Characterization and modeling the viscoelasticity on pharmaceutical tablets

Leo Desbois, Vincent Mazel, Pierre Tchoreloff

Univ. Bordeaux, Arts et Métiers ParisTech, I2M UMR CNRS 5295, France

Introduction

The influence of the compaction speed on the final tablet properties is an important challenge during scale-up of solid dosage forms. Evolution of the compaction properties of powders with the compaction speed is often referred to as strain rate sensitivity (SRS):

Strain Rate Sensitivity →
- Friction
- Air entrapment
- Viscoplasticity
- **Viscoelasticity**

This work is focused on time dependent elastic deformation, the viscoelasticity. An original experimental methodology was developed to characterize the viscoelasticity of the tablet in the die on a compaction simulator. This methodology made it possible to separate the viscoelasticity and the other types of time-dependant deformations like viscoplasticity and plastic deformation.

Material

Powder and compression

- STYL'ONE compaction simulator (MEDEL'PHARM)

  - Instrumentation
    - Axial pressure
    - Radial pressure
    - Punch displacements
    - External lubrication (Magnesium Stearate)
- Round flat Compact:
  - Ø 11.28 mm (diameter)
  - Thickness of 3 mm
- Two pressure levels:100 and 200MPa
- Four strain rate levels: 0.001 to 1s^{-1}
- Four excipients:
  - Lactose Monohydrate (Glac)
  - Anhydrous Calcium Phosphate (ACP)
  - Microcrystalline Cellulose (MCC)
  - Starch

Numerical simulation

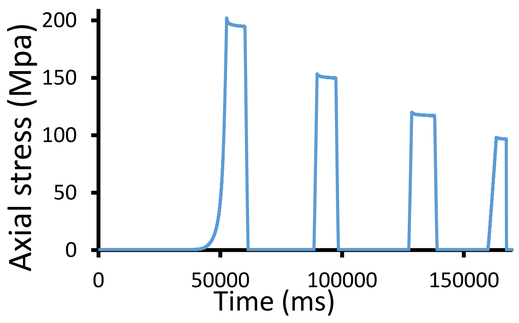
- Finite elements method (Abaqus® Standard 6.13)
- Modeling
  - Compaction process: A die and two punches with analytical rigid surfaces
  - Tablet: Continuous solid deformable
- A kinematic friction coefficient dependent of the speed (Desbois et al.,2019)
- Behavior law:
  - Linear elastic: Hooke's law
  - Viscoelastic: Prony series:

$$G(t) = G_\infty \left(1 + \sum g_i e^{-\frac{t}{\tau_i}}\right)$$

$$K(t) = K_\infty \left(1 + \sum k_i e^{-\frac{t}{\tau_i}}\right)$$

Methodology

Experimental protocol



- First three compressions used to cancel the plastic and viscoplastic effects
- Fourth compression: tablets compressed to the same strain at different strain rate to characterize viscoelasticity
- For each strain rate, the viscoelastic behavior of the tablet can be approximated by an apparent linear elastic behavior. The apparent elastic constants are determined for each strain rate (Young's Modulus (E), Poisson's ratio(v), Bulk modulus(K), Shear modulus(G)).

Numerical determination of the viscoelastic constants

- Previous experiment were reproduced to determine the different constants of the series prony (k_i , g_i)
- Three term Prony series were considered with three characteristic times: 0.03s, 0.3s and 3s.
- Experiments at 0.001s^{-1} were considered as quasi-static: first approximation of K_∞ and G_∞
- Prony series parameters were manually adjusted in order to obtain in the simulations the same apparent linear elastic constants as in the experiment

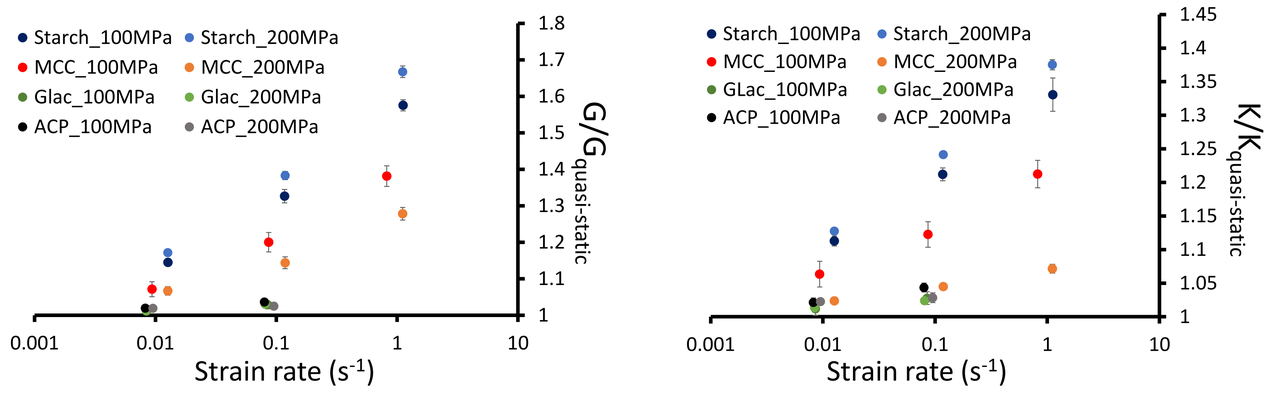
Results

Experimental assessment of viscoelasticity

- Values of the quasi-static moduli (strain rate 0.001 s^{-1})

	Starch			MCC			Glac			ACP		
	100MPa	200MPa		100MPa	200MPa		100MPa	200MPa		100MPa	200MPa	
$G_{quasi-static}$(MPa)	237 ± 1	253 ± 2		540 ± 8	739 ± 5		1760 ± 17	2060 ± #		4082 ± 17	3079 ± 22	
$K_{quasi-static}$(MPa)	649 ± 3	729 ± 1		1344 ± 19	2331 ± 6		2857 ± 26	3738 ± #		5330 ± 19	3959 ± 24	

- A viscoelastic product should present an evolution of apparent moduli with the strain rate
  - Representation of the ratio between the value measured and the quasi-static value



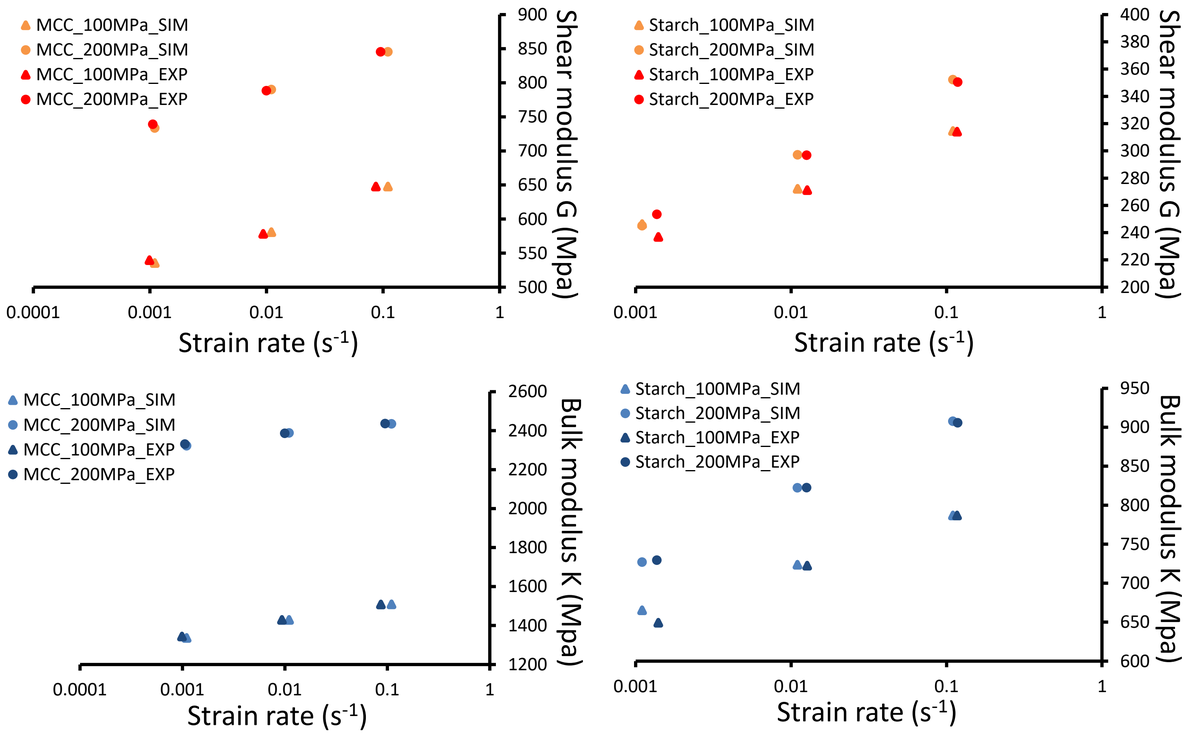
- Two groups:
  - ACP and Glac: Increase of the moduli always below 5%: Neglectable viscoelasticity
  - MCC and Starch: Apparent elastic moduli (G and K) dependent on the strain rate. Large evolution of the moduli (sometimes above 50%): visco-elastic products
- Evolution of G and K → Deviatoric part more important but we can't neglect the volumetric part for the viscoelasticity

Prony series and modeling

- Exemple of prony series parameters

		Gi	Ki	Ti (s)
MCC	**200 MPa**	**0.1990**	**0.0377**	**0.03**
		0.0540	**0.0107**	**0.3**
		0.1120	**0.0405**	**3**

- Comparison of numerical and experimental results



Prony series make it possible to represent numerically the viscoelastic behavior of pharmaceutical tablets

Conclusion

- Development of an original methodology to characterize the viscoelastic properties independently of the other time dependent properties.
- Application to classical pharmaceutical excipients: quantitative determination of the viscoelastic behavior
- Prony series make it possible to include the viscoelasticy in FEM simulation : good agreement between simulations and experimental data

L. Desbois, P. Tchoreloff, V. Mazel, Characterization and modeling of the viscoelasticity of pharmaceutical tablets, International Journal of Pharmaceutics, 2020

ANR-17-CE08-0015 (CliCoPha project)