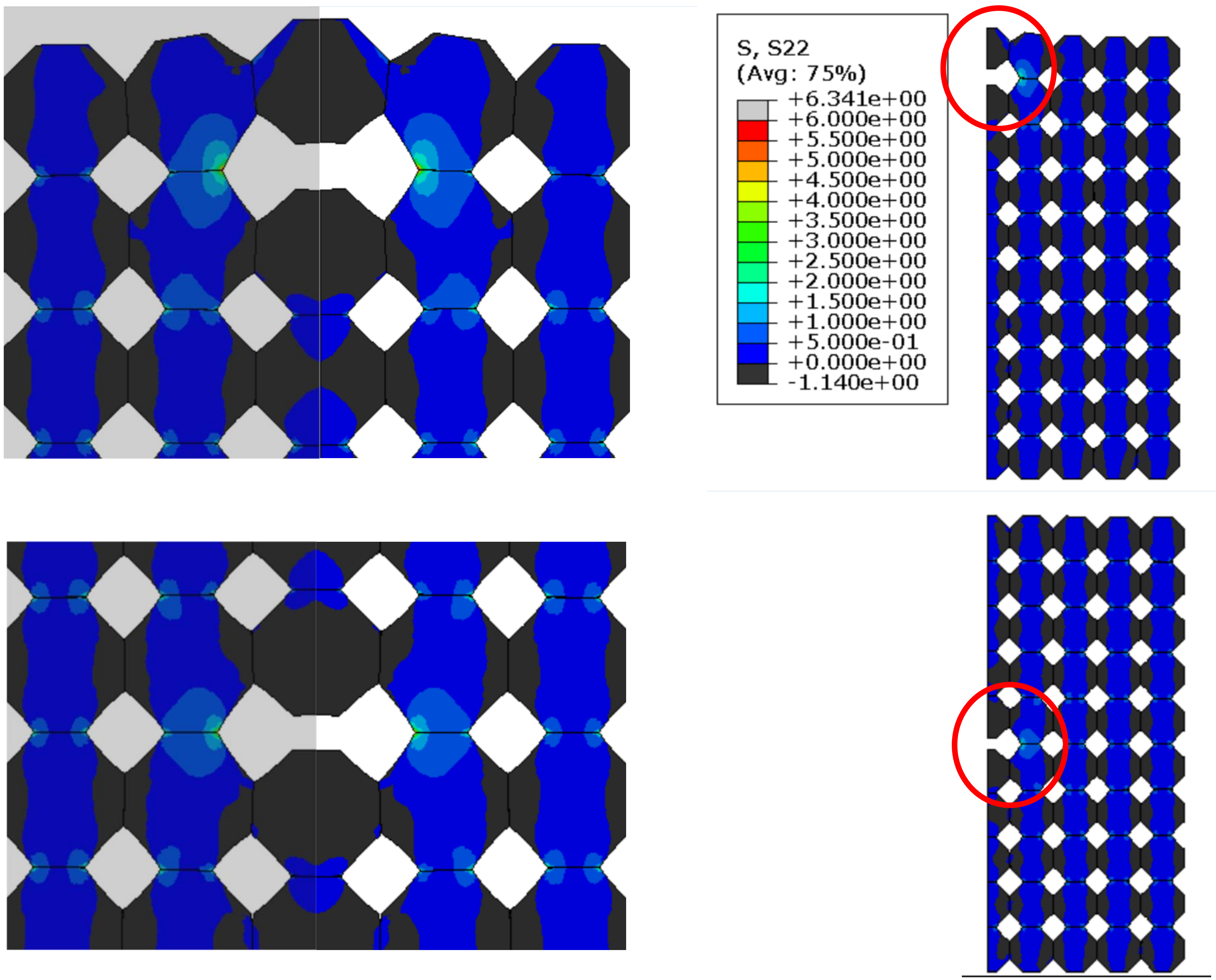
Under internal air pressure a weakened crack opens and induces a tensile stress in the neighboring contacts

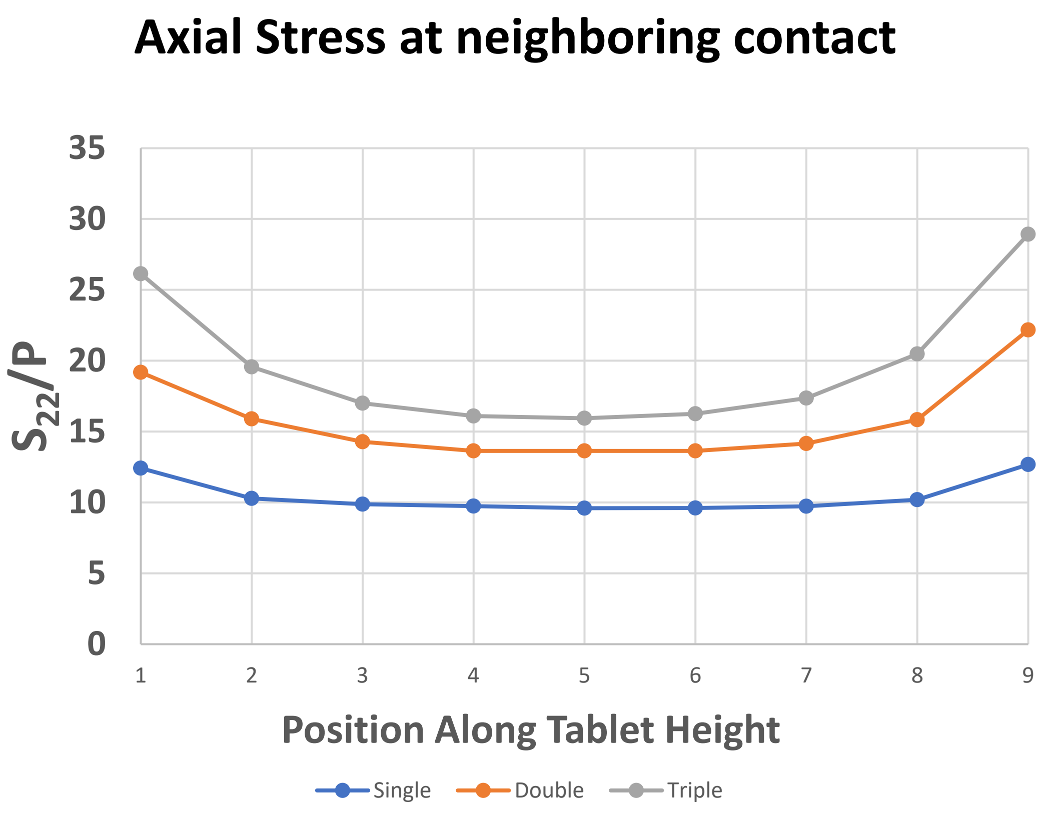


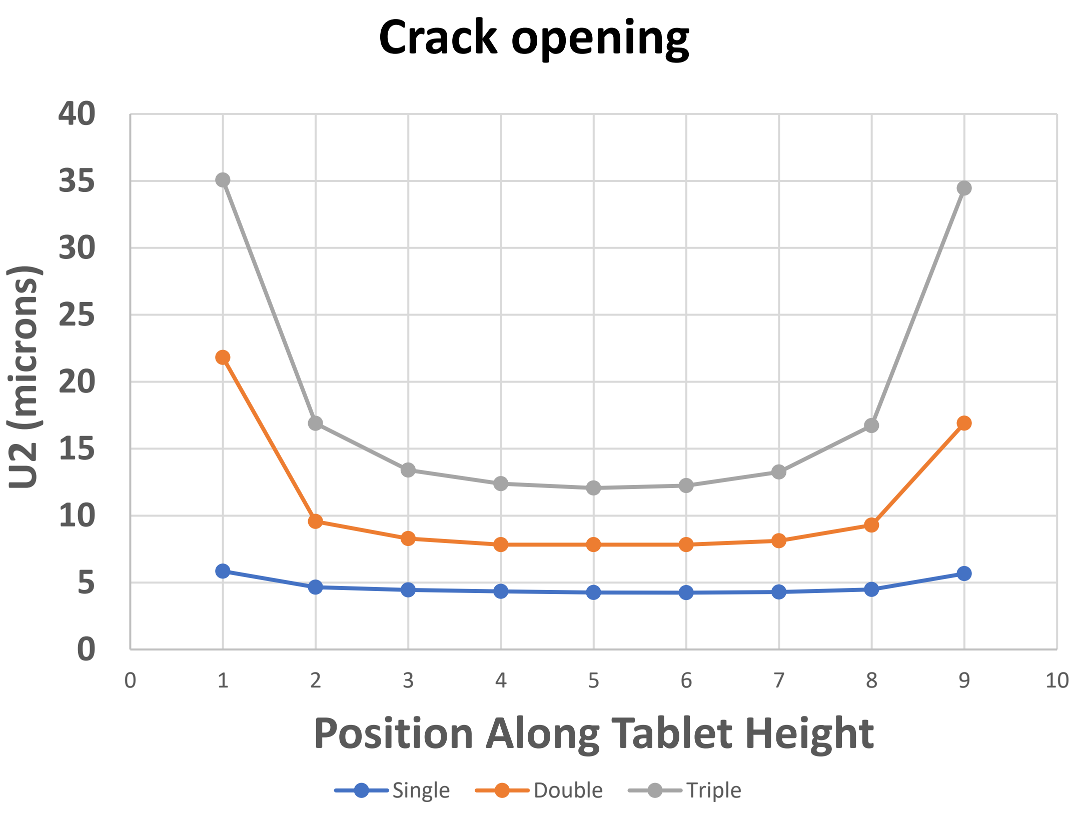


- The effect on a crack is estimated by
  - the local tensile stress at the tip of a neighboring contact (rough estimate)
  - the "crack" opening

A CRACK NEAR THE FREE SURFACE OF THE TABLET IS **WORSE** THAN ONE IN THE CENTER UNDER THE SAME INTERNAL PRESSURE







- **A weakened contact is more prone to propagation at the edge of the tablets**
- **The effect is amplified when more than one neighboring contacts are weakened**
- **This result indirectly points out to a particle size effect that needs to be examined.**

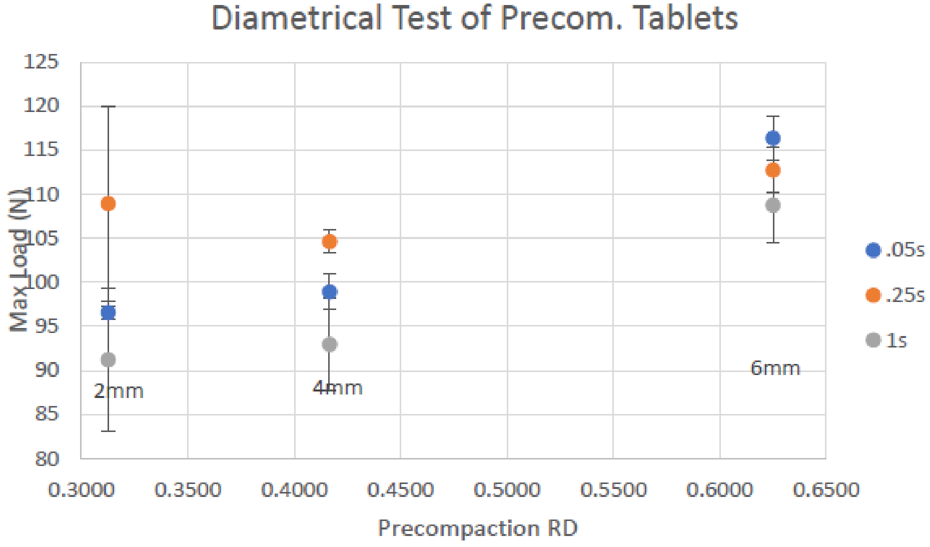
CONCLUSIONS

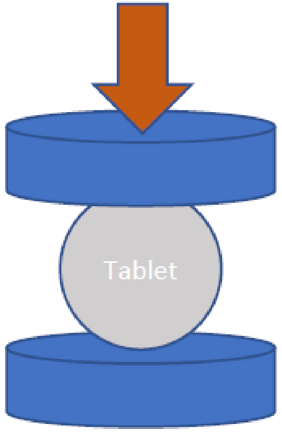
- **A framework for the analysis of the local pressure of entrapped air has been presented**
- **The approach provides an estimate of local air pressure by taking into account: (a) initial and final relative density, (b) speed of compaction, (c) compact permeability as a function of relative density, (d) the presence of tolerances between punch and die, and (e) any air between tablet and punch and allows to assess risk for entrapped air induced defects**
- **Experimental approach confirms salient features of the model but predicts maximum pressure at a different position than the area of the air bubble formation**
- **Microtomography work shows that many times micro and macrocracks normal to the compaction direction are also present together with the formed air bubble**
- **A crack-based model demonstrates that cracks just under the tablet top surfaces are more susceptible to propagation than those in the center of the tablet under the same pressure. This provides a partial reconciliation of the point above.**

FURTHER WORK

- Finalize experimental work on the effect of precompaction
- Understand the role of residual radial stress on the die wall on the formation of microcracks
- Develop of local risk assessment criterion for defect formation
- Scale up (from the compaction simulator to the rotary press)

DIAMETRICAL BREAKING - PRECOMPACTION





- Max load before breaking notably heightened given a precompaction relative density of .6250
- MicroCT images show no visible defects in those samples
- Some error may arise from separating tablets from carbon tape post-MicroCT scan