PQRI Workshop:
Managing Excipient and API Impact on Continuous Manufacturing
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Product Quality Research Institute

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Characterization of Powder Properties Important to Continuous Manufacturing of Tablets

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Requirements for An Ideal Tablet CM Process

1. Manufacturable at high speeds

2. Continuous manufacturing, if possible

3. Tablets meeting all quality requirements
    a) dissolution
    b) stability
    c) content uniformity
    d) Friability

4. Developed quickly and using little material

Pertaining USP Chapters

<**429**> Laser Diffraction Measurement of Particle Size
<**616**> Bulk Density and Tapped Density
<**699**> Density of Solids
<**701**> Disintegration
<**711**> Dissolution
<**786**> Analytical Sieving
<**846**> Specific Area
<**881**> Tensile strength
<**891**> Thermal analysis
<**905**> Uniformity of dosage unites
<**941**> Characterization of crystalline and partially crystalline solids by X-ray diffraction (XRPD)
<**1062**> Tablet compression characterization
<**1063**> Shear Cell Methodology for Powder Flow Testing
<**1087**> Apparent intrinsic dissolution—dissolution testing procedures for rotating disk and stationary disk
<**1088**> In vitro and in vivo evaluation of oral dosage forms
<**1174**> Powder flow
<**1216**> Tablet friability
<**1217**> Tablet breaking force
<**1236**> Solubility measurements

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Challenges in Tablet Manufacturing

1. **Powder flowability**
2. **Powder tabletability**
3. **Tablet dissolution**
4. **Content uniformity**
5. **Tablet friability**
6. **Speed sensitivity**
7. **Punch sticking**
8. **Stability**

For **Low** dose drugs

For **High** dose drugs

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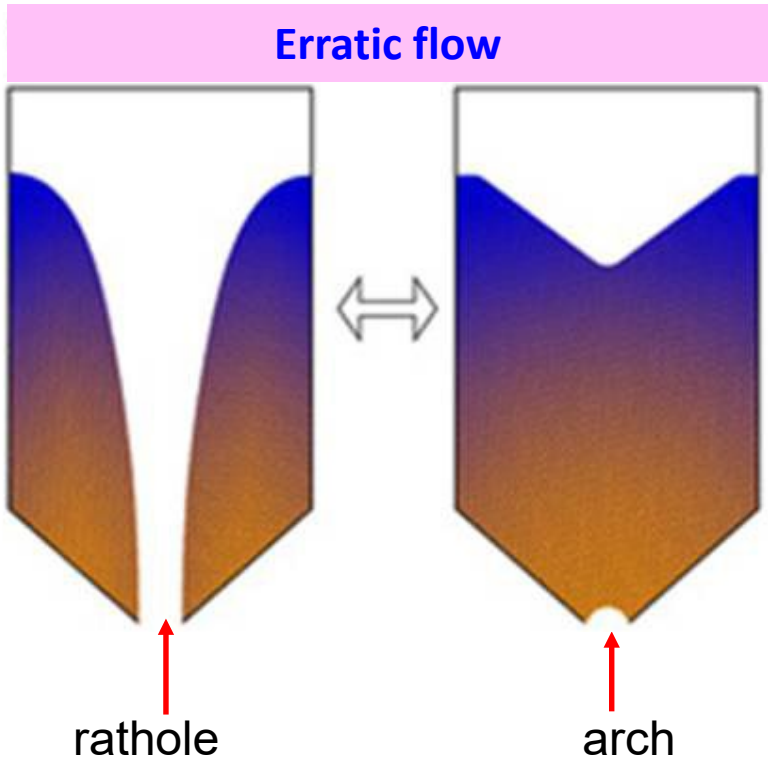
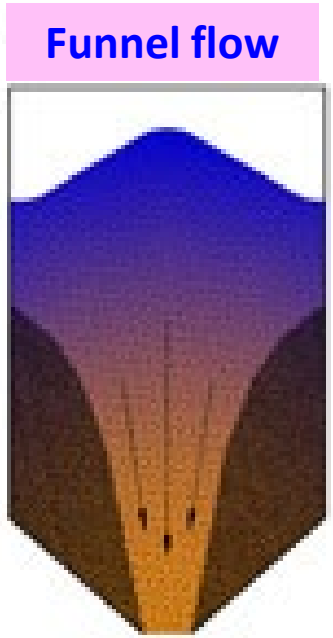
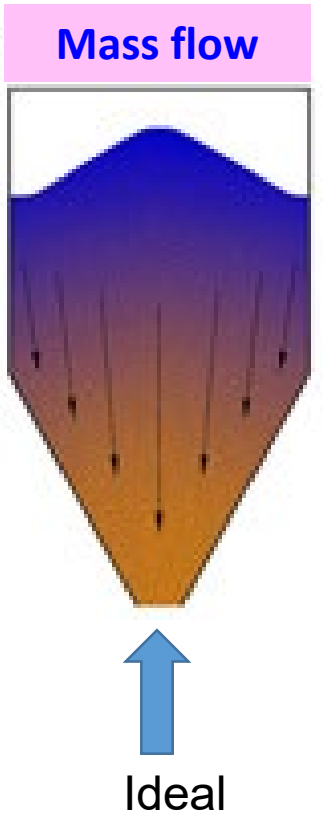
1. Powder Flowability - Common flow behavior





http://www.jenike.com/Solutions/poorflow.html

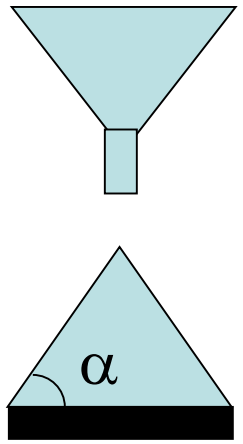


- A result of alternating occurrences between an arch and a rathole
- Always problematic

Characterization of Powder Flowability

<1174> Powder flow

1. Angle of repose

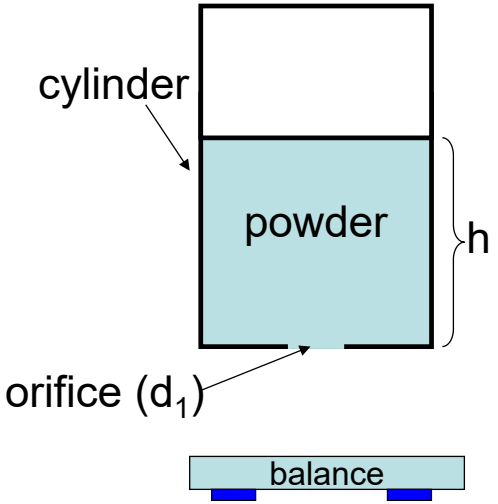


2. Compressibility Index/Hausner ratio

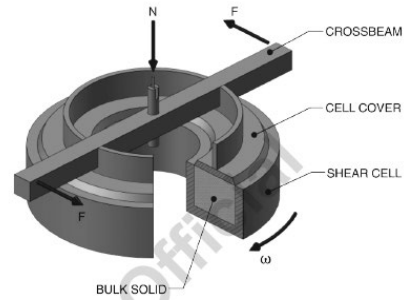
$$Compressibility\ Index = 100 \times \left(\frac{\rho_{tapped} - \rho_{bulk}}{\rho_{tapped}} \right)$$

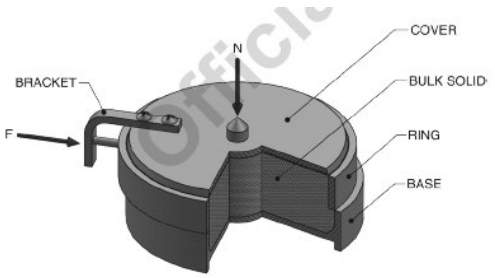
$$Hausner\ \ Ratio = \left(\frac{\rho_{tapped}}{\rho_{bulk}} \right)$$

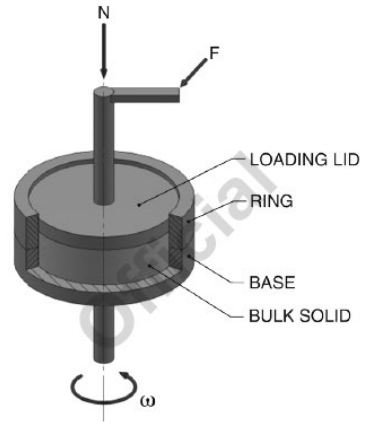
3. Flow through an orifice



4. Shear cell methods







Can a material with acceptable flowability for high speed tableting be identified?

<**1063**> Shear Cell Methodology for Powder Flow Testing

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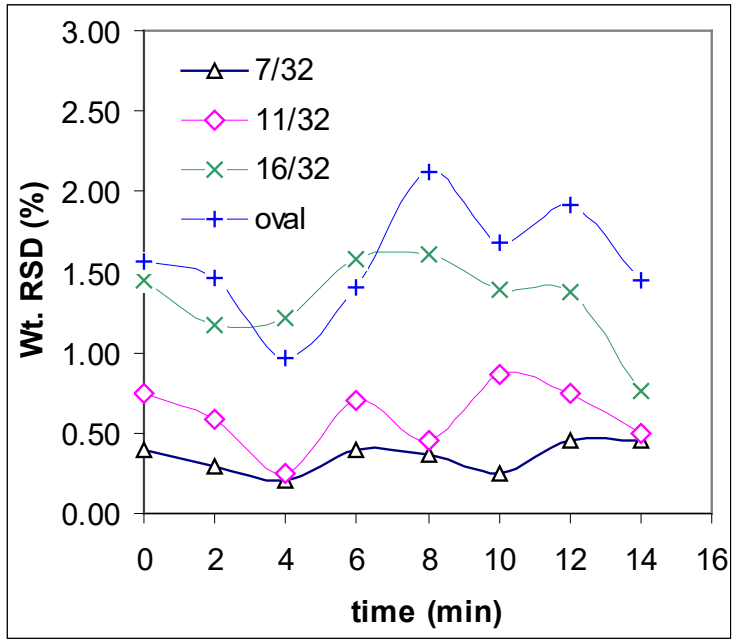
Setting the Bar for Powder Flow

70 rpm → 90 rpm

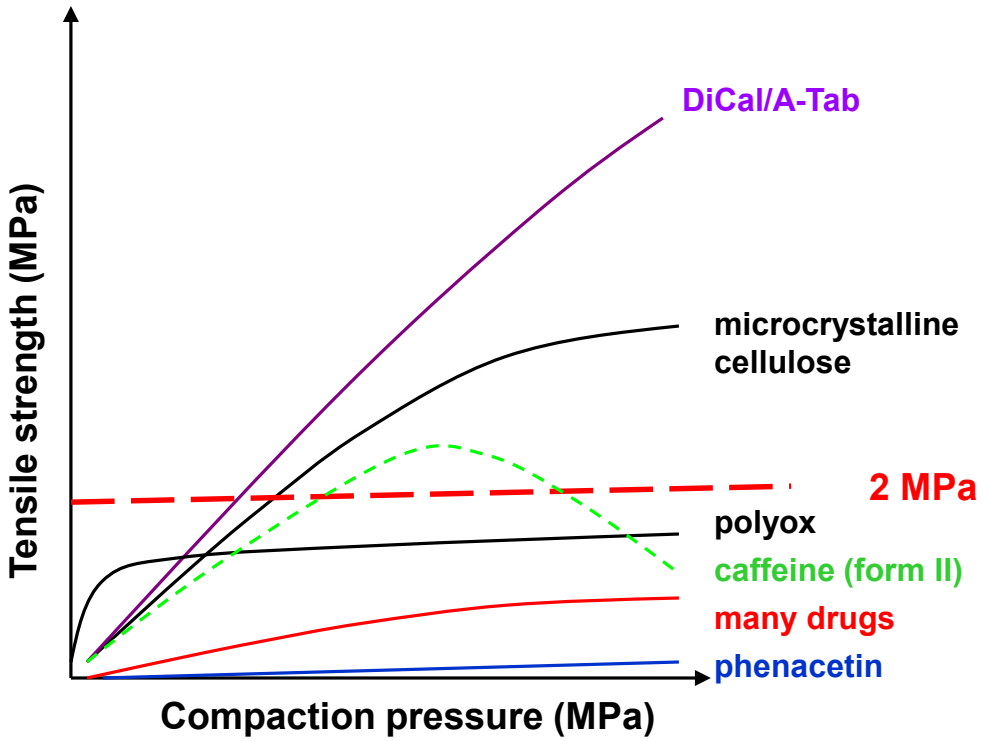


Excellent die filling performance → Non-processible

Avicel PH102 lies near the boundary between acceptable and non-acceptable regions of powder flow properties for high speed tableting.

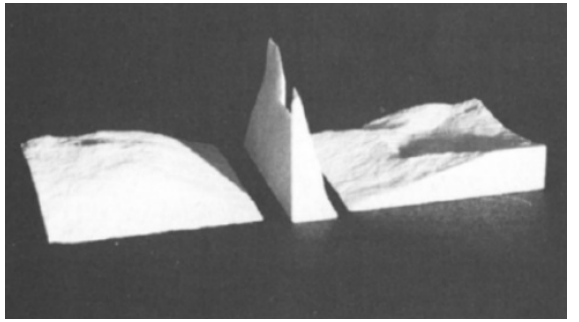
Sun, 2010, Powder Technol., 201:106-108

2. Tabletability

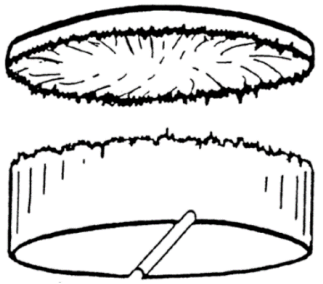


Sun, 2011, *J. Adh. Sci. Technol.* 25:483-499 (2011)

Fracture

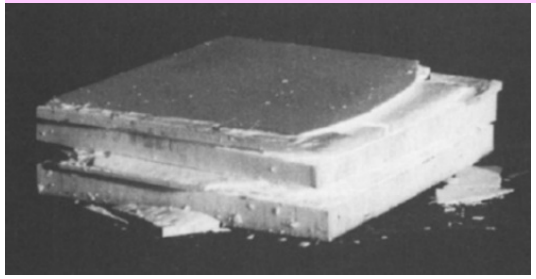


Capping



L. Lachman *et. al.* (1986)

Lamination

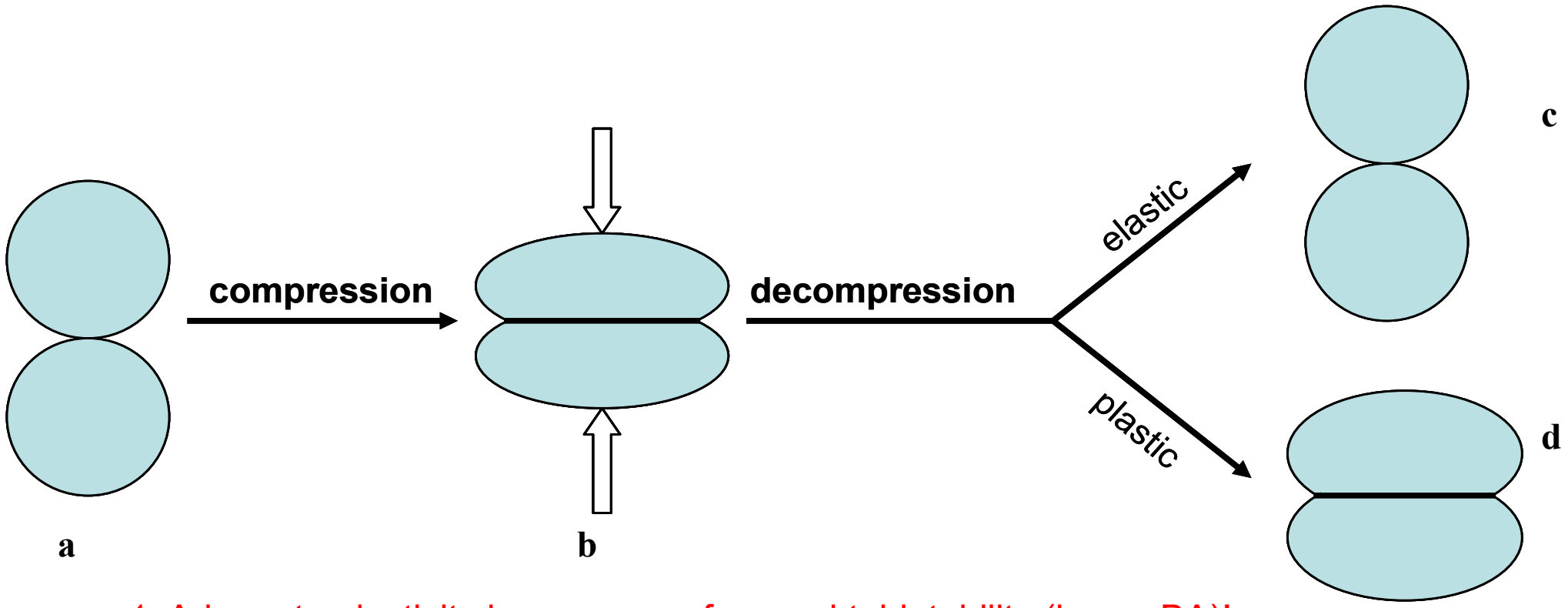


E. N. Hiestand *et. al. J. Pharm. Sci.* 66:510-519 (1977)

<1217> Tablet breaking force

<1062> Tablet compression characterization

Tabletability (Bonding Area - Bonding Strength)

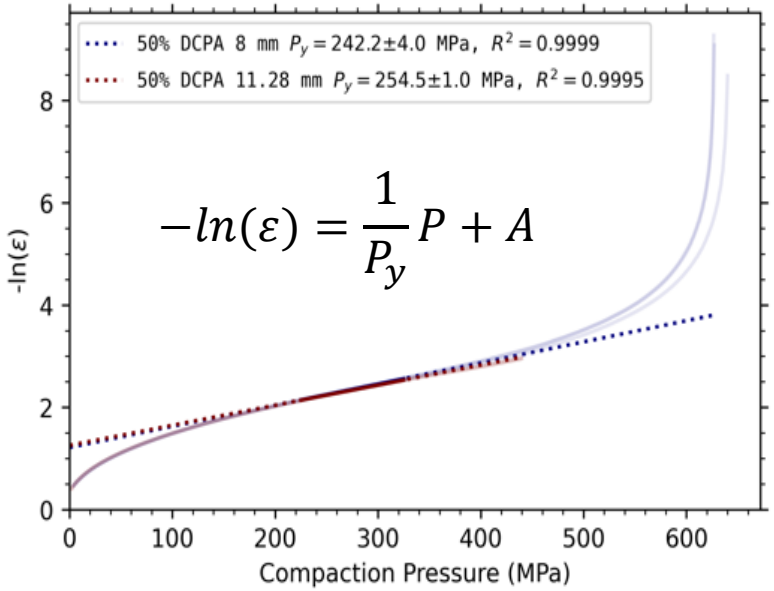


1. Adequate plasticity is necessary for good tabletability (larger BA)!
2. Higher bonding Strength (BS) also favors good tabletability!
3. Reason for incorporating plastic excipients in a tablet formulation

Sun, 2009, *J. Pharm. Sci.* 98:1671-1687

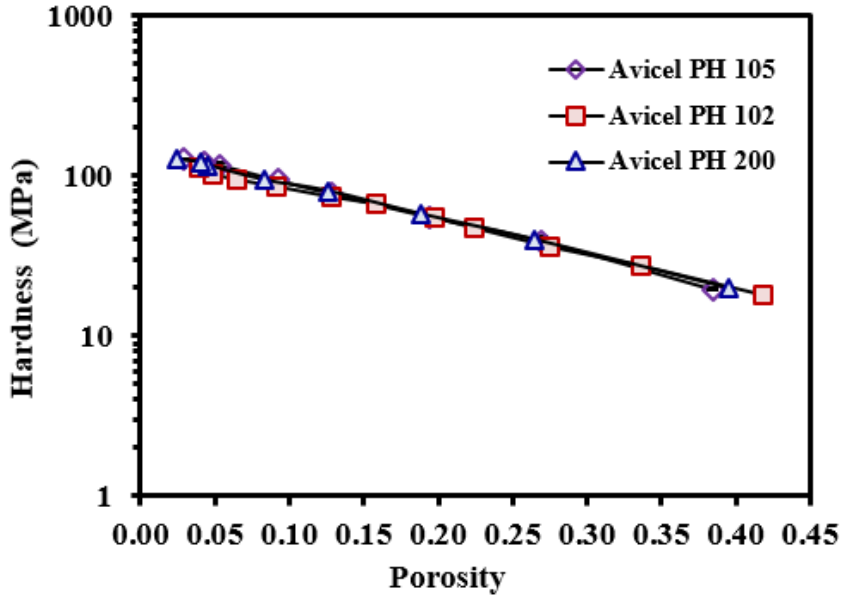
Plasticity Quantitation

Heckel analysis



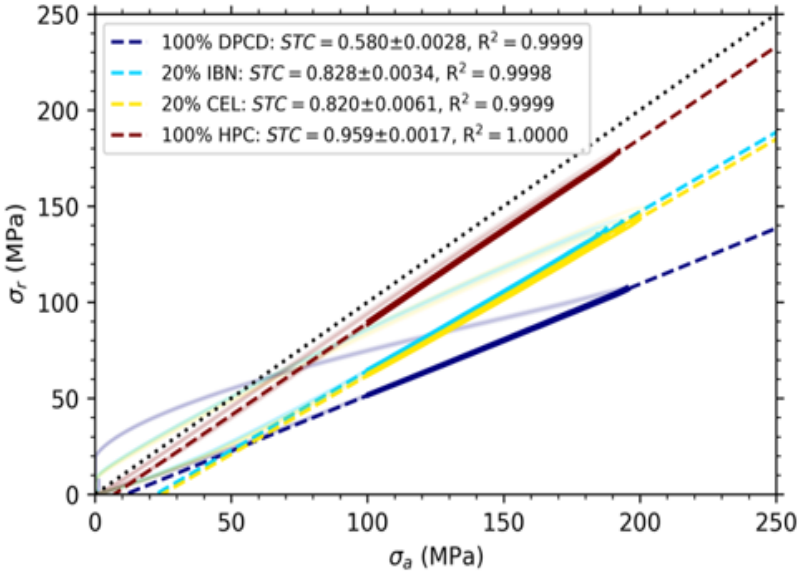
Vreeman & Sun, 2021, *Int. J. Pharm. X* 3:100094

Macroindentation



Patel & Sun, 2016, *Int. J. Pharm.* 506:262-267

Stress transmission Coefficient

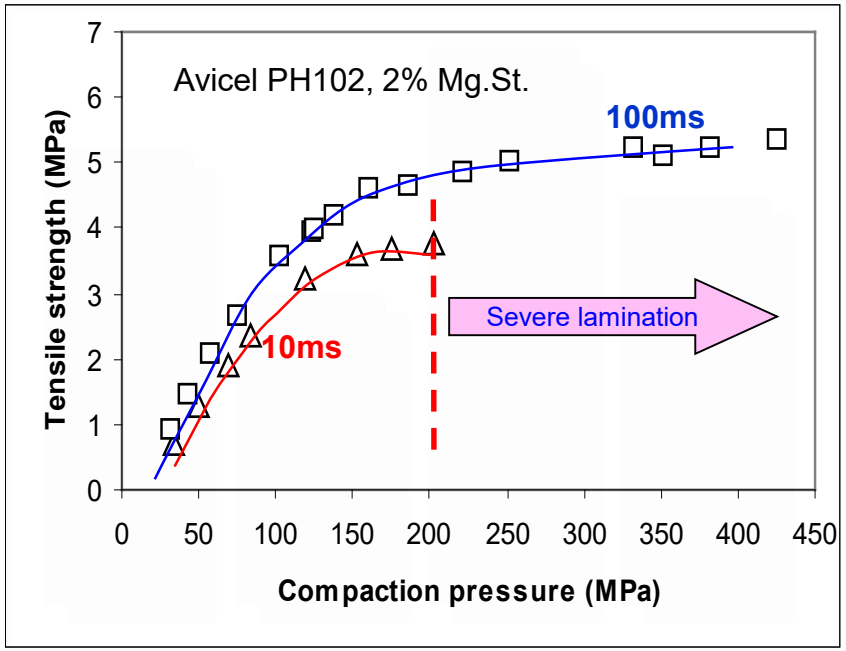


Vreeman & Sun, 2021, *Powder Technol.* 398: 117066

Tableting Speed Sensitivity

Strain Rate Sensitivity (**SRS**) = $$\frac{|Propertity_{SR2} - Propertity_{SR1}|}{Propertity_{SR1}}$$

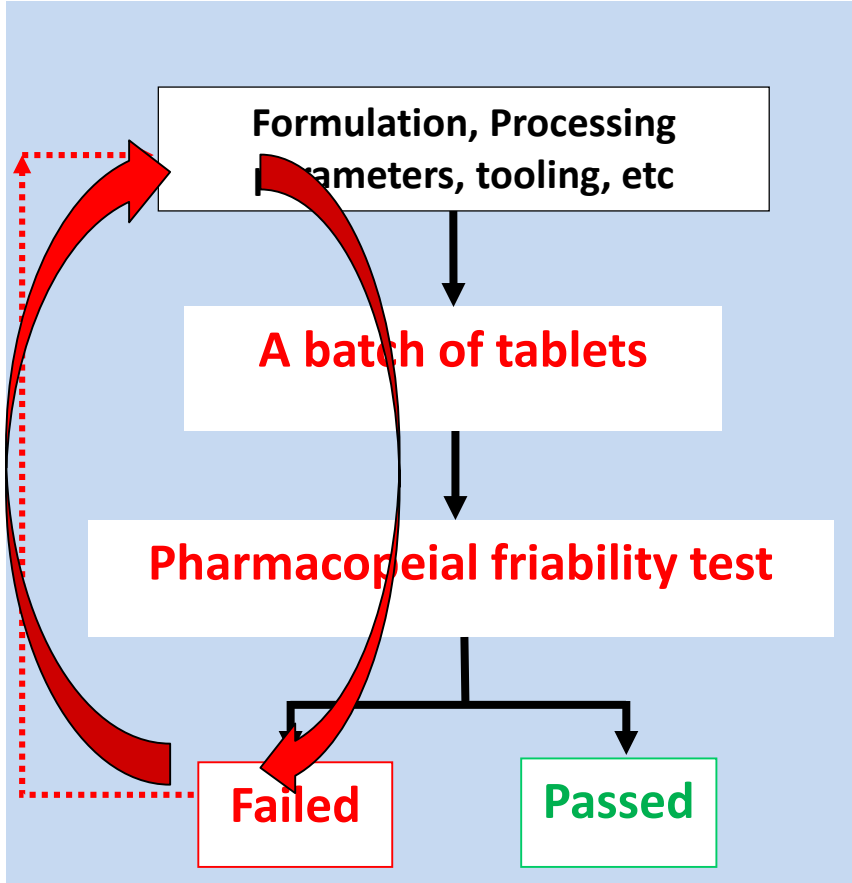
Compaction simulation at different speeds

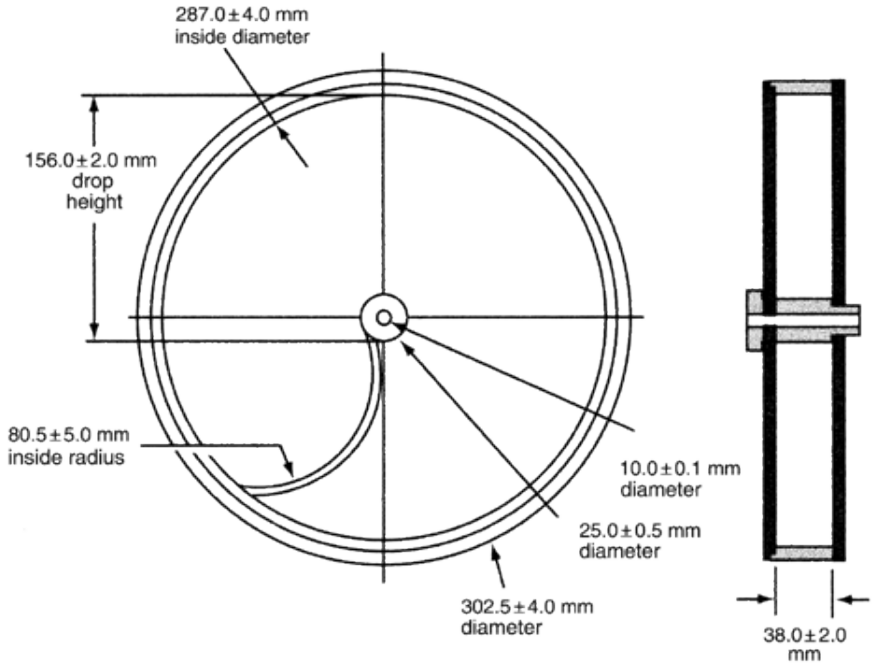


The lamination problem would have not been expected without compaction simulation data!

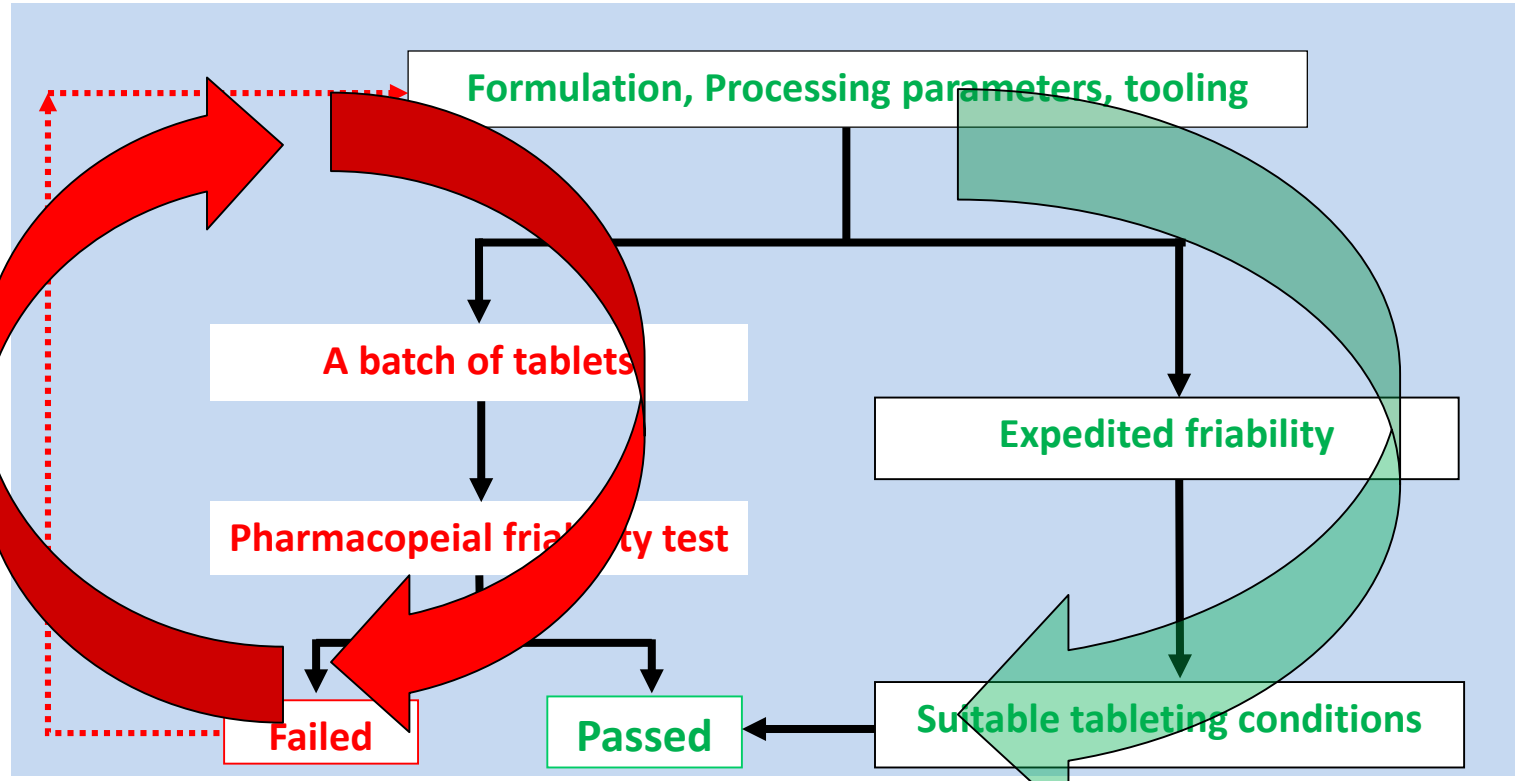
3. Tablet Friability – a performance test

<1216> Tablet friability





Traditional vs. Expedited Friability Test



Several iterations are usually needed to succeed

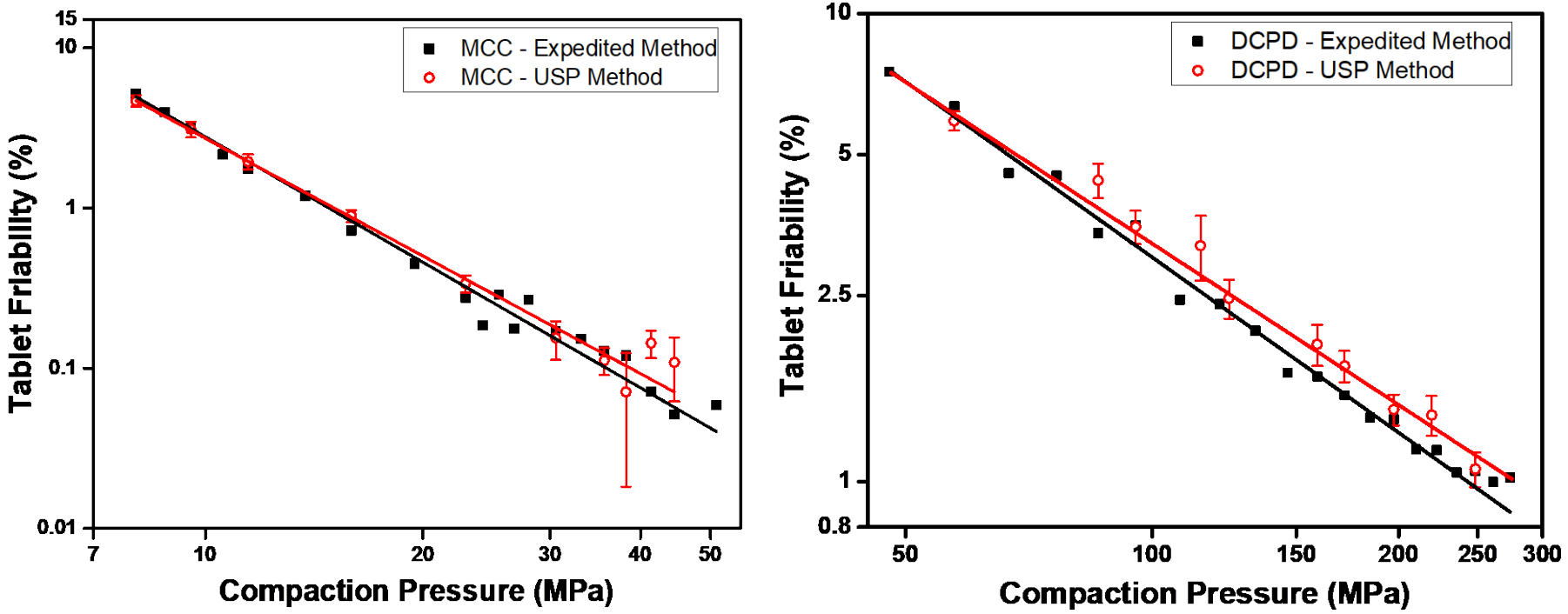
Material & labor intensive

One pass

Reformulation is data driven.

Osei-Yeboah & Sun, 2015, *Int. J. Pharm.*, 484:146–155

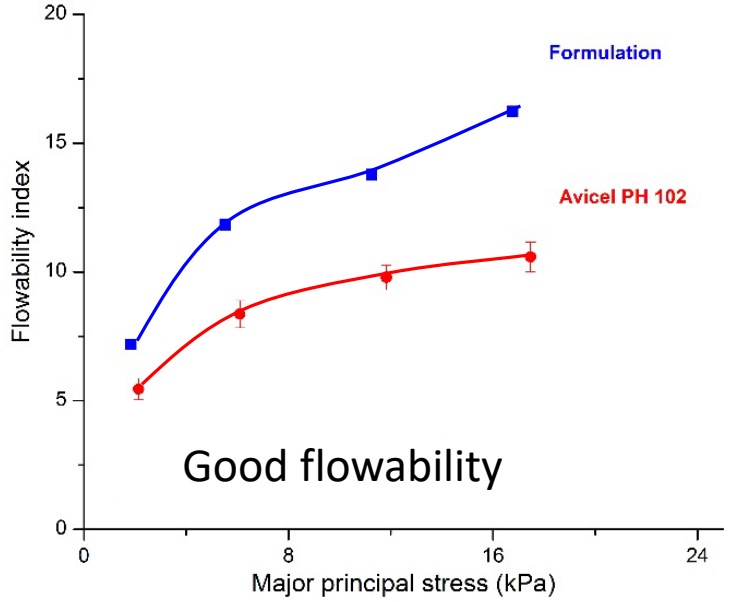
Validity of the Expedited Friability Test

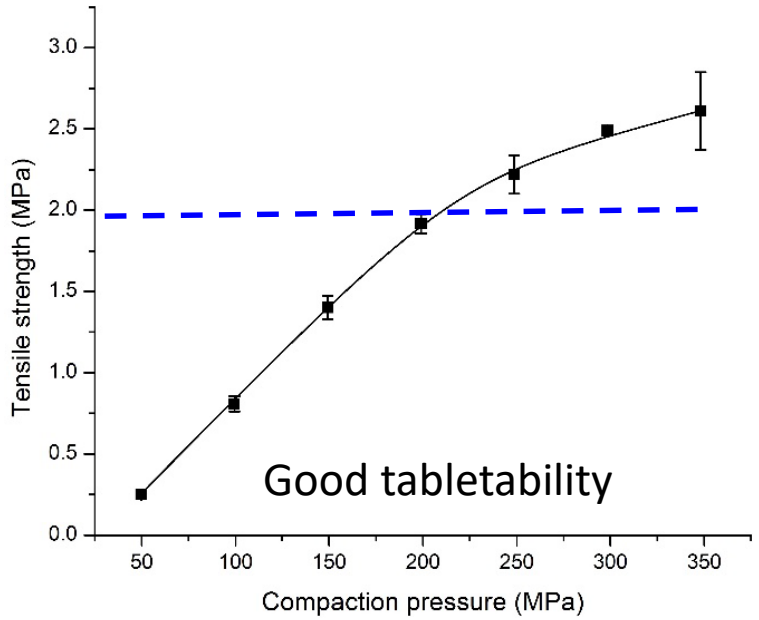


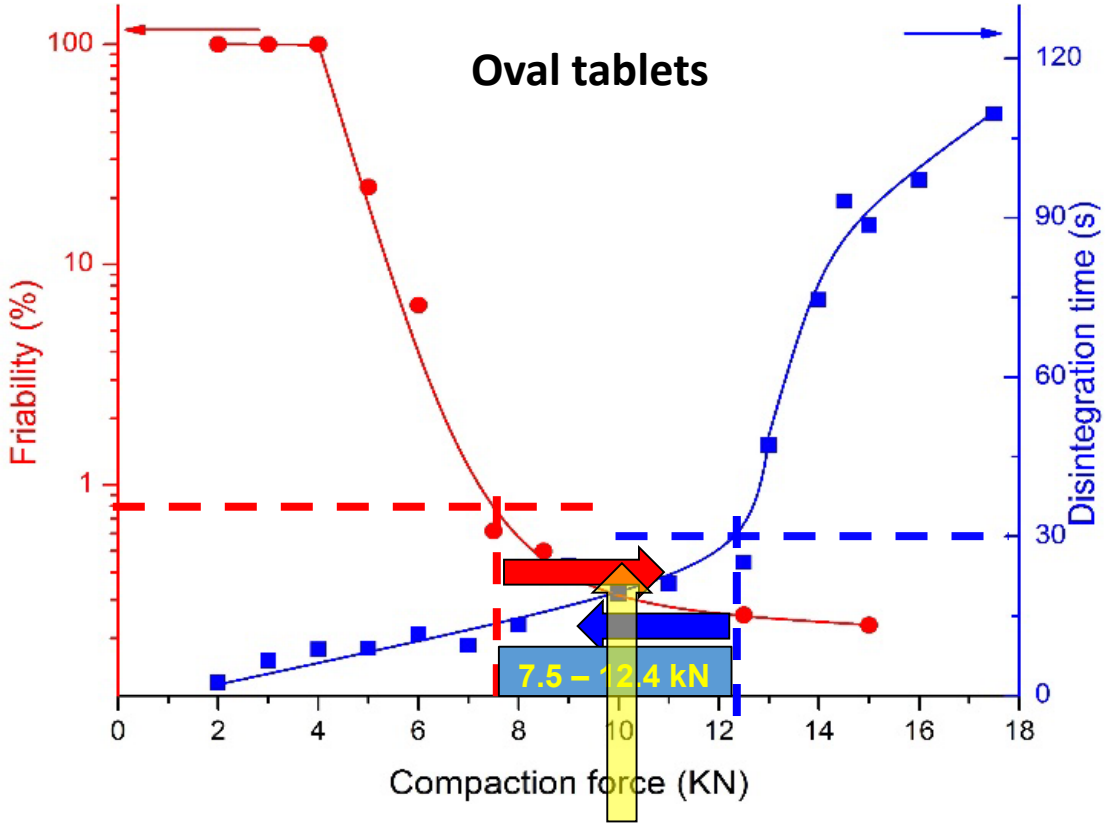
Impact stress on individual tablets is independent of mechanical strength of other tablets in the batch

Osei-Yeboah & Sun, 2015, *Int. J. Pharm.,* 484:146–155

An Example: Manufacturability of An ODT Formulation







10 kN

A batch of tablets was made:

D.T. < 30 s & friability < 0.8%

Wang, et al., 2017, Int. *J. Pharm.* 532:435-443

Conclusions

1. Many USP Chapters are available to guide characterization of powder properties important for successful CM of tablets
2. Adequacy of powder flowability can be qualitatively assessed by comparing to a suitable reference powder
3. Tabletability can be characterized using a compaction simulator
4. Tablet friability can be done in an expedited manner to guide formulation development
5. Combined performance tests, e.g., DI time and friability, help define a process window for successful tablet CM

Acknowledgements

Current and former students
postdocs, and visiting scholars
Many colleagues

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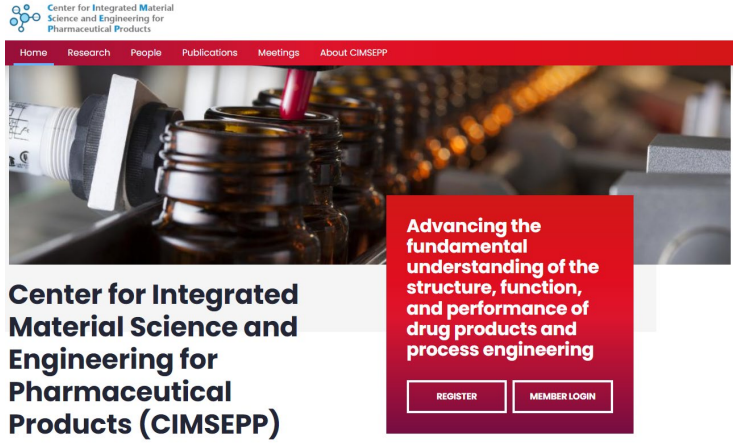
Cima Labs
DFE Pharma
Eli Lilly
Huadong Pharmaceutical
Merck
NSF - CIMSEPP
NSF - CPPR
Pfizer
PhRMA Foundation
Univ. of Minnesota
US FDA

Sun Lab

https://www.pharmacy.umn.edu/departments/pharmaceutics/changquan-calvin-sun-lab

NSF-CIMSEPP

- Established March 1, 2022
- Currently 13 companies
- Two sites: UMN & NJIT (lead)
- We are seeking to expand partnership with the industry!



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