Application Note
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# Rheology of Pharmaceutical Suspensions

Key words:

- Rheometer
- HAAKE MARS
- "21 CFR part 11" tools for HAAKE RheoWin
- suspensions
- stability

Rheology Application Notes

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## Introduction

The rheological behaviour of pharmaceutical suspensions influences a wide range of applications, like production, bottling process and storage. Thermo Electron's solutions for the rheological characterization of pharmaceutical products consists of a modular rheometer platform HAAKE MARS, which enables an easy adaptation to new or individual applications, a software which fulfils the requirements of the FDA and IQ/OQ services including documentation.

## Stability of pharmaceutical suspension

In addition to the actual medicinal components, often only available in milligramm amounts, a drug contains a number of additives which give the preparation its required form. (eg. tablets, solution, gel, emulsion).

Many pharmaceutical products are produced in the form of a suspension. Suspensions are usually dispensed in bottles or sachets and are taken from a spoon. The rheological properties of both liquid and semi-solid pharmaceutical products are important for the bottling process (pumps, dispensers) and for the selection of suitable packaging. For example, a nose spray needs to demonstrate a certain viscosity so that the active ingredient can be applied via a spray. Similarly, all products that are administered by drops (eg. eye drops, ear drops), must drop out of the bottle slowly under the effect of gravity. With suspensions there is also the question of storage and transportability. The sinking of solid particles is not usually desirable. Even without the bottle being shaken prior to use, the solid particles should be evenly distributed throughout the liquid and remain suspended. That is why stabilisers are added to a medicine in the form of polymers to give the product its required properties. During extensive tests, employing the shaking of the products as well as temperature changes, the newly developed medicines were divided into stable and unstable products.

## Description of samples and rheometer

Rheology can help development chemists make reliable predictions about the stability of a new formulation at an earlier stage. In the following rheological tests were carried out on two suspensions: a stable and an unstable sample.

For the described measurements [1] an air bearing rheometer is required, like the new rheometer platform HAAKE MARS (fig. 1) and a coaxial cylinder measuring geometry (Z40 DIN) at 20°C.
The new rheometer platform HAAKE MARS features a modular design to enable it to adapt quickly and flexibly to the requirements of various different applications or tests. All rheological measurements can be performed in CR (controlled rate), CS (controlled stress) and CD (controlled deformation) mode, in rotation and in oscillation. A new normal force sensor allows positive and negative normal forces up to ±50 N. The design of the HAAKE MARS makes it easy to handle, while expansion space and optional adjustments to the base frame allow individual additional modules to be connected.
Not only the instrument is designed for easy handling, but also the measuring and evaluation software HAAKE RheoWin has a strong customer focus. With HAAKE RheoWin measuring and evaluation procedures can be created using predefined

*Figure 1: HAAKE MARS a Modular Advanced Rheometer System*

elements via "drag & drop". For this software help tools are available to create suitable "jobs" and in addition HAAKE RheoWin can be extended with optional modules. E.g. for pharmaceutical applications "21 CFR part 11" tools are available, which fulfil the strong requirements from the Food and Drug Administration. IQ/OQ documentation is available and trained service engineers do carry out IQ / OQ installations.

## Measurement and results

In order to gain a first impression of the two pharmaceutical products, a flow curve was measured in CR (controlled rate) mode. As neither product demonstrated thixotropy (i.e. dependency of the viscosity on the time exposed to certain shear conditions), the flow curve can be plotted as a simple, upward curve.

The fundamental difference between product A (the stable suspension), and product B (unstable), can be recognised by comparing the two flow curves. Product A demonstrates a higher yield stress than product B, which can be seen at the start of the flow curve. The viscosity of product B is much lower over the whole shear rate range. In order to determine the

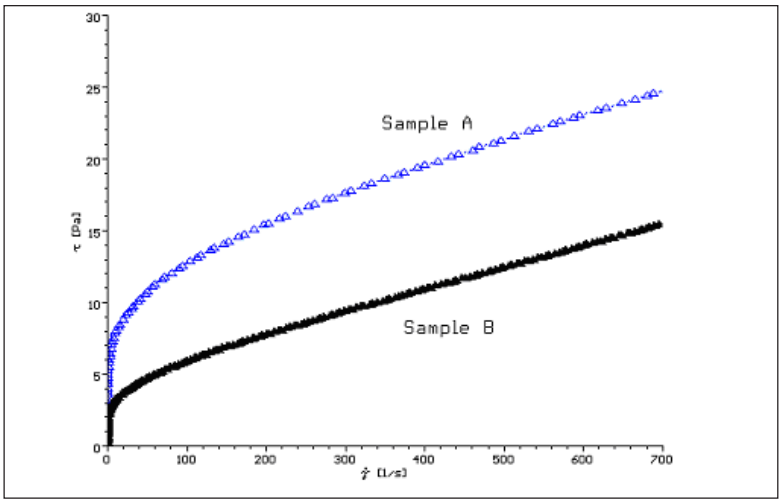


*Figure 2: Flow curves of two suspensions*

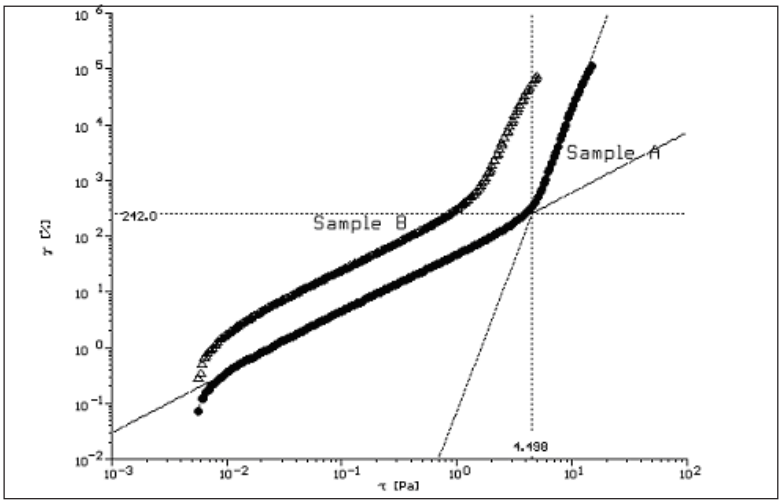


*Figure 3: Determination of the yield stress*

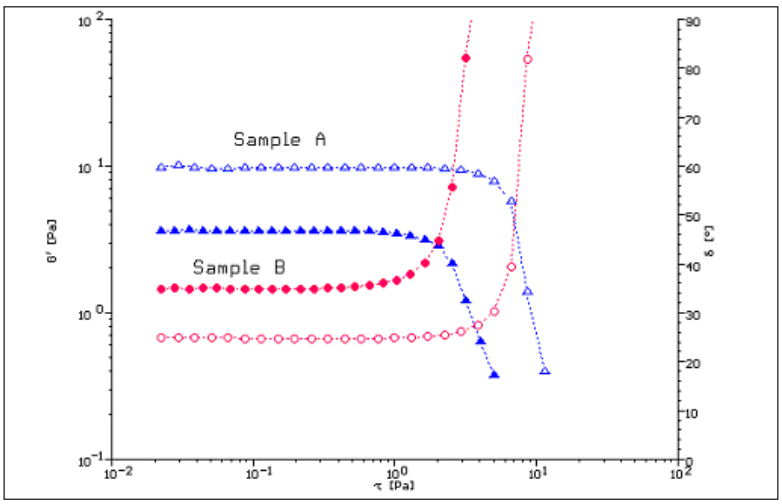


*Figure 4: Amplitude sweeps at 1 Hz for two suspensions*

yield stress it is recommended to perform a CS (controlled stress) ramp and to plot the deformation γ as a function of the stress τ in a double-logarithmic plot (see Fig. 3).
The tangent crossover has been taken as the yield stress as recommended by DIN Technical Report No. 143 (2005). The yield stress of sample A was established as being around 4.5 Pa, whilst that of sample B was only 1.5 Pa.

It is also very interesting to compare the visco-elastic properties of both products. This can be seen for example, by performing an oscillation stress sweep: With a constant oscillation frequency of 1 Hz the amplitude was increased over three decades. In diagram 4 the storage = elastic modulus G' (triangles), is compared with the phase displacement angle δ (crosses) for both products. The range up to a certain critical amplitude, in which the value of G' and δ (as well as G*, η*) remain constant, is described as the linear visco-elastic region.
A higher stability is generally expected from products with a wide linear visco-elastic region. This can be seen in the diagram where the stable suspension A demonstrates a higher critical amplitude.
If one defines the critical amplitude as the value where δ starts to increase, we get 2.5 Pa for product A and for product B only 1 Pa.
Additionally product A demonstrated greater elasticity. This can be seen from the smaller phase shift angle δ when compared with suspension B (solid symbols).
The loss factor tan δ is also found here, which describes the relationship between the elastic and viscous components of the product. The storage modulus G' that was measured for A is higher than that for B. Below the critical amplitude, the values of G' for sample A were 9.7 Pa, when δ was at 24.5°. The corresponding values for product B were 3.6 Pa and 34.7°.

## Summary

The use of the air bearing rheometer HAAKE MARS is beneficial to the development of a new storage-stable suspension. With the minimum investment of time, various parameters for stability can be reliably established and reproduced. In order to fulfil the strong requirements of the FDA the measuring and evaluation software HAAKE RheoWin can be extended with "21 CFR part 11" tools.

*References:*
*[1] Thermo Application Report "Rheological Analysis of the Stability of Pharmaceutical Suspensions" Eva-Maria Kutschmann (V154).*

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