Viscosity Testing of Solutions and Suspensions for Litigation Purposes

A technical primer for attorneys

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1. Introduction: What is Viscosity?

Viscosity is a property of a fluid that quantifies the fluid's resistance to flow. In simple terms, a fluid with a high viscosity (sometimes called a "thick" fluid) is a fluid that requires a lot of effort to move (like mashed potatoes) while a fluid with low viscosity (sometimes called a "thin" fluid) flows easily with small effort (like air or water).

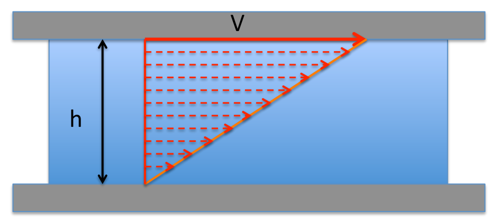

Figure 1: *Definition of shear viscosity – parallel plate geometry. The figure displays a velocity gradients V/h between two parallel plates, with the top plate moving with velocity V.*

In its simplest form, viscosity is defined using the simple shear flow between two parallel plates (Figure 1). The parallel plate geometry is one of the most common systems used to measure viscosity, and it is the conceptual basis of the concentric cylinder rheometer, one of the most common types of instruments. In this simple geometry, the fluid is "sandwiched" between two parallel flat plates. The top plate moves at a constant velocity V, the lower plate is stationary, and points within the fluid move at a velocity proportional to their distance to the top plate. Experiments show that a force is required to maintain this movement. The force F is proportional to the area A of the plates and the velocity V of the top plate, and inversely proportional to h, the distance between the plates. In simple mathematical terms,

$$F = mAV/h,$$

Or alternatively,

$$F/A = t = m(V/h) = mg$$

Here, $t = F/A$ is the shear stress, $g = (V/h)$ is the velocity gradient, and the shear viscosity m[1] is the proportionality constant between the stress and the velocity gradient.

[1] Extensional flow rheometers are also used in scientific research to measure the "extensional viscosity" of a material. However, such measurements appear much less often in patents and are not discussed here in the interest of brevity.

Fluids exhibit two kinds of behavior: Newtonian fluids, which are simpler fluids such as air, water, wine, glycerin, and gasoline, have viscosities that are independent of the shear rate, and typically depend only on temperature. Non-Newtonian fluids, which are more complex fluids such as ketchup, polymer solutions and melts, slurries, foams, and pastes, have viscosities that depend not only on temperature but also on the shear rate. For such fluids, the measurement method can have strong effects on the results.

2. How is Viscosity measured?

Entire books have been written about shear viscosity measurement (a component of a field of physics called rheology) and its implications. Briefly, shear viscosity is often measured (or estimated) using two main types of devices:

Viscometers are older instruments where the flow has different shear rates in different locations. Such devices typically rely on a correlation between the instrument's measurement (typically the torque required to rotate a shaft, or the time required by the fluid to flow thorough a specified volume) and fluids with known viscosity (called "viscosity standards"). This correlation is provided by the instrument manufacturer or in some cases is established by the user, and then is used to estimate the viscosity of an unknown sample.

Controlled Shear Rheometers are more modern instruments designed to have a uniform velocity gradient (and therefore a uniform shear stress) everywhere in the sample. The most common rheometers are the concentric cylinder type and the cone and plate type. In such devices, much more accurate measurements are possible for all kinds of fluids.

This has practical implications:

- For a Newtonian fluid with a viscosity that is independent of shear rate, the value of the viscosity is the same throughout the instrument whether the shear rate is constant or not. For such fluids, a properly calibrated viscometer can provide an accurate viscosity measurement.
- However, if the fluid is non-Newtonian, using a viscometer with different shear rates at different locations often leads to inaccurate results, because the sample, itself, will have different viscosities at different locations, and this variation, itself, will be different for different fluids.
- In a rheometer, because the shear rate is the same everywhere, the fluid viscosity is the same everywhere (whether the fluid is Newtonian or non-Newtonian), and an accurate, meaningful measurement can be obtained (subjected to a few additional constraints, some of which are discussed below).

3. Why are viscosity measurements important for patent prosecution or patent litigation?

Viscosity is a key characteristic of a fluid, and as such, viscosity measurements appear in patents in different situations in a variety of ways.

- Viscosity is used as a defining attribute of a product ingredient. For example, many common polymers such as Polyethylene oxide (PEO), Polyvinylpyrrolidone (PVP), substituted celluloses, polyacrylates, etc., are used in the manufacture of drugs, paint, toothpaste, and a myriad other products. The grades of these ingredients are often selected or specified based on their viscosity in their solutions in various solvents.
- Viscosity, as an attribute of a solution or a suspension, is sometimes used to define the scope of an invention. Examples include language such as "using a *thickening agent* such that the resulting solution (or suspension) will have a viscosity of at least 100 centipoises". Other rheological behaviors, such as "shear thinning" (thixotropic) viscosity is often required.
- Even when it is not directly or explicitly mentioned in the patent claims, viscosity is often a defining attribute of an invention, determining, for example, whether particles in a suspension will settle at a certain rate, or whether fluids will flow though a needle at a certain flow rate (or at all), or whether a film can be cast, or whether a melt can be extruded or injection-molded, or topical preparations can easily spread on skin. In such cases, regardless of whether viscosity is explicitly mentioned in patent specifications or claims, values of viscosity can play an important role in arguments discussing whether two processes or two products are equivalent.

Viscosity measurements have been standardized by entities such as the ASTM and, in some cases, by specific industry organization (for example, the US Pharmacopeia) for certain applications. Almost universally, the literature will require the user to specify the conditions of the measurement, including temperature, instrument, and test conditions. In many cases, for specific materials or specific instruments, the standards (and the published literature) will advise the technician to implement additional controls, for example, to ensure the instrument is properly calibrated, to use a certain amount of fluid, to perform the measurement within a certain range of torque values or flow rates, etc. A detailed list of methods and specifications is beyond the scope of this brief note, but the reader is cautioned to examine background information before selecting and implementing a method. In our experience, viscosity measurements required caution and care.

4. Viscosity testing in pharmaceutical patent litigation

In our experience, viscosity plays an important role in pharmaceutical patent litigation. This is due to several reasons, some of which have already been mentioned:

- The purported "inventive concept" of a formulation or a product might include the use of an ingredient having a specific value of viscosity under a certain set of conditions (for example, PEO grades used in opioid formulations, Polaxamer with different molecular weights are used dermatological preparations or topical ophthalmic products, etc.).

- The purported "inventive concept" of a product might require the pharmaceutical product to exhibit a certain viscosity under certain conditions (for example, a solution might need to have viscosities in certain ranges to be "injectable"; a pediatric syrup might need to exhibit a certain viscosity to create the desired "mouth feel"; an ophthalmic ointment might require a certain viscosity to provide relief to dry eyes; the alteration of rheological properties of suppositories, which are mainly made from fatty bases, at rectal temperatures may affect the release profile of drugs from these suppositories, etc.)

Different aspects of pharmaceutical litigation can use viscosity test results:

- Literal infringement: when the patent claims contain explicit language regarding viscosity values of ingredients or products, tests performed on an accused product can support or rebut arguments of literal infringement (or non-infringement).

- DOE infringement: even when explicit language is not present in the claim, viscosity test results can be used to support arguments that two ingredients, two formulations, or two manufacturing processes, are "equivalent", for example, to state that the accused manufacturing process is insubstantially different from the patented process, or whether the accused process performs substantially the same function in substantially the same way to obtain the same result. For example, in a case where the product performance required preventing the settling of a suspended particle, it was argued that an accused product containing a different gum was "equivalent" to an invented product because the accused product contained an ingredient that was playing "the same function" (i.e., thickening agent), in the same way (by using a viscosity increasing agent) to obtain "the same result" (prevention of settling)[2].

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[2] We note in passing that other fluid properties, such as yield strength, may play the key role regarding whether particles in a suspension would settle.

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- Invalidity due to anticipation or obviousness: if the claim contains explicit language about a viscosity value, or similarly, a function that would require a certain value of viscosity to define the "product of the invention", viscosity testing results can demonstrate that prior art formulations were already achieving, or could be expected to achieve, the "inventive" result (such as preventing settling of suspended particles, enabling or preventing injectability, etc.)

- Invalidity due to indefiniteness: as mentioned, the viscosity test can be performed in a variety of equipment, and results can depend strongly on how the test was performed.

    - For simple Newtonian fluids, viscosity values can depend strongly on temperature. If the material tested is a solution, composition is also a very significant variable, including the concentration of all dissolved ingredients, the composition of the solvent, the presence of salts or other solutes, etc.
    - For more complex non-Newtonian fluids, viscosity values will also depend on the shear rate and often on the instrument utilized to measure viscosity, the method used to prepare and store the samples, and a number of other variables.

In our experience, patents often neglect to disclose all the relevant conditions, giving rise not only to indefiniteness but sometimes also lack of written description arguments.

5. Viscosity testing in other types of disputes

Viscosity can also play a key role in the control of a manufacturing process. Viscosity of materials during processing is often measured to determine whether a process is proceeding according to specifications. A common situation is encountered during the coating of pharmaceutical tablets, where viscosity determines how well a coating suspension can be sprayed, whether tablets will stick to one another, and whether an adequate film can be formed.

Sometimes the measurement of viscosity is indirect. For example, when the measurement is the torque required to operate an extruder or an impeller, or when the measurements is the pressure drop required to maintain a certain flow rate, the physical quantity that is really being monitored is actually the fluid viscosity, because torque and pressure drop (and many other observed quantities) are directly proportional to viscosity. In these situations, viscosity values of samples of the material obtained during or after processing might indicate whether a process was performed incorrectly.

Viscosity determination is extremely critical in some pharmaceutical products, for example *in situ* gels, which are liquid preparations before use and become gels after application to the body. Gelation occurs due to change in some conditions such as pH or/and temperature (2). For example, measurement of the rheological properties, including gelation temperature, is an essential criterion to evaluate in-situ thermo-sensitive gels containing Polaxamer (3).

Viscosity measurements also play a role in quality control for a manufactured product. Paints, for example, must have viscosities in a certain range in order to form appropriate films. Engine lubricants must have viscosities in specific ranges to prevent damage to equipment. A substantial decrease in viscosity during processing can be an indication of molecular degradation of a polymer. In these situations, viscosity values displayed by a product might indicate whether a product is defective and might have caused harm to the user.

6. Analyzing and comparing viscosity test results

In almost every situation involving viscosity test results (whether from new test results or from historical data from documents, laboratory notebooks, etc.), the need will emerge to compare viscosity values, either with other test results, or with pre-determined specifications. Such comparisons can be performed in multiple ways, to various degrees of statistical rigor. Statistical methods to perform comparisons (such as the t-test, ANOVA, etc.) are extensively described in the literature and will not be discussed here.

However, an important issue worth mentioning is that it is always important to evaluate whether the data being compared **is actually comparable**. Given the number of factors that can affect viscosity test results, it is critical to ensure that all relevant factors have been properly controlled, and that the methods are equivalent, or in the alternative, that they are producing equivalent data. For non-Newtonian fluids, different viscometers often generate different results, even for the same samples. Even when using rheometers, different tests can produce different results. Thus, proper selection of measurement method is essential and critical to the reproducibility, reliability, and comparability of the obtained results.

7. Common pitfalls and errors in performing viscosity measurements

When viscosity test results are used in litigation, in addition to the issues already mentioned, a number of common criticisms can emerge, including:

- *Was the instrument properly calibrated?* Both viscometers and rheometers require calibration, for a variety of reasons.
    - Instruments can age or sustain damage from repeated use, and calibration is essential to ensure that they are generating correct measurements.
    - As mentioned, viscometers rely on calibration measurements to create correlations between the measurement and the viscosity of an unknown sample.
    - Rotational rheometer results, when obtained at very low shear rates, can be affected by even very small irregularities in the shape of the rotating element or its position with respect to the stationary vessel. Rotational mapping is a form of calibration that can be used to reduce the impact of this source of error.

- *Was the test properly performed?* A number of errors can occur during test performance:
    - Most instruments used to test viscosity have an operational range (a range of viscosity values) of maximum accuracy. While in many cases, the ranges recommended by instrument manufacturers are conservative and accurate measurements can be obtained outside the recommended range, this issue needs to be checked for the specific situation using viscosity standards.
    - Many instruments can use a variety of attachments to increase the range of viscosities that can be tested; for example, rotational rheometers often allow the use of multiple assemblies. Selection of the proper assembly is important to the accuracy of the measurement. Moreover, for some instruments, whenever the assembly is replaced, a new rotational mapping is required to maximize accuracy.
    - It is important to ensure that the correct sample volume was used. A partially filled instrument can cause erroneous results
    - Similarly, large amounts of bubbles must be avoided, since air (and gases in general) has much lower viscosity than fluids and can cause erroneous results
    - Also it is important to ensure that a sufficient, but not excessive, amount of time was used to perform the test. For low shear rate tests, it can take a long time for the sample to equilibrate during testing; measurements taken at very short times can be erroneous. Likewise, excessive testing times, in particular at higher temperatures, can cause sample degradation or sample evaporation, both of which are undesirable and detrimental to the quality of the data.

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- *Was the proper test implemented?* Since viscosity tests can be implemented in a variety of ways, often leading to quite different results, a common concern is whether the test has been implemented in a fair and representative manner, or alternatively, whether the specific method selected is idiosyncratic and is selected to achieve a pre-determined result. A common example is encountered in shear thinning fluids (such as polymer solutions), where the measured viscosity can vary over several orders of magnitude depending on the shear rate used during testing.

6. Resources Available at Acumen Biopharma

Our experts have extensive experience regarding the role of viscosity testing in process performance, product formulation and quality control, and the various uses of viscosity data in litigation. We can assist attorneys in understanding the role of viscosity measurements in a given case, both for background purposes or for litigation purposes.

When tests are needed, we can typically specify the test that is required, and perform the test, in as little as two weeks. We have developed protocols to support the selection of the proper test for a given purpose. Given the wide range of issues relevant to viscosity test results and their use in litigation, Acumen Biopharma maintains service agreements with multiple academic and industrial laboratories to enable us to specify and perform a wide variety of viscosity tests quickly and reliably. Our service providers include DEA licensed labs that can handle controlled substances.

Moreover, since our experts have assisted many law firms in analyzing and performing test results, our protocols include effective methods for ensuring data quality and integrity, including chain of custody protocols, equipment and method calibration, and extensive documentation practices that include electronic record keeping, laboratory notebooks, photographs and videos.

We are always happy to discuss technical issues. Many more details are available upon request. For more information, please contact us.

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