Rheological Analysis of the Stability of Pharmaceutical Suspensions

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In addition to the actual medicinal components, often only present 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. A well known example are anti -acids which contain magnesium and aluminium hydroxide. Alongside these are sugar substitutes like Sorbit and Mannit as well as preserving agents (parabens). 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.

Rheological research can help development chemists make reliable predictions about the stability of a new formulation at an earlier stage. In the following example rheological tests were carried out on two suspensions. One of these suspensions is unstable whilst the second demonstrates the required properties. The measurements were made using the air bearing rheometer, HAAKE Rheostress® and a cylinder geometry Z40 DIN at 20°C.
In order to gain a first impression of the products, a flow curve was performed in the CR mode. As neither product demonstrated thixotropy (ie. dependency of the liquid properties on shear rate and time spent under shear conditions), the flow curve can be produced as a simple, upward curve (in this example, 0 - 700 s^{-1} in three minutes, 200 data points).

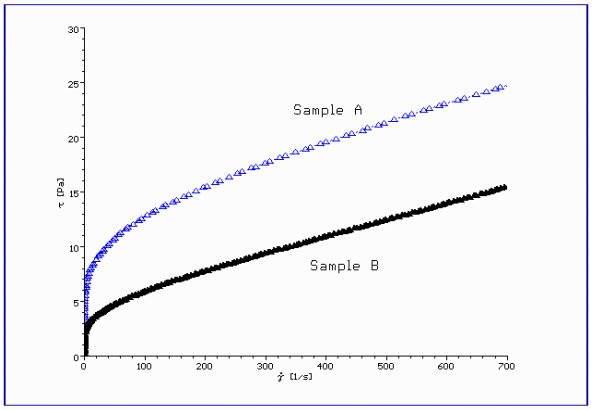

Fig. 1: Flow Curves of the 2 Suspensions

The fundamental difference between product A (the stable suspension), and product B (unstable), can be recognised from the flow curve. Product A demonstrates a higher yield point - this can be seen at the start of the flow curve. The viscosity of product B is much lower at the same shear rate. In order to determine the yield point it is recommended to perform a controlled stress flow curve. The yield point can also be established by applying the deformation γ as a function of a the controlled stress τ in a logarithmic axis calculation (see also HAAKE application report V97-137 D/E).

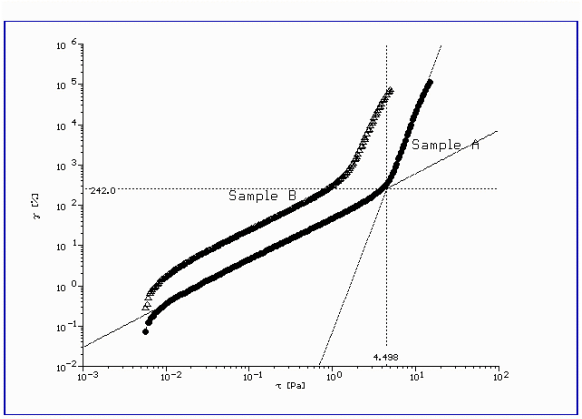

Fig. 2: Determination of the yield point.

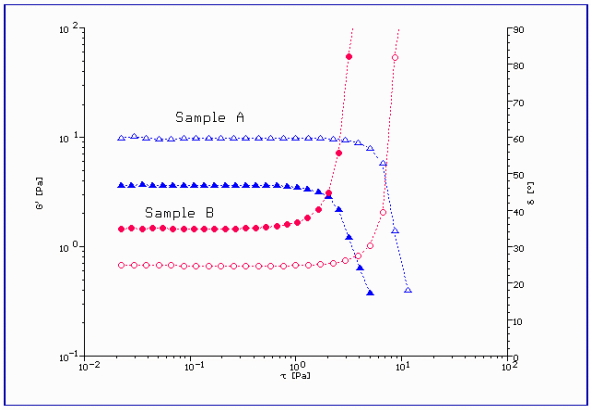

Fig. 3: Amplitude Sweep at 1 Hz.

The yield point 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 1Hz the amplitude was increased. In the diagram modulus G' (triangle symbols), is compared with the phase displacement angle δ (crosses) for both products. The area 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 point of critical amplitude as where the increase of δ is shown, a reading of 2.5 Pa for product A will be shown, for 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 °.

The use of an air bearing CS Rheometer with a cylinder geometry 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.

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