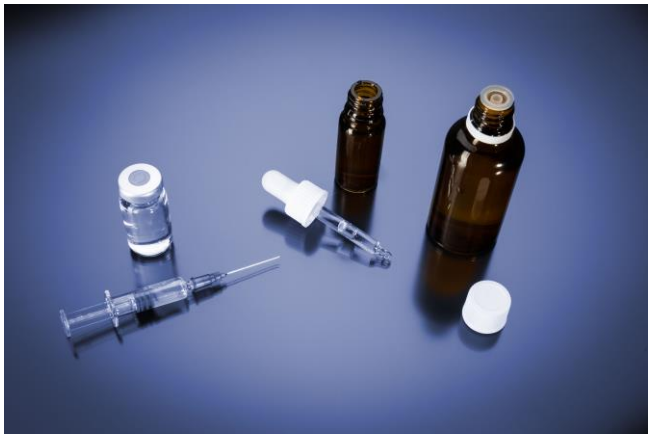
Viscosity Measurements of Methylcellulose Solutions Used for Pharmaceutical Products

Relevant for: Pharmaceuticals, Methylcellulose, Viscosity Curves, Shear-Thinning, Monograph M52230

Rheological measurements are only partially established in the pharmaceutical industry. To determine the viscosity, often only a single point determination is carried out, while the rheological behavior over a certain shear-rate range is not taken into account. The aim of this work was to determine and illustrate flow curves and viscosity curves for methylcellulose in different concentrations and shear rates with an Anton Paar Modular Compact Rheometer (MCR), while meeting the conditions required by Monograph M52230. In addition, the significance of the behavior of the medical product at different shear rates in the respective application areas is discussed.



1 Introduction

Methylcellulose is a commonly-used substance in the pharmaceutical industry.

It is used as a

- gelling agent
- thickener
- suspension stabilizer
- filler in capsules
- binder in tablets
- disintegrant

Methylcellulose is a white, odorless, nontoxic, hydrophilic powder, with good solubility in cold water. It slowly swells to form a colloidal dispersion. The solubility in water decreases with increasing temperature from approx. 50 °C. A viscous gel-like solution is formed (thermal gelling behavior). Thus, the solubility of methylcellulose is very dependent on the water temperature (soluble below 40 °C).

There is a wide range of applications for methylcellulose, extending from very low-viscosity solutions to highly viscous substances. Just a few of the practical applications include drugs such as eye drops, infusion solutions, and gelatin creams, as well as solid powder in tablets.

In eye drops, methylcellulose is expected to contribute to the liquid's ability to wet the entire eye. But in infusion solutions, it should have a viscosity that corresponds with that of blood so that laminar flow in the blood vessels is maintained.

Because of the dynamic nature of the physical properties of methylcellulose, as well as the potentially life-altering effects of the end products that it is included in, the ability to reliably analyze and accurately quantify its viscosity values under various conditions is extremely important.

1.1 Viscosity

Viscosity describes the internal friction of substances. Liquids such as water and oils are ideally viscous, or known as Newtonian liquids. This means the viscosity does not change at different shear rates. However, most liquids and viscoelastic substances actually change their viscosity at different shear rates, showing shear-thinning or shear-thickening behavior. Shear-thinning describes the effect of a decreasing viscosity at higher shear rates. In contrast, shear-thickening materials will display an increasing viscosity at higher shear rates. (1)

Please note: When measured at only a single shear rate or speed, shear-thinning or shear-thickening properties of the sample cannot be determined

For Newtonian fluids, a single point viscosity measurement would be sufficient, since the viscosity does not change over a wide shear-rate range. The situation is different for liquids which do not show Newtonian behavior. If only the viscosity at a certain shear rate is determined, then no statement can be made about the viscosity properties (shear-thinning or shear-thickening) of the substance. Only an analysis over a wide shear-rate range, a multiple point viscosity determination, provides information about the viscosity.

In addition, it should be noted that absolute measuring systems are used for a rheometer, whereas viscometers work with relative measuring systems. The advantage of absolute measuring systems is that absolute values are determined (here viscosity). In contrast to relative measuring systems, absolute measuring systems comply with clearly-defined shear conditions that are defined by standards specific to the measuring systems, such as ISO 3219 and DIN 53019. (1)

2 Experimental Setup and Sample Preparation

2.1 Equipment

The measurements were carried out on a ViscoQC (Figure 1) and on a Modular Compact Rheometer (MCR) from Anton Paar (Figure 2). With the ViscoQC, the measurements were performed with spindle measuring systems; and for the MCR, measurements were performed with a cone-plate measuring system (CP).

In order to confirm the measurement data, double determination was carried out in each case.

2.2 Sample Preparation

Methylcellulose solutions of 1, 2, 3 and 5 $\%_{w/w}$ were prepared as described in Monograph M52230 (2).

A sample mass of 500 g is recommended for measurements with the ViscoQC.

The methylcellulose powder was put into a closable wide-neck bottle according to the concentration, which was then filled up to 500 g with hot distilled water (about 90 °C). The suspension was stirred for 15 minutes at a rotational speed of 450 rpm. Subsequently, the sample was stirred at 450 rpm for 45 minutes in an ice bath held at a temperature of less than 5 °C.

2.3 Setup of the ViscoQC

The rotational speed (Revolution) was dependent on the approximate viscosity of the methylcellulose. The spindle (each labeled with a rotor number) and the rotational speed set for the measurement (Revolution) were used as described in Monograph M52230 and are listed in Table 1.

According to Monograph M52230, the measurements should be carried out at 20.0 °C ± 0.1 °C. Since it is not possible to adjust the temperature of this sample amount (500 g) with the ViscoQC, the temperature of the methylcellulose solutions had to be controlled in a climatic chamber at 19 °C overnight, so that the measurements could be performed at 20.0 °C, as the sample was warmed by the room temperature environment. The temperature was monitored with a Peltier PT100.

Labeled Viscosity [mPa·s]	Rotor Number	Revolution [rpm]
600 - 1400	3	60
1400 - 3500	3	12
3500 - 9500	4	60
9500 - 99500	4	6
> 99500	4	3

Table 1: Spindle (Rotor Number) and rotational speed (Revolution) (rpm) for measuring the viscosity value.

Figure 1: ViscoQC viscometer.

2.4 Setup of the MCR

The measuring systems that were used are listed in Table 2. A P-PTD (Plate-Peltier Temperature Device) was used to control the temperature of the samples to 20.0 °C. This device makes it possible to regulate the temperature quickly (in just a few minutes), and only a small sample quantity of sample (approximately 1 mL) is required.

Note: "CP" indicates a Cone-Plate measuring system with a diameter of 50 mm or 25 mm, respectively.

Methyl-cellulose [%w/w]	Measuring System Used
1	CP50
2	CP50
3	CP25
5	CP25

Table 2: Measuring systems used with the MCR.

Figure 2: Modular Compact Rheometer (MCR).

3 Results and Discussion

3.1 ViscoQC Measurements

Single point viscosity measurements were carried out with the relative measuring set-up and settings as described in M52230 and in section 2.3. The measurements were carried out at 20 °C. The results are displayed in Table 3. As expected, an increasing viscosity can be observed for increasing concentrations. The viscosity increase was about one order of magnitude between the chosen methylcellulose concentrations.

Methyl-cellulose [%w/w]	ViscoQC Viscosity Results [mPa·s]
1	268
2	3729
3	21300
5	296400

Table 3: Viscosity values of different concentrations of methylcellulose solutions measured with a viscometer (ViscoQC).

3.2 Rheological Measurements

Multi-point viscosity measurements with an absolute measuring set-up over a wide shear-rate range were carried out. The shear-rate-dependent viscosities of methylcellulose solutions with different concentrations were investigated and are displayed in Figure 3. The measuring systems used depended on the viscosity and was selected by a visual check of the sample - whether it was aqueous or gel-like (see Table 2).

All methylcellulose solutions displayed the same general behavior. The viscosity was constant at low shear rates and then continuously decreased with increasing shear rates. This is shear-thinning behavior. In the low-shear-rate range there was a region where the viscosity remained constant. This plateau is called the "zero-shear viscosity" range (see Figure 3).

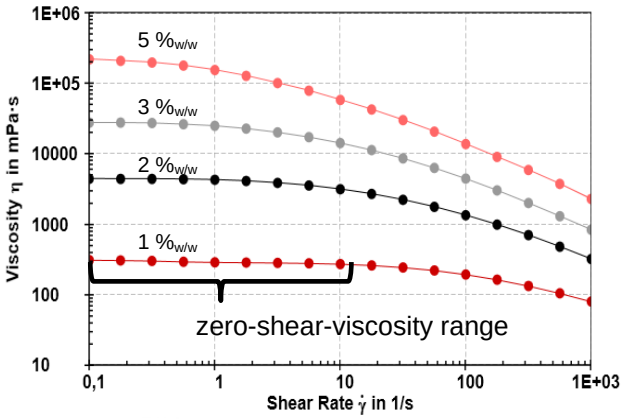


Figure 3: Viscosity curves of the methylcellulose solutions at different concentrations. Dark red 1 %w/w; black 2 %w/w; gray 3 %w/w and light red 5 %w/w.

This behavior can be explained by the fact that the long, non-cross-linked polymer molecules form energetically favorable clusters, counteracting shear-induced disentanglement of the polymer chains when such a substance is at rest or when the shear rate approaches zero.

If the shear rate is increased, then the molecules disentangle and align, and consequently the flow resistance (and therefore the viscosity) decreases. (1) This disentangling effect occurs at higher concentrations even at low shear rates. Thus, with increasing concentration, the shear-thinning behavior already appears at lower shear rates (see Figure 3).

3.3 Relating Single-Point and Shear-Dependent Measurements

Figure 3 showed how important it is to determine viscosity values over a wide shear-rate range. The flow curves measured with the MCR displayed a clear shear-thinning behavior for methylcellulose solutions, which cannot be detected with a single-point measurement.

The viscosity values obtained with the MCR (CP) measuring system were taken from the measuring points in the zero-shear viscosity range (range where viscosity is constant, as can be seen in Figure 3 and Figure 4) and are also listed in Table 4. The viscosity measurements obtained with the viscometer (preset constant rotational speed and with a spindle) are displayed as solid lines in Figure 4.

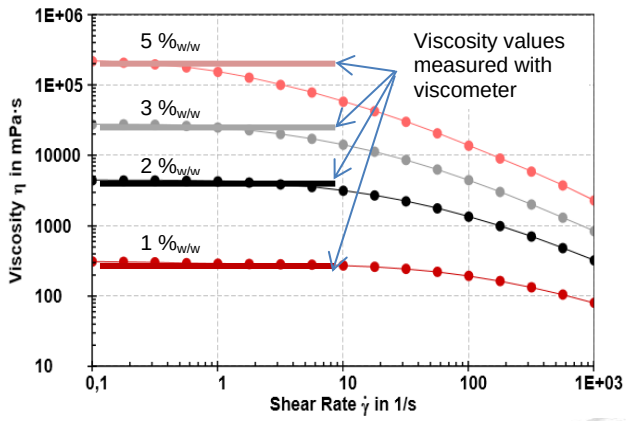


Figure 4: Viscosity curves of methylcellulose solutions obtained with a rheometer (dotted lines) and a viscometer (solid lines). Dark red 1 %w/w; black 2 %w/w; gray 3 %w/w and light red 5 %w/w.

The viscosity values obtained with the viscometer ViscoQC and MCR rheometer measurements are displayed in Table 4. The slight deviation in the viscosity values between the different measuring systems can be explained by the fact that the CP system (cone-plate) is an absolute measuring system, while the spindles are relative measuring systems. The calculation of a shear rate from a rotational speed is only possible with absolute measuring systems.

Due to the large gap (i.e. the gap is not clearly defined) between the spindle and the beaker wall in the viscometer, there are no clearly-defined shear conditions when using relative measuring systems. Therefore it is not possible to calculate the shear rate directly from the rotational speed, making a direct comparison of the results difficult.

Methyl-cellulose [%w/w]	ViscoQC Viscosity Values [mPa·s]	MCR (CP) Viscosity Values [mPa·s]
1	268	289
2	3729	3960
3	21300	21680
5	296400	289890

Table 4: Comparison of the viscosity values of different concentrations of methylcellulose solutions, measured with the viscometer (ViscoQC) and with the MCR with the CP measuring system.

In order to uphold comparability of results, it is also possible to use the relative measuring spindles on the MCR. A suitable adapter can be used to attach the spindle to the MCR.

4 Conclusion

The measurements showed that single-point measurements can give fast results; but they do not necessarily show the whole picture. Especially non-Newtonian liquids like polymer solutions display shear-rate dependent behavior. Therefore rheological tests over a wide shear-rate range can provide essential added information and value.

When a precise determination of viscosity curves is desired, then it is recommended to have:

- ✓ an absolute measuring system (not spindles)
- ✓ the ability to measure over a wide shear-rate range
- ✓ precise temperature control
- ✓ the possibility of measuring only a small sample amount

5 References

1. T. G. Mezger, Applied Rheology
2. Pharmacopeia USP, Monograph M52230

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