Introduction to Q3

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How to Characterize Similarity?

- Q1: Qualitative Similarity
  - Same components
- Q2: Quantitative Similarity
  - Same amounts of the same components
- Q3: Structural Similarity
  - Same amounts of the same components arranged in the same way

How do you measure Q3?

What does Q3 similarity imply about bioequivalence?

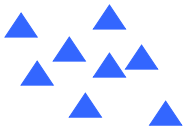
Definition of Q3

- Structural Similarity
  - Arrangement of matter
  - State of aggregation

Example: Polymorphs

Form A

Form B



Same Substance

Q3 is different

Example: Suspension

A

B

Same Substance

Q3 is different

What Determines Q3?

- Equilibrium states
  - Example: solution
  - Q2 implies Q3
- Non-equilibrium states
  - Examples: suspension,cream,ointment,gel
  - Determined by history
    - Manufacturing
    - Storage
    - Physical state of starting materials

How To Measure Q3?

- Different materials require different methods
- General features
  - Particle/Droplet/Polymer size distribution
  - Spatial arrangement/homogeneity
  - Particle/Droplet/Polymer interactions or crosslinks or surface chemistry

Semi-Solid Dosage Forms

- Most topical products are semi-solids
  - aka complex fluids, soft condensed matter, viscoelastic fluids
- Intermediate between liquid and solid
  - Sometimes they are solids
  - Sometimes they are liquids
- Rheology is very sensitive to formulation differences in semi-solids

Size Distribution and Uniformity

- Size distribution
  - Microscopy
  - Light scattering
- Is the material uniform
  - Density profile
- Spatial arrangement of particles

Interactions

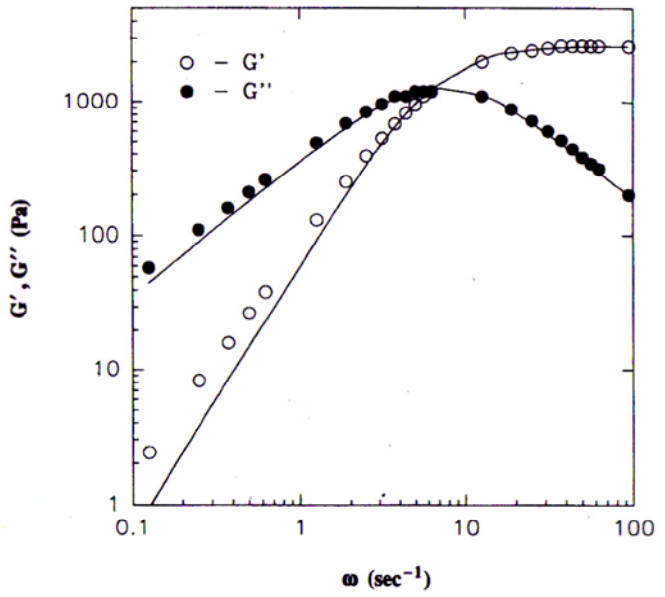
- Interactions between components determine the rheology
  - Particle attraction or repulsion
    - Surface Charge
    - Excipients/Stabilizers
  - Polymer or gel crosslinking

Rheology of Complex Fluids

- Linear Viscoelasticity
  - Material response to oscillatory strain combines solid and liquid behavior
- Stress-Strain Rate Relation
  - Viscosity depends on shear rate
- Yield Stress
  - Stress required to induce flow

Linear Viscoelasticity

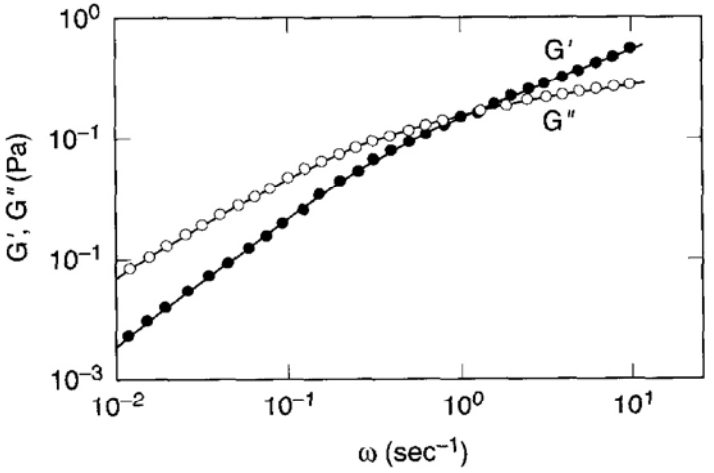
- G' represents solid like behavior
- G'' represents liquid like behavior
- Key Features
  - Solid-Liquid behavior depends on frequency
  - Relaxation time

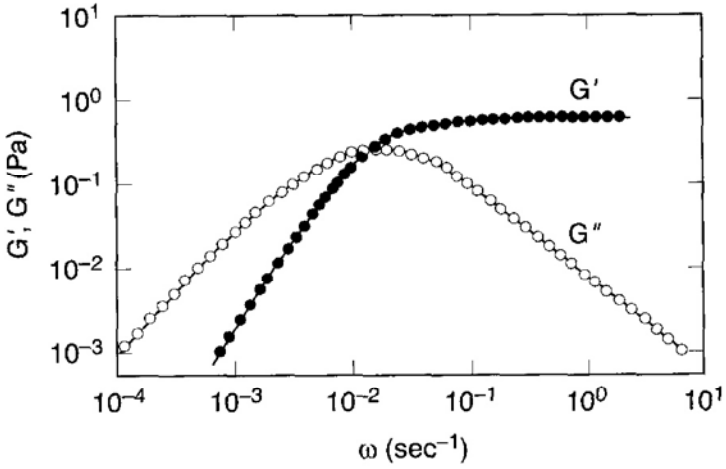


Linear Viscoelasticity

Surfactant Solution

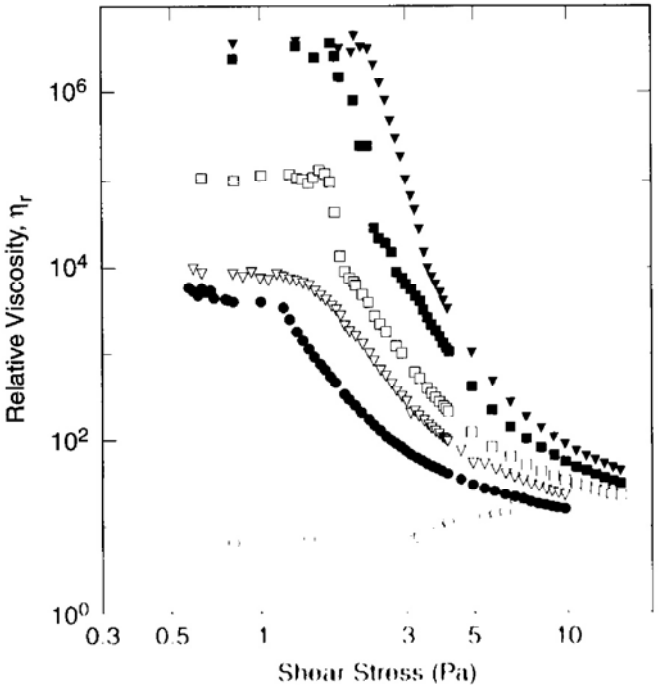
- Sensitivity to small formulation changes
- Top: 11 mM NaSal
  - Gel: Relaxation time 1 sec
- Bottom: 12.5 mM NaSal
  - Solid: Relaxation time 100 sec

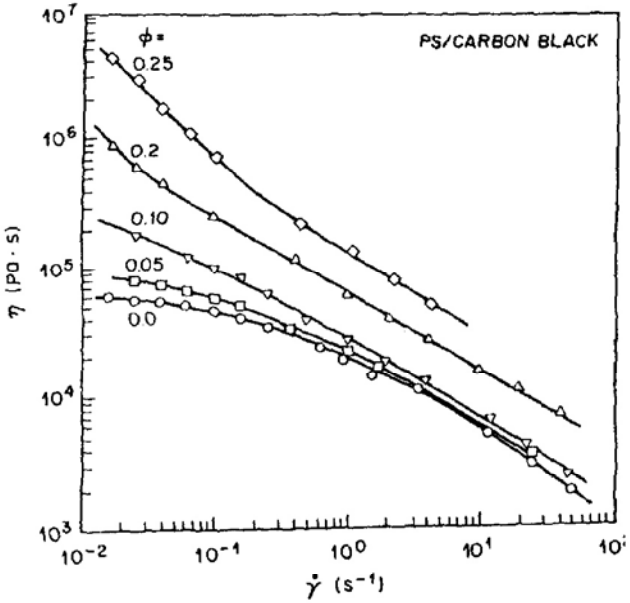




Viscosity Depends on Shear Rate

Most Semi-Solids
are shear thinning

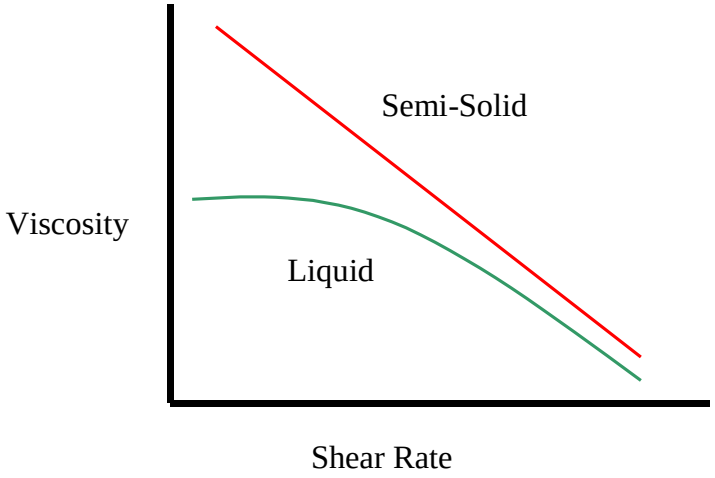




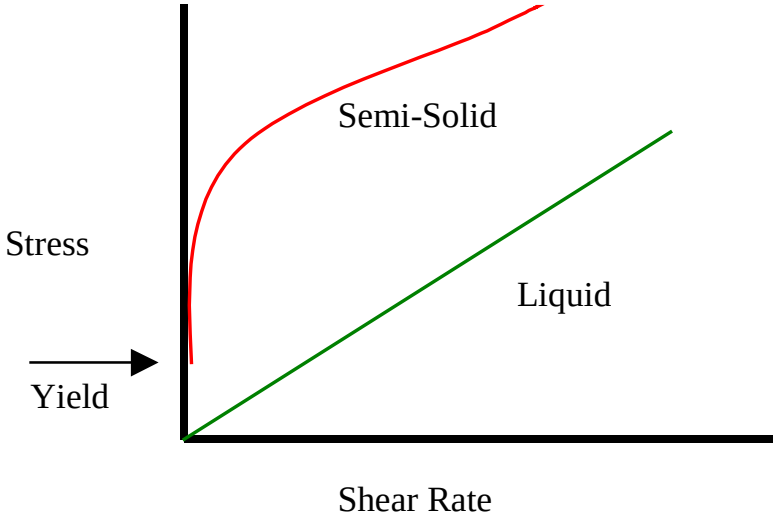
Small changes in excipients
(0.1%-1.0%) alter viscosity

Liquids and Semi-Solids

At low shear rates either
Constant viscosity: Liquid
or
Diverging viscosity: Yield Stress



A stress-shear rate plot shows semi-solids have a yield stress below which there is no flow while liquids do not.



Yield Stress

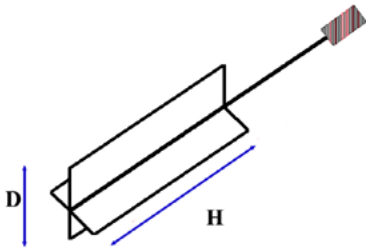
- Minimum stress required to initiate flow.
- Part of the refined classification scheme for semi-solid dosage forms

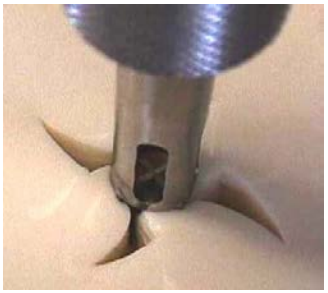
Measurement

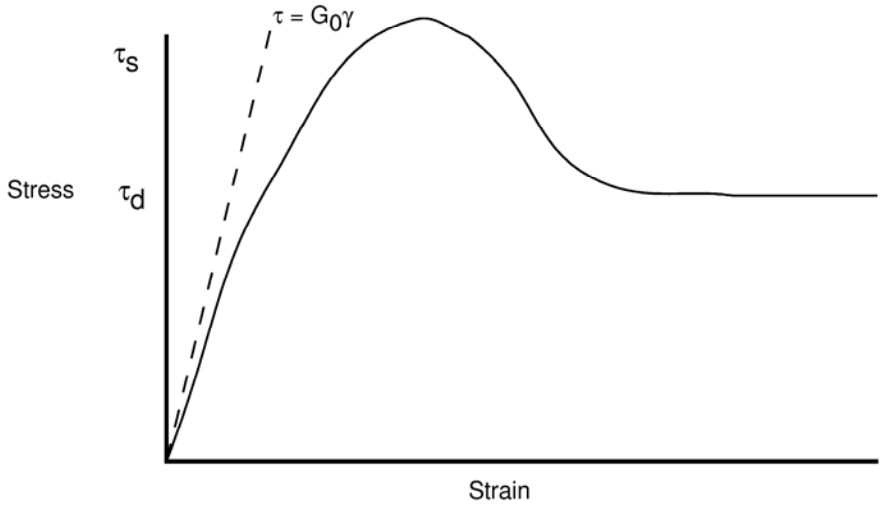
•Traditional rheometer: Extrapolate to low strain rate

•Constant stress rheometer

•Vane technique: Direct measure of stress to start flow



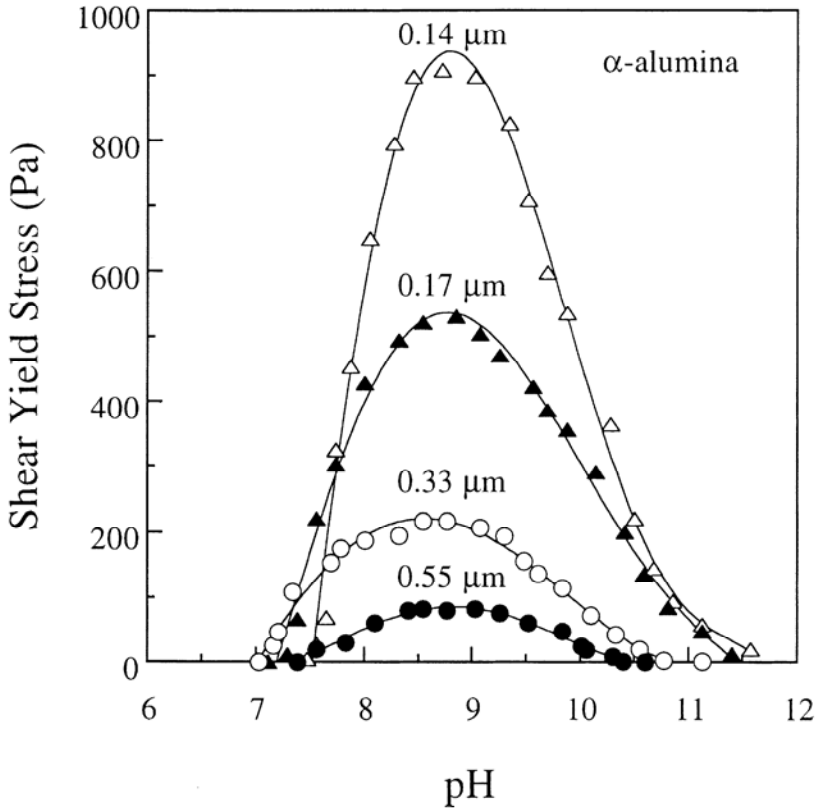




Vane: Apply a very slow strain and the maximum stress is the static yield stress

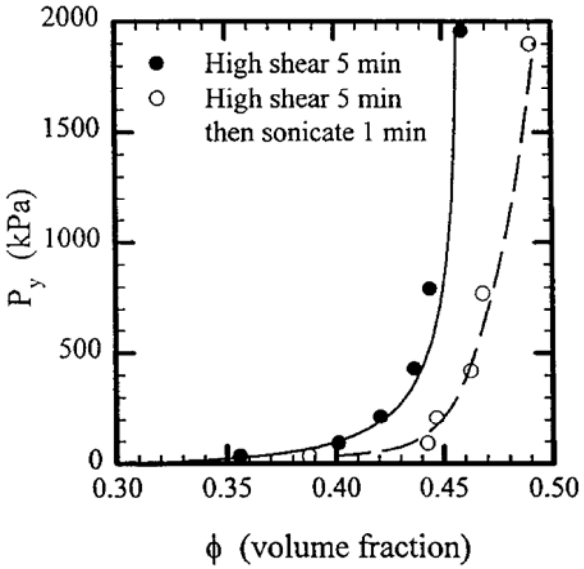
Sensitivity of Yield Stress

Examples from Flocculated Suspensions



Changes in particle size or pH alter the yield stress

Changes to the manufacturing process alter the yield stress



Zhou, Z., Solomon, M.J., Scales, P.J., Boger, D.V., 1999. *J. Rheol.* **43**, 651–671.

Greeb and Boger *Ind. Eng. Chem. Res.* 1997**, 36**, 4984-4992

Measurement Overview

- Reproducible techniques
  - NIST standards
  - Round robin tests
- If material is not a semi-solid, but a simple liquid
  - No yield stress
  - Constant viscosity
  - Relaxation time set by viscosity

Relation of Q3 to Topical Product Performance

- For topical products rheology matters
  - Similar spreadability requires viscosity-shear rate curves and yield stress be the same
- Drug release rate from formulation
  - How is the active ingredient contained in the formulation?
- Is Q3 too sensitive?
  - Will Q3 differentiate products that are bioequivalent?

Regulatory Role of Q3

- Products that are Q3 to each other will be bioequivalent!

- Level of confidence in Q3 determination
  - Did we measure the appropriate property?
  - How similar must measurements be to be Q3?

Q3 Validation

- How to prove that Q3 determination is valid
- University of Kentucky project
  - Measure rheology and drug release rates
  - Formulations with manufacturing differences
  - Formulation where generic was superior, not equivalent, in a clinical trial

Q3 Scientific Challenges

- Characterize complex formulations with particles of excipients and particles of actives