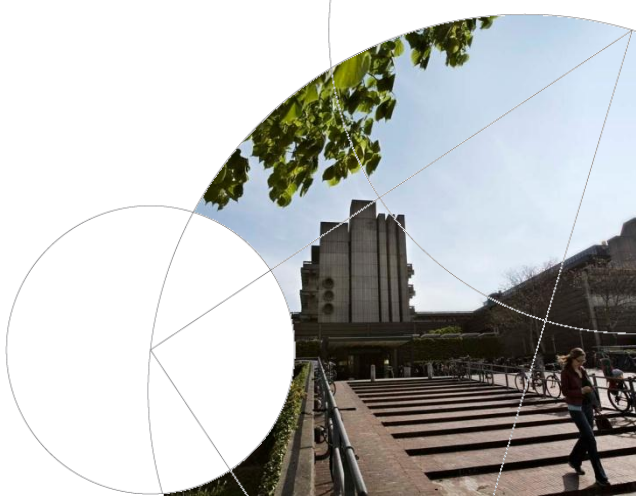
Impact of physiologically relevant viscosity on intrinsic dissolution rate of poorly soluble compounds in simulated gastric media.



Agenda

- Introduction
- Aim
- Viscosity characterization of human gastric aspirates
- Preparation/viscosity characterization of viscous biorelevant dissolution media
- Dissolution study
- Conclusion
- Perspectives

Introduction

- Physiologically relevant conditions are important dissolution testing.
- The purpose of biorelevant dissolution media (BDM) is to simulate the conditions in the gastrointestinal tract.
- Several factors such as pH, osmolality and surface tension has been taken into account.
- Viscosity is a factor not considered in currently used BDM.
- The viscosity of gastrointestinal fluid is expected to be higher than BDM due to the presence of mucus.
- An increased viscosity is supposed to decrease the dissolution rate.

Aim

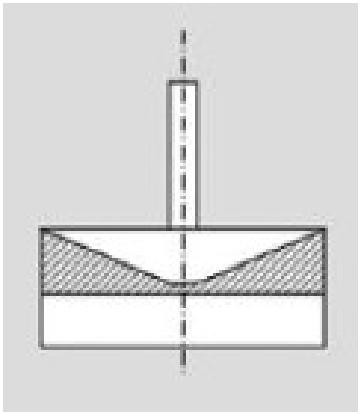
- Determine the viscosity range of human gastric fluid.
- Produce biorelevant dissolution media based on commonly used biorelevant dissolution media with viscosities similar to human gastric fluid.
- Investigate whether the dissolution rate is altered compared to traditional biorelevant dissolution media.

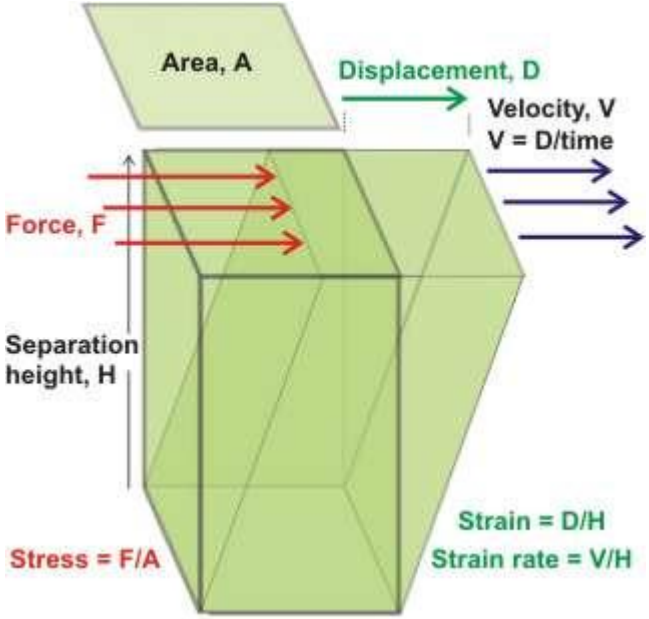
Experimental approach

- Viscosity characterization of human gastric aspirates.
- Preparation/ characterization of viscous biorelevant dissolution media.
- Dissolution study

Theory - Characterization of the viscosity of human gastric aspirates

Rheology is the study of flow and deformation of matter.





$$shearstress = \frac{F}{A} \qquad shearrate = \frac{V}{H} \qquad viscosity = \frac{shearstress}{shearrate}$$

Experimental - Viscosity characterization of human gastric aspirates

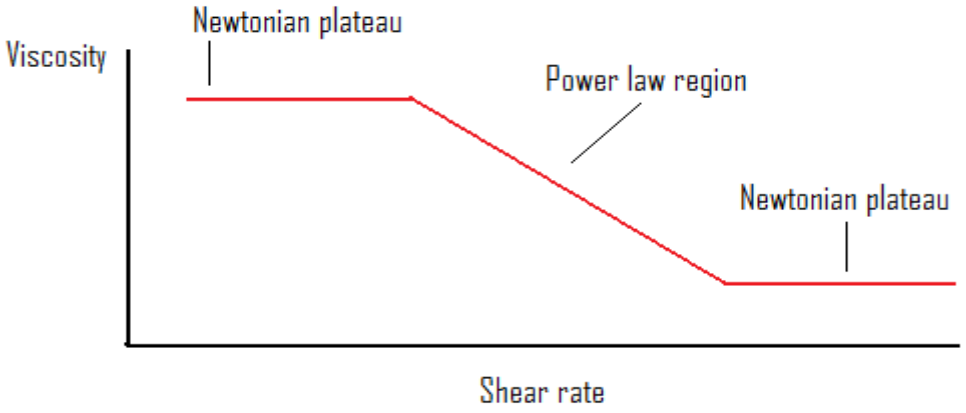
- Viscosity measurements were performed on human gastric aspirates from 7 volunteers
- Viscosity characterization was based on a steady-state flow test
- The apparant viscosity was measured as a function of shear rate

Experimental - Characterization of the viscosity of human gastric aspirates

It was expected to observe following:

- Shear-thinning behavior as shown below

- An apparant viscosity above the viscosity of water (<1 mPa·s)



Steady-state flow profile of a typical shear thinning fluid.
Modified from TA Instruments Rheology Symposium.

Results - Viscosity characterization of human gastric aspirates

Steady-state flow test:

- Newtonian behavior at high shear rates
- Supposed shear-thinning behavior at lower shear rates
- Measured at a shear rate of 30 to 1000 sec^{-1}
- Viscosities between 1.7 and 12 mPa·s at 178 s^{-1} were found

Preparation of viscous biorelevant dissolution media

Viscous biorelevant dissolution media (BDM) were based on fasted-state simulated gastric fluid (FaSSGF).

FaSSGF contains physiologically relevant amounts of bile salts and pepsin, and properties such as pH, osmolality and surface tension are close to *in vivo* data.

Composition of FaSSGF and *in vivo* data of human gastric fluid[1]

Composition	FaSSGF	*In vivo* data
Sodium taurocholate (μM)	80	~80
Lecithin (μM)	20	-
Pepsin (mg/mL)	0.1	~0.8, 0.11 – 0.22
Sodium chloride (mM)	34.2	68 ± 29
Hydrochloric acid q.s.	pH 1.6	-
Properties		
pH	pH 1.6	1.4 - 2.1
Osmolality (mOsm/kg)	120.7 ± 2.5	191 ± 36
Surface tension (mN/m)	42.6	~40

[1]Vertzoni, M., Dressman, J. B., Butler, J., Hempenstall, J., Reppas, C.: Simulation of fasting gastric conditions and its importance for the in vivo dissolution of lipophilic compounds. Eur. J. Pharm. Biopharm. 2005; 60:413–417

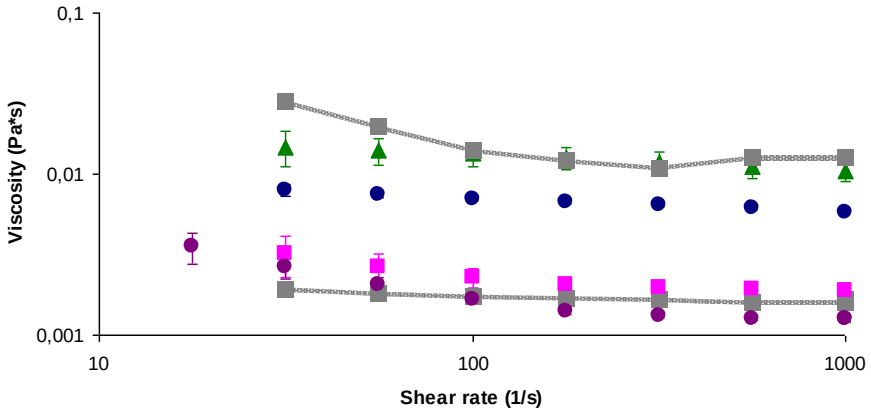
Results – Characterization of the viscosity of human gastric aspirates

Steady-state flow tests:

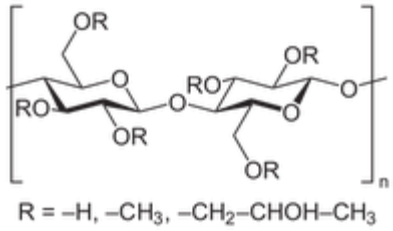
Samples are proposed to display a shear-thinning behavior

HPMC:

0.2 – 0.6 % HPMC represents physiologically relevant viscosities



Steady-state flow test conducted on FaSSGF containing different concentrations of HPMC (n=3; mean ± SD). ■ Represents the viscosity range found in human gastric aspirates. ● FaSSGF, ■ 0.2 % HPMC, ● 0.4 % HPMC and ✤ 0.6 % HPMC.



Hydroxypropyl methylcellulose (HPMC):

- Semi-synthetic polymer
- Non-charged

Theory - Dissolution study

The dissolution of a drug compound is divided into two steps:

- The liberation of molecules from the tablet surface under the creation of a saturated boundary layer adjacent to the surface
- Transport of the solutes from the boundary layer and into the bulk solution

The dissolution process can be described by the Noyes-Whitney equation[2]:

$$\frac{dM}{dt} = \frac{D \cdot A(C_S - C)}{h}$$

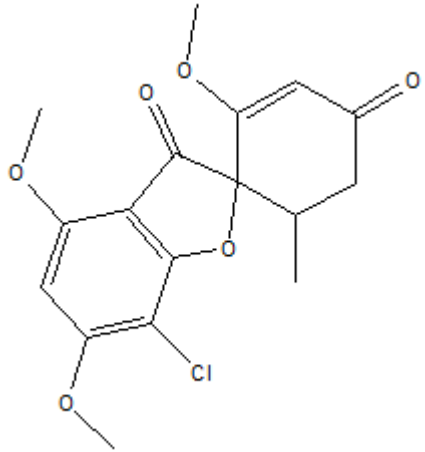
It is expected to observe a decreased intrinsic dissolution rate (IDR) as the viscosity is increased.

[2]Noyes, A. S., Whitney, W. R.: The rate of solution of solid substances in their own solutions. J. Amer. Chem. Soc. 1897; 19:930– 934

Dissolution study – Model drugs

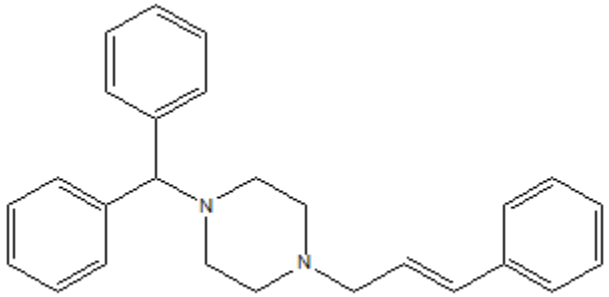
Griseofulvin

logP	2.18
Solubility (water)	10 µg/ml
MW	352.766 g/mol
BCS	II



Cinnarizine

logP	5.8
pK_a 1	1.95
pK_a 2	7.5
Solubility (1 M HCl)	0.29 mg/ml
Solubility (phosphate buffer, pH=7.2)	0.002 mg/ml
MW	368.514 g/mol
BCS	II

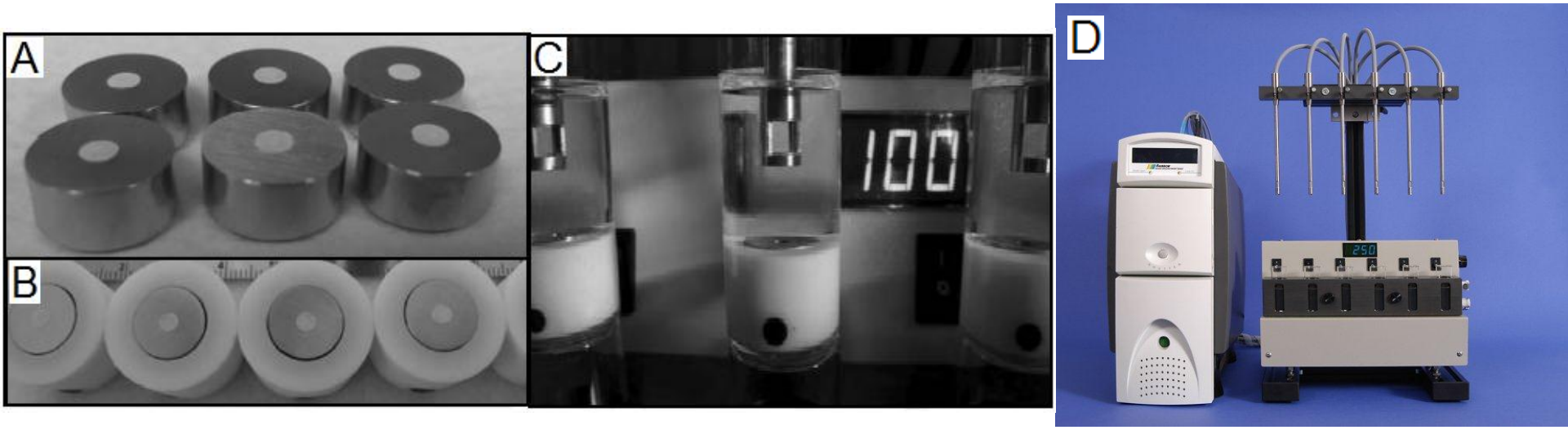


Experimental - Dissolution study

Dissolution experiments using HPMC were performed using the µDISS Profiler system at 37 ºC and 100 RPM. Vials were covered with para-film.

Intrinsic dissolution rate was calculated by the software as

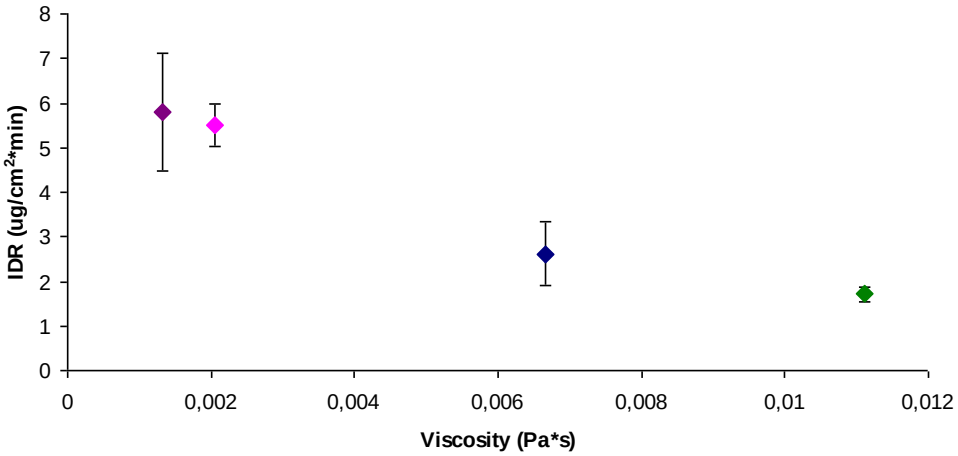
$$IDR = DR_{\max} / A$$



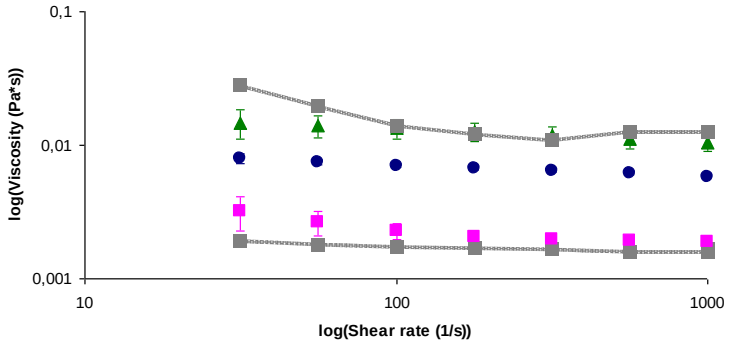
Parts of the µDISS profiler system. A) Steel dies with compressed powder. B) Dies inserted into teflon rotating disk carriers. C) Rotating disk carriers with dies placed on the bottom of the glass vials. Fibre optic probes are immersed into dissolution medium. D) µDISS Profiler. (Pictures from avdeef and Tsinman 2008)

Results - Dissolution study

IDR obtained from dissolution of Griseofulvin in FaSSGF containing different amounts of HPMC:



IDR's obtained from dissolution of Griseofulvin in FaSSGF of different viscosities. ◆ FaSSGF, ◆ 0.2 % HPMC, ◆ 0.4 % HPMC and ◆ 0.6 % HPMC. The viscosities are measured at 178 s^{-1}.

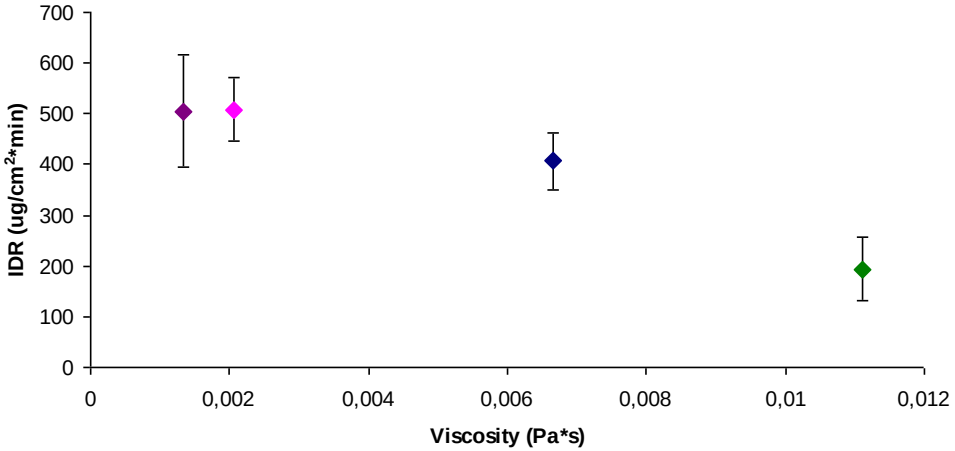


Steady-state flow test conducted on FaSSGF containing different concentrations of HPMC (n=3; mean ± SD). ■ represents the viscosity range found in human gastric aspirates. ■ 0.2 % HPMC, ■ 0.4 % HPMC and ▲ 0.6 % HPMC.

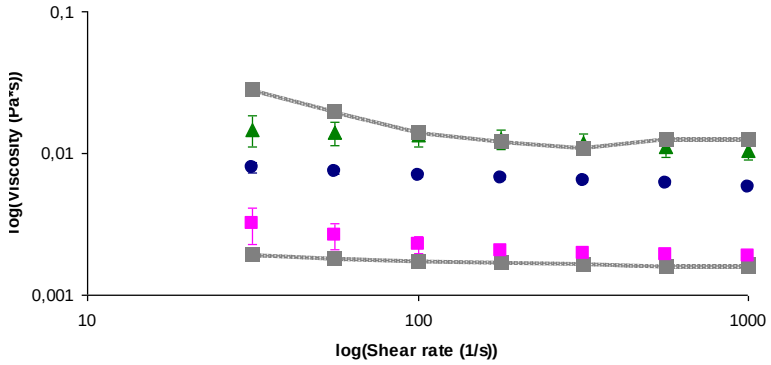
IDR was decreased up to 70 % within the viscosity range found for human gastric fluid.

Results - Dissolution study

IDR obtained from dissolution of Cinnarizine in FaSSGF containing different amounts of HPMC:



IDR's obtained from dissolution of Cinnarizine in FaSSGF of different viscosities. ◆FaSSGF, ◆ 0.2 % HPMC, ◆0.4 % HPMC and ◆0.6 % HPMC. The viscosities are measured at 178 s^{-1}.



Steady-state flow test conducted on FaSSGF containing different concentrations of HPMC (n=3; mean ± SD).■ represents the viscosity range found in human gastric aspirates ■ 0.2 % HPMC, ■ 0.4 % HPMC and ▲ 0.6 % HPMC.

IDR was decreased up to 62 % within the viscosity range found for human gastric fluid.

Results - Dissolution study

- The IDR is decreased in viscous BDM

- The IDR of Griseofulvin and Cinnarizine could be influenced by:
- different drug-polymer interactions
- size of the model drug

- Differences in IDR is attributed to the significant different solubility of the drugs at pH 1.6

- Cinnarizine is positively charged and Griseofulvin uncharged at pH 1.6 which can explain some of the solubility differences.

Conclusion

The viscosity of human gastric fluid was investigated.

- An apparent viscosity of 1.7 - 12 mPa·s at a shear rate of 178 s^{-1} was found for human gastric aspirates.

Addition of the viscosity enhancer HPMC was tested.

- Addition of 0.2 – 0.6 % HPMC to FaSSGF produced media with viscosities in the range found in human gastric fluid.

Dissolution analyses were performed on the physiologically relevant BDM containing HPMC.

- The IDR of Griseofulvin was lowered up to 70 % in FaSSGF containing up to 0.6 % HPMC.

- The IDR of Cinnarizine was lowered up to 62 % in FaSSGF containing up to 0.6 % HPMC.