Anton Paar

Intrinsic Viscosity of Microcristalline Cellulose for Highest Tablet Quality

Several types of microcristalline cellulose are available on market-depending on the used raw material and production conditions. Tests of purity, intrinsic viscosity and molecular weight,...guarantee the perfect behavior according to the desired application.

Relevant for: pharmaceutical industry, food industry, cosmetic industry, ASTM Test Method D1795 and USP 36 - NF 31, Monograph: Microcristalline Cellulose

1 Introduction

Microcristalline cellulose is a very versatile substance used in the lab. As the name implies, microcrystalline cellulose is basically cellulose and is typically derived from high quality wood pulp.

It is a commonly used excipient in the pharmaceutical industry and has revolutionized tableting because of its unique compressibility and carrying capacity. It compacts well under minimum compression pressures, has high binding capability and creates tablets that are extremely hard yet disintegrate rapidly. Other advantages include low friability, inherent lubricity and the highest dilution potential of all binders.

The chemical composition and physical structure of microcrystalline cellulose depend significantly on the characteristics of the used raw material and the manufacturing conditions. As a result, several types of microcrystalline cellulose are available in the market with different physicochemical and thermal properties. These differences can affect the compactibility and compressibility and subsequently the application of the material.
As a consequence their characterisation must undergo extensive tests for identity, purity, degree of crystallinity, molecular structure and molecular weight (or intrinsic viscosity) to guarantee the behavior of the excipient according to its application.

This application report shows how to measure the intrinsic viscosity of microcrystalline cellulose with the combination DMA 4500 M Density Meter and Lovis 2000 ME Microviscometer Module. The measurement is performed according to ASTM Test Method D1795, the sample preparation according to USP 36 - NF 31, Monograph: Microcristalline Cellulose.

2 Instrumentation

Fig. 1 DMA M Density Meter with Lovis 2000 ME Microviscometer Module

The measuring system shown in Figure 1, comprising a DMA M Density Meter and a Lovis 2000 ME Microviscometer Module for the simultaneous determination of density and viscosity is subsequently described in more detail.

2.1 DMA 4500 M Density Meter

Fig. 2 DMA M Density Meters

The instrument electronically excites the U-tube to simultaneously oscillate at the fundamental resonant frequency and its harmonics. The oscillation

characteristics are measured, with respect to the integrated reference oscillator. The reference oscillator is positioned in close thermal contact with the oscillating U-tube and enables the reference oscillator to compensate for all drifts arising from temperature stress applied to the U-tube. From these measurement results the density is determined with utmost accuracy.

2.2 Lovis 2000 ME Microviscometer Module

Fig. 3 Lovis 2000 ME Microviscometer Module

The Lovis 2000 ME Microviscometer Module measures the rolling time of a ball through transparent and opaque liquids according to the "Rolling Ball Viscometer Method <913>", published in the US pharmacopoeia (USP 36, NF 31).

Via Peltier elements the measured samples are brought to the desired measuring temperature extremely fast and with utmost accuracy. Three inductive sensors measure the rolling time of a metal ball inside an inclined capillary. The measurements can be performed at variable angles, meaning to measure at different shear rates.

The integrated software calculates the kinematic or dynamic viscosity, provided the density value is known.
Out of the rolling times of the solvent and the sample solutions at defined concentrations the relative viscosity and all other polymer specific values (specific viscosity, reduced viscosity, inherent viscosity, intrinsic viscosity, molar mass, K-value) are calculated automatically and displayed on the screen immediately after the measurement.

3 Measurement

For the determination of the intrinsic viscosity the "Lovis Polymer (Single Concentration)" method was used.

When choosing this method, the instrument measures the solvent and one cellulose solution at one defined concentration. For the calculation of the relative viscosity it is possible to select between runtime ratio, dynamic viscosity ratio and kinematic viscosity ratio.

For this application report the dynamic viscosity ratio was used. The densities of the solvent and cellulose solution show a slight difference and should therefore also taken into account when calculating the relative viscosity.

Fig. 4 Polymer Settings - Calculation Method - Dynamic viscosity ratio

For cellulose measurement the calculation of the intrinsic viscosity is done according to **the Intrinsic Viscosity Table of ASTM Test Method D1795** with the **Martin equation**. The k-slope for the Martin calculation formula is 0.3 and has to be entered once in the Polymer Settings window:

Fig. 5 Polymer Settings - Single Point Intrinsic Viscosity Calculations - Martin - k-Slope Settings

3.1 Samples

Carboxymethyl cellulose, fine white powder
Sample Weight: 1.3031 g (conc.: 0.0261 g/mL)

3.2 Solvent

Copper(II)ethylenediamine – Solution
Product Number: A1804
Company: AppliChem GmbH

3.3 Sample Preparation

The sample preparation was performed according to the U.S. Pharmacopoeia and National Formulary USP 36 – NF 31, NF Monograph: Cellulose – Microcristalline Cellulose.

Procedure

Sample: *1.3 g of Microcrystalline Cellulose, accurately weighed to 0.1 mg*

Analysis: *Transfer the sample to a 125 mL conical flask. Add 25.0 mL of water and 25.0 mL of 1.0 M cupriethylenediamine hydroxide solution. Immediately purge the solution with nitrogen, insert the stopper, and shake on a wrist-action shaker, or other suitable mechanical shaker, until completely dissolved.*

3.4 Instrument Settings

Measuring Method Lovis Polymer (Single Concentration)

Measuring Settings:

Measuring Temp.: 25°C
Equilibration Time: 30 s
Measurement Cycles: 5
Manual Angles: 20°, 18° and 15°
Variation Coefficient: 0.3 %
Measuring Distance: Long

Settings for calculation of the intrinsic viscosity:

Calculation Method: Dynamic viscosity ratio
Zero shear scan: deactivated
Concentration unit: g/mL
k-Slope for Martin: 0.3 (according to USP)

Used material:

Capillary diameter: 1.8 mm
Serial No.: 18050493
Ball diameter: 1.5 mm
Ball material: Gold coated
Batch No.: 81406/122587/Au01/4
Ball density: 7.88 g/cm^3

3.5 Filling of the DMA 4500 M and Lovis 2000 ME

For this application report the instruments were filled by the manual flow-through filling method (see Fig.1). But for higher sample throughput or if automatization is required the Xsample 122 sample changer upgraded with the "Retrofit Kit for Xsample 122 Chemical" will be the best choice.

3.6 Cleaning

To ensure the proper function and accuracy of the instruments, thorough and regular cleaning is essential. After measurement the capillary and U-tube were first rinsed with cupriethylenediamine, followed by thorough rinsing with water. As a last step the capillary and U-tube were rinsed with ethanol and dried with the internal air pump. Once a week, to remove possible cellulose deposits, Mucasol® can be used. As Mucasol® may attack the glass surfaces it should not be used in concentrations higher than 3% solution. Additional care has to be taken to prevent foam production, to which Mucasol® has a tendency. Due to these two reasons (glass attack and foaming) a thorough rinse with water is required after Mucasol® cleaning. If there are still cellulose residues after Mucasol® treatment the capillary can be cleaned additionally with diluted sulfuric acid.

4 Calculation of the Polymer/Cellulose Specific Values

4.1 Calculation of the Relative Viscosity

When using the Microviscometer the relative viscosity can directly be calculated by the runtime of the solution (t) and the runtime of the solvent (t_0). But this relation only works if the density of solvent and polymer solution do not differ too much. For this application report we calculated the relative viscosity by the dynamic viscosity ratio. Due to the high concentration of the cellulose solution, the densities of the solvent and solution are significantly different (see 5 "Results").

Relative viscosity:

$$\eta_r = \frac{\eta}{\eta_0} = \frac{t}{t_0}$$

4.2 Calculation of the Intrinsic Viscosity

For the calculation of the intrinsic viscosity the Martin equation was used:

$$\log[(\eta_{rel}-1)/c] = \log[\eta] + k[\eta]c$$

where k = 0.3

5 Results

5.1 Densities

Density cupriethylenediamine (at 25°C)	1.0830 g/cm^3
Density of cellulose solution (at 25°C)	1.0475 g/cm^3

5.2 Measurement at an inclination of 20°

Dynamic viscosity cupriethylenediamine	1.722 mPa.s
Dynamic viscosity cellulose	16.41 mPa.s
Relative viscosity	9.53
Intrinsic viscosity Martin	123.87 mL/g

5.3 Measurement at an inclination of 18°

Dynamic viscosity cupriethylenediamine	1.704 mPa.s
Dynamic viscosity cellulose	16.41 mPa.s
Relative viscosity	9.63
Intrinsic viscosity Martin	124.60 mL/g

5.4 Measurement at an inclination of 15°

Dynamic viscosity cupriethylenediamine	1.690 mPa.s
Dynamic viscosity cellulose	16.46 mPa.s
Relative viscosity	9.74
Intrinsic viscosity Martin	125.40 mL/g

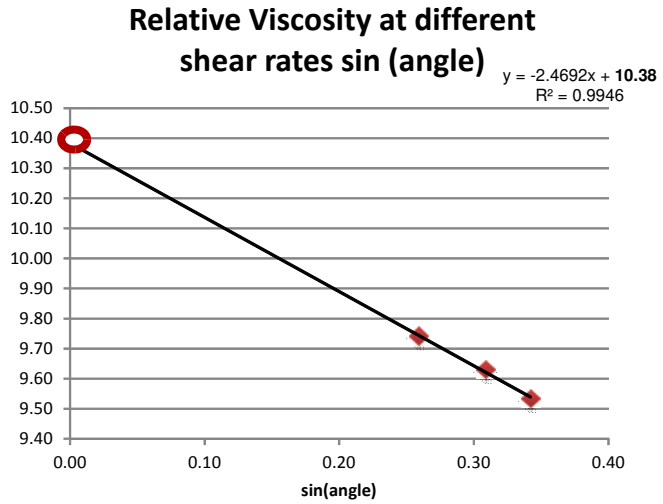

Fig. 6 Relative viscosity at different angles (15°,18° and 20°)

The red mark is the relative viscosity at a hypothetical zero shear rate: 10.38

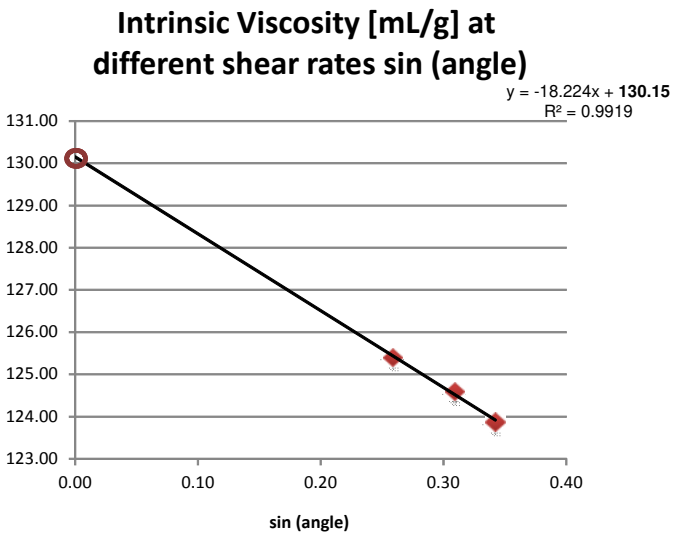

Fig. 7 Intrinsic viscosity (Martin) at different angles (15°, 18° and 20°)

The red mark is the intrinsic viscosity at a hypothetical zero shear rate: 130.15 mL/g

6 Conclusion

By using the Lovis 2000 ME and DMA M with the integrated polymer software, the results are calculated automatically after the measurement and displayed on the main screen. There is no need for an external PC and software. The Lovis 2000 M can be operated also stand-alone without simultaneous density measurement.

The Lovis 2000 ME with its many special features and polymer software is the ideal instrument for polymer solution investigations:

- Due to the small capillary sizes only little sample volume is required (starting from 100 µL).
- The variable inclination angle of the measurement allows the variation of the shear rate.
- Due to the closed system any contamination and evaporation can be avoided.
- The instrument is highly modular and easily connected to other Anton Paar instruments; it can be combined with DMA M Density Meters for automated calculation of dynamic and kinematic viscosity.
- It can also be combined with an Xsample sample changer for automatic filling and cleaning of the capillary and measurements with high sample throughput.

Contact Anton Paar GmbH:

Tel: +43 316 257-0
Fax: +43 316 257 257
support-visco@anton-paar.com
www.anton-paar.com

Appendix A – What is Microcristalline Cellulose

Microcrystalline cellulose $(C_6H_{10}O_5)_n$ is refined wood pulp. It is a white, free-flowing powder. Chemically, it is an inert substance, is not degraded during digestion and has no appreciable absorption. In large quantities it provides dietary bulk and may lead to a laxative effect.

Microcrystalline cellulose is a commonly used excipient in the pharmaceutical industry. It has excellent compressibility properties and is used in solid dose forms, such as tablets. Tablets can be formed that are hard, but dissolve quickly. Microcrystalline cellulose is the same as cellulose, except that it meets USP standards.

It is also found in many processed food products, and may be used as an anti-caking agent, stabilizer, texture modifier, or suspending agent among other uses.

A.1 Producing Microcristalline Cellulose

Processing of the cellulose microfibrils begins with shredding the sheets of high purity alpha grade pulp. The shredded pulp is immersed in hot bath of mineral acid that dissolves the amorphous regions of the microfibrils while leaving the microcrystalline segments intact. The object is to break down the long polymer chains. Hydrolysis is carried to the point where a leveling off degree of polymerization (LODP) is achieved. Consistency in LODP is checked routinely by quality control personnel.

Following hydrolysis, chemicals and impurities are removed through a water-washing step.
This is followed by spray drying. The slurry is sprayed through hot air jets to evaporate the water. This process produces particles of the desired size and moisture content.

The product quality is directly tied to various parameter of the process in terms of time, temperature, pressure and purity of materials and the manufacturing environment.

A.2 Drug Release Characteristics depending on the Intrinsic Viscosity of the Microcristalline Cellulose

Hydrophilic matrix tablets are prone to mechanical stress while passing through the gastrointestinal tract, which may result in inappropriate drug-release characteristics.

The intrinsic viscosity and consequently the molar mass are physical polymer properties that can be correlated with the mechanical susceptibility of swollen matrix tablets in the gastrointestinal tract. The intrinsic viscosity has a major influence on the water uptake, kinetics and erosion rate and thereby determines the robustness during periods of increased physical stress in the gastrointestinal tract. The viscosity of the nascent gel layer can be adjusted by using different viscosity grades of the polymers and by varying the amount of the polymer in the tablet bulk.

The intrinsic polymer viscosity is correlated specifically with the mechanical susceptibility (MS) of matrix tablets. The term "mechanical susceptibility" refers to the decreased integrity of the swollen gel layer of matrix tablets after the application of mechanical stress. The more pronounced or higher the mechanical susceptibility of the gel layer, the faster the release of the incorporated drug substance after mechanical manipulation. An increased intrinsic viscosity value results in a decrease of mechanical susceptibility of the swollen gel layer.