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# ADVANCEMENTS IN CHARACTERIZING THIXOTROPIC PROPERTIES FOR ENHANCED DRUG DELIVERY SYSTEMS: A COMPREHENSIVE REVIEW

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## ABSTRACT

The way a substance's thickness changes under stress, known as thixotropy, is vital for many drug products like liquids and creams. It means a substance gets thinner when stirred or shaken, then thickens again when left still. This behavior is key to keeping medications stable, ensuring consistent doses, and controlling how quickly the drug is released into the body, which improves how well the medicine works and how easy it is for patients to use. Thixotropy is typical in fluids that don't behave like water, where thickness changes with force. The opposite, where a substance thickens with stress (rheopexy), also matters in some drug formulations. To measure thixotropy, scientists use both older and newer methods. Older methods, like hysteresis loops, assess the energy needed for structural changes, but they have limitations. Newer techniques, such as SAOS and 3ITT, offer more precise measurements of how the substance breaks down and recovers. SAOS looks at how materials react to small stresses, while 3ITT examines recovery by applying different stress levels. Incorporating real-time monitoring through PAT has transformed how thixotropy is managed in drug manufacturing. Tools like in-line viscometers and Raman spectroscopy allow for continuous quality checks, ensuring consistent batches and optimized processes. Regulatory bodies like the USFDA encourage PAT to improve process understanding and maintain high quality. Real-time monitoring of thickness changes and structural recovery has boosted manufacturing efficiency, reduced errors, and increased product reliability. For example, gels made with methylcellulose show structural recovery, which is essential for controlled drug release. This underlines the importance of detailed analysis for creating effective drug formulations. Future improvements in thixotropy analysis will likely include combining real-time monitoring with machine learning for better quality control. Combining traditional and modern tools will provide a deeper understanding of thixotropy in complex drug systems, enhancing stability, manufacturing, and patient outcomes. This overview examines thixotropy in drug formulations, covering measurement techniques, applications, and the role of PAT in quality control. By blending classic and innovative monitoring tools, the pharmaceutical industry can achieve more accurate formulation development, highlighting thixotropy's critical role in drug design and delivery.

**KEYWORDS:** Thixotropy, PAT Tools, Newtonian, Non-Newtonian, Viscosity.

## INTRODUCTION

The determination of Thixotropy is crucial in ensuring the stability and consistency of pharmaceutical suspensions, gels, and creams, allowing for controlled drug release. Thixotropy is a complex rheological behavior that has drawn attention due to its relevance in industrial processes, product formulation, and biological systems. It is characterized by a decrease in viscosity when subjected to shear stress and a gradual recovery of viscosity when the stress is removed. This phenomenon is significant in various fields, including material science, rheology, and industrial applications, as it influences the flow behavior and stability of numerous products such as paints, cosmetics, and pharmaceuticals. This article provides a comprehensive introduction to thixotropy, its fundamental principles, methods for its determination, and a discussion of recent research developments and integration of process analytical technology in the determination of the thixotropy and USFDA Regulatory Guidelines for PAT.

### a) Thixotropy

Thixotropy is the property of certain fluids and gels of becoming thinner when a constant force is applied and after reduction of the force the viscosity recovers fully to the initial state in an appropriate period of time.[1,2] Thixotropy is a reversible, isothermal, time-dependent decrease in the apparent viscosity when a material is subjected to increased shear rate. The reversibility of the process results that the viscosity recovers, i.e. Structure builds up, again when the shear rate is eliminated or reduced.[3] The term thixotropy is derived from the Greek

words thixis (to touch) and trepo (to change), which reflects the property's nature of changing its viscosity when subjected to external forces.[4] Thixotropy in pharmaceutical products is vital for ensuring product quality, efficacy, and patient compliance. With advancements in rheological testing methods, pharmaceutical scientists can better design formulations with desirable thixotropic properties this property is observed in certain non-Newtonian fluids or gels. Non-Newtonian fluids are fluids where the flow curve is not linear or does not pass through the origin are non-Newtonian fluids.[5] Many fluids do not demonstrate a simple relationship between shear rate and shear, for example, colloidal solutions, emulsions, liquid suspensions, ointments molten polymers, paints and varnishes, building materials, and food.

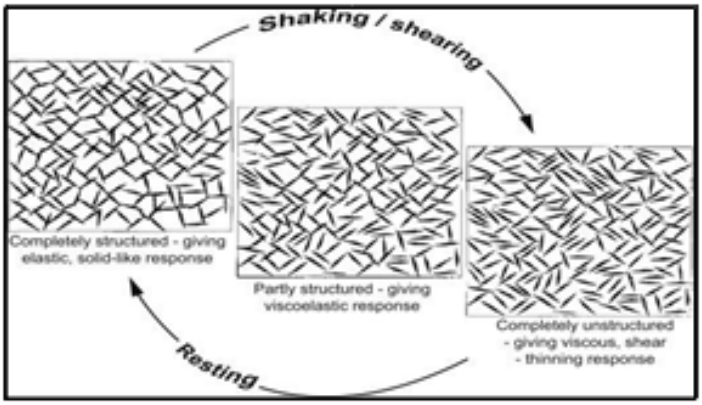
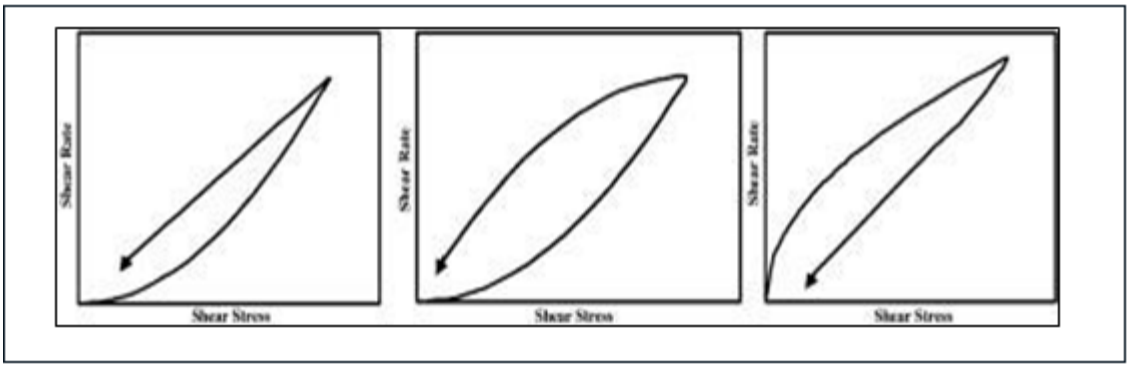



**Figure No. 01: Thixotropic Behavior of Material.**

Non-Newtonian fluids are of three types
1. Plastic fluid
2. Pseudoplastic
3. Dilatant




**a) pseudoplastic** **b) Dilatant** **c) Plastic**

**Figure No. 02: Graphical representation of thixotropy in Non-Newtonian fluid.**

**Figure (a):** Thixotropy is the property exhibited by the pseudoplastic systems which exhibit the time-dependent change in the viscosity. Thixotropic systems demonstrate a decrease in viscosity with time under the constant shear. An enhancement of shear due to progressive breakdown of the structure of liquid and further rebuilding of the structure due to Brownian motion, which makes the particles move to their most favorable positions from a structure entropy perspective, is assumed to be the reason for pseudoplasticity.

**Figure (b):** The systems, whose viscosity increases with an increase in the rate of shear, as shown in, are called as shear thickening systems (e, also known as dilatants). This property is exhibited by dispersions containing high percentage of small, deflocculated particles, for example clays, stumes, suspensions of starch in water, aqueous glycerin or ethyelene glycol.

**Figure (c):** In case of plastic materials, it is observed that there is no flow until it reaches the yield value as shown in. When stress above the yield value is applied, they exhibit free flowing liquid nature. Materials exhibiting this type of flow property are also termed as Bingham Bodies.

**B. Anti-thixotropy or negative thixotropy**

Ant thixotropy, also known as rheopexy, is the opposite of thixotropy. It describes a time-dependent increase in viscosity when shear stress is applied. Unlike thixotropic materials, which become less viscous under stress, anti-

thixotropic materials become more viscous as they are subjected to shear.[6,7]

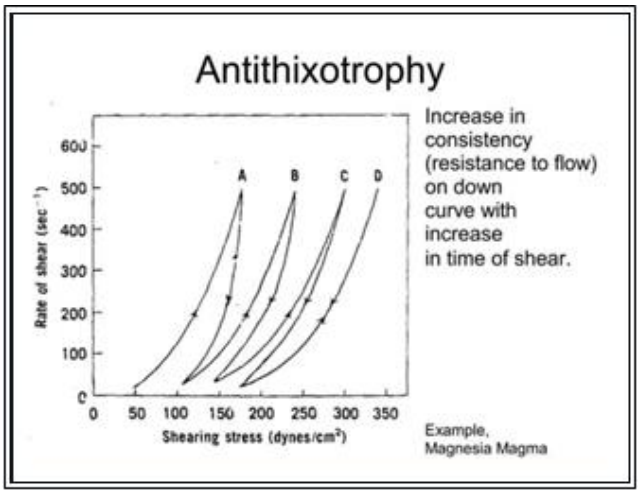



**Figure No. 03: Graphical representation of Antithixotropy.**

This increase in thickness or resistance to flow with increased time of shear was observed in the rheologic analysis of magnesia magma. It was detected at shear rates of greater than 30 sec; below 30 sec the magma showed normal thixotropy, the downcurved appearing to the left of the upcurve. anti thixotropy had been reported by other investigators but not in pharmaceutical systems. It was observed that when magnesia magma was altered-nately sheared at increasing and then at decreasing rates of shear, the magma continuously thickened (an increase in shearing stress per unit shear rate) but at a decreasing rate, and it finally reached an equilibrium state in which further cycles of increasing-decreasing shear rates no longer increased the consistency of the material. The antithixotropic character of magnesia magma is demonstrated in Figure No. 03, Rheogram of magnesia magma showing antithixotropic behavior. The material is sheared at repeated increasing and then decreasing rates of shear. Furthermore, the study of time-dependent shear thickening is also crucial in areas such as drug delivery systems and biomedicine, where the control of fluid dynamics is necessary for the effective transport of therapeutic agents.[8,9]

**Method of Thixotropy Determination**

**1. Traditional method**

**a. Hysteresis loop method**

The hysteresis loop method is used in rheological studies to understand thixotropic behavior, which refers to the time-dependent decrease in viscosity when a material is subjected to shear stress and the recovery of viscosity once the stress is removed. Thixotropy is characteristic of materials like gels, paints, and certain biological fluids, which have an internal structure that breaks down under shear and reforms when at rest.[10,11]

**Principle**

The principle of the hysteresis loop method is based on applying a controlled shear rate or shear stress to a material, increasing it gradually to a peak value, and then reducing it back to zero. This process creates a loop when plotting the shear stress against the shear rate, where the loop's area represents the energy required to break down and rebuild the structure of the material. The larger the area, the more thixotropic the material is, as it signifies greater structural breakdown under shear and slower recovery.[12,13]

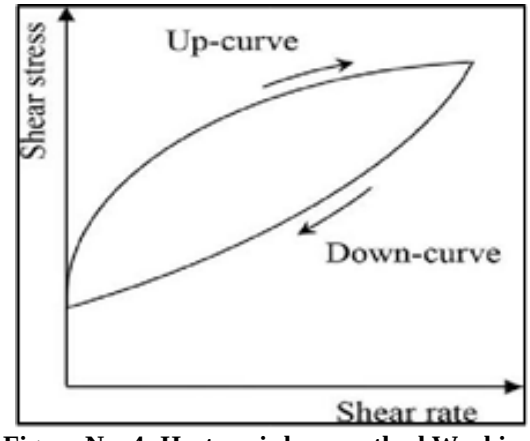



**Figure No. 4: Hysteresis loop method Working.**

**1. Preparation of the Material**

The material, such as a gel, paste, or fluid, is placed in a rheometer. The rheometer should be calibrated and equipped with a suitable measuring geometry, such as a cone plate or parallel plate, depending on the material type. The temperature is maintained constant throughout the testing process since temperature fluctuations can influence viscosity and thus thixotropic behavior.

**2. Shear Rate Ramp-Up**

A shear rate (or shear stress) is gradually increased from zero to a predefined maximum value. This process is conducted at a controlled rate to avoid introducing sudden changes in the material's structure. As the shear rate increases, the viscosity of the material decreases due to structural breakdown, which is common in thixotropic systems. This process is known as the "upward curve" and reflects the breakdown of internal bonds and microstructures.[14,15]

**3. Shear Rate Ramp-Down**

After reaching the peak shear rate, the ramping process is reversed, gradually reducing the shear rate back to zero. This phase records the "downward curve" as the material starts to rebuild its structure and regain its viscosity. The recovery rate during this phase reflects how quickly the internal structure reforms once the external shear is diminished. It provides insights into the stability and resilience of the thixotropic structure**.**

**4. Formation of the Hysteresis Loop**

The data from both the ramp-up and ramp-down phases are plotted on a graph with shear stress (y-axis) against shear rate (x-axis), creating a loop. The area enclosed within this loop represents the degree of thixotropy. A larger loop area indicates a greater degree of thixotropy, meaning the material has undergone significant structural breakdown during shear and slower recovery when shear is removed. Conversely, a smaller area indicates less energy loss and faster recovery.[12,14]

**5. Calculation of the Thixotropic Index**

The thixotropic index can be quantified by calculating the area of the hysteresis loop. This area corresponds to the energy dissipated during the structural breakdown and recovery process [14]. For better comparison across different materials or testing conditions, the thixotropic index can be normalized by dividing the loop area by parameters such as the maximum shear rate, stress, or testing time.[15]

**Advantages of the Hysteresis Loop Method**

**Direct Visualization of Thixotropy:** This method provides a clear visual representation of how the material's structure responds to changes in shear rate, making it easier to analyze thixotropic behavior.

**Quantitative Measurement:** The area of the hysteresis loop allows for a quantitative assessment of the energy involved in structural changes, enabling a direct comparison between different materials.

**Applicability to Various Materials:** The hysteresis loop method can be applied to a wide range of materials, including gels, pastes, and suspensions, making it versatile for industrial and research applications.

**Disadvantages of the Hysteresis Loop Method**

**Sensitivity to Test Conditions:** The results are highly sensitive to the testing conditions, such as ramp rate and temperature. Variations in these parameters can significantly impact the hysteresis loop area, leading to challenges in standardization.

**2. Non-equilibrium Measurements:** The method involves ramping up and down shear rates, which are non-equilibrium conditions. This can sometimes limit the understanding of steady-state behavior and recovery times.

**Interpretation Complexity:** The interpretation of the loop area requires expertise, as different loop shapes and sizes can indicate different material behaviors under similar conditions.

**Cup and Bob Method for Thixotropy Determination**

The **cup and bob method** are a traditional and widely used technique for measuring the thixotropic and rheological properties of pharmaceutical products. This method provides a detailed analysis of viscosity changes under shear stress over time, making it ideal for studying materials like creams, gels, and suspensions.

**PRINCIPLE**

The cup and bob viscometer is based on the measurement of torque exerted by a cylindrical spindle (bob) rotating within a concentric stationary cup containing the sample. As the bob rotates at controlled shear rates, the resistance to motion (shear stress) is measured. This resistance is proportional to the viscosity of the material. The method allows for determining time-dependent viscosity changes, enabling the observation of thixotropic behavior characterized by structural breakdown and recovery under shear. The hysteresis loop generated during the shear rate ramp-up and ramp-down provides quantitative data on the material's behavior, making the cup and bob method invaluable for precise rheological studies.[18,19] The principle behind the cup and bob method ensures accurate viscosity measurements by maintaining uniform shear distribution across the sample. The geometry and spacing between the bob and cup ensure consistent results, making it suitable for both Newtonian and non-Newtonian materials. This method remains a gold standard for evaluating pharmaceutical formulations requiring controlled rheological properties.[17]

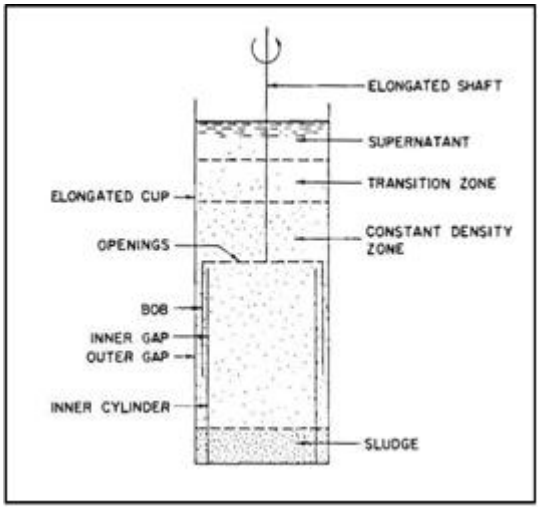



**Figure No. 05: cup and bob viscometer.**

The following instrument is used as an elongated double gap cup and bob geometry for aqueous magnetite suspensions exhibiting zone-settling properties.[16] They positioned the bob in an elongated cup so that the measurement was made within a constant density zone of the settling suspension, away from the upper and lower zones. The bob consisted of a hollow cylinder attached to a shaft with three spokes so that the openings in the top of the bob allowed the particles to settle freely through them and prevent their accumulation on the top surface of the bob. Vertical grooves were cut in the shearing surfaces of the bob and the cup to minimize wall slip.[15,16]

**3. Modern Method**

**a) Small Amplitude oscillatory shear**

The SAOS technique has broad applications in understanding the properties of complex fluids across industries such as polymers, food products, pharmaceuticals, and cosmetics. The ability to characterize materials without significantly altering their structure makes SAOS a preferred method for evaluating formulations, processing conditions, and storage stability.

**Principle**

Small Amplitude Oscillatory Shear (SAOS) is a rheological technique used to study the linear viscoelastic behavior of materials. In SAOS, a material is subjected to a small, sinusoidal deformation or stress, typically within the linear viscoelastic regime where the material's response is proportional to the applied stress or strain.

**Mechanism**

Thixotropy is characterized by the material's ability to regain its structure after a period of shear. The SAOS method is particularly effective for analyzing the kinetics of this structural recovery through the following procedures:

**Time Sweeps for Recovery Observation:** Time sweeps are performed to monitor changes in overtime after applying a high-shear flow, which temporarily disrupts the material's structure. As time progresses after the cessation of shear, an increase in indicates that the material is rebuilding its internal structure.[18] This recovery is a direct measure of thixotropy. The slope of over time during a time sweep reflects the rate of structural rebuilding, with a steeper slope indicating faster recovery.[19]

**Structural Breakdown and Reformation Cycles:** Repeated cycles of high-shear followed by low-amplitude oscillatory shear allow researchers to analyze how the material's structure is disrupted and then rebuilt.[20] This method is effective for studying reversible structural changes in materials, such as gels or suspensions. A consistent pattern of reduction in during high shear followed by a gradual recovery during low-amplitude oscillation indicates thixotropic behavior.

**Three-Interval Thixotropy Test (3ITT)**

The Three-Interval Thixotropy Test (3ITT) involves three phases: rest, shear, and recovery. This method provides a detailed analysis of thixotropic materials by separating the breakdown and recovery phases. During the test, the material's viscosity is measured in each interval, allowing insights into its structural recovery after shear application.

**Principle**

The Three-Interval Thixotropy Test (3ITT) is a rheological method used to assess the thixotropic behavior of a material. The test consists of three distinct phases:

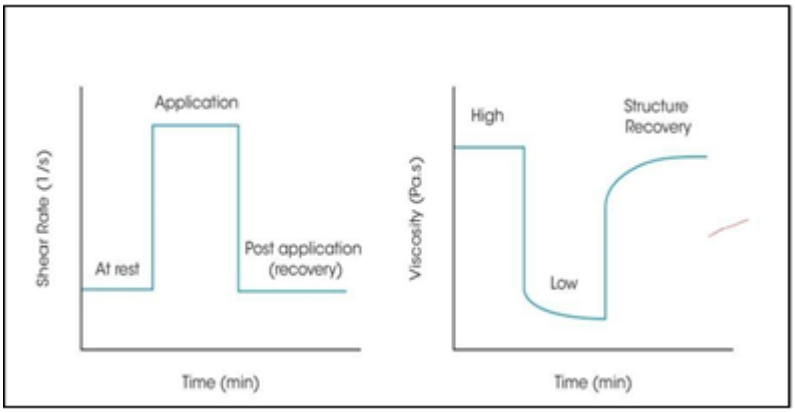



**Figure No. 06: 3ITT method and the viscosity behavior of a thixotropic material.**

**Rest Phase:** The material is allowed to rest at a low or zero shear rate, during which time the internal structure of the material remains undisturbed.

**Shear Phase:** A high shear rate is applied to the material, causing the breakdown of its internal structure, leading to a decrease in viscosity.

**Recovery Phase:** The material is allowed to rest again at a low or zero shear rate, during which time the structure begins to rebuild, and the viscosity starts to recover.

**Working Mechanism**

**Phase 1 (Rest Phase):** The initial viscosity of the material is measured while the material is at rest. This phase provides a baseline for the material's structure before any shear is applied.

**Phase 2 (Shear Phase):** A high shear rate is applied to the material for a specific period. During this phase, the material's internal structure is disrupted, causing a decrease in viscosity. The extent of this decrease reflects the material's shear-thinning properties.

**Phase 3 (Recovery Phase):** After the shear stress is removed, the material is allowed to rest again. The viscosity is measured during this phase to determine the extent and rate of structural recovery. By comparing the viscosity in the recovery phase to the initial viscosity in the rest phase, researchers can quantify the thixotropic behavior, including the rate and extent of structural recovery.

**ADVANTAGES**

**Detailed Insights:** The 3ITT provides a detailed view of the material's structural recovery after shearing, allowing for the separate quantification of both the breakdown and recovery phases.[32,32]

**Quantification of Thixotropy:** It enables researchers to accurately quantify the thixotropy by comparing the viscosity values across the three phases.[33]

**DISADVANTAGES**

**Sophisticated Equipment:** Conducting the 3ITT requires more sophisticated rheological equipment capable of precise control over shear rates and timing.

**Complex Experimental Control:** The method requires precise control over experimental parameters, which can make it more challenging and less accessible for routine industrial applications.[21,22]

**PAT Tools Used in Thixotropy Determination**

**Anton Par MCR 302 and MCR 502**

The Anton Paar MCR 302 and MCR 502 rheometers are widely utilized in the pharmaceutical industry, particularly for the analysis of thixotropy in various formulations. These rheometers enable precise measurement of time-dependent viscosity changes under shear, which is crucial for ensuring the stability and consistency of products like gels, creams, and suspensions. Their advanced modular design allows for a broad range of rheological tests, offering critical insights into the flow and deformation behavior of complex fluids used in drug development and manufacturing. The Anton Paar MCR 302 and 502 rheometers operate on the principle of rotational and oscillatory testing to determine the flow and deformation behavior of materials. In pharmaceutical applications, these rheometers are crucial for measuring thixotropy, the time-dependent recovery of viscosity after shear stress. The devices utilize a powerful EC motor with a precise air bearing and a normal force sensor to apply controlled stress or strain. The modular design allows customization for different tests, such as temperature-dependent rheology, ensuring detailed analysis of non-Newtonian fluids in drug formulations.[23,24]

**Figure No. 07: Anton Par MCR 302 and MCR 502.**

**Mechanism**

Rheological tests help measure and understand the flow and deformation properties of materials. Two key types of tests performed by a rheometer are rotational tests and oscillatory tests, each serving different purposes depending on the material and what property needs to be assessed.

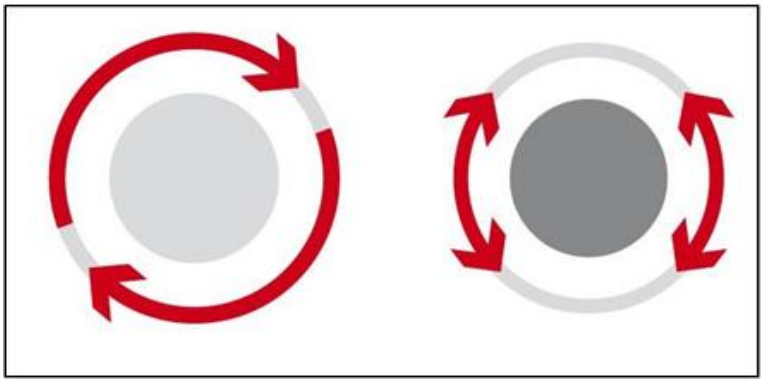


**Figure No. 08: Rotatory and oscillatory movement in SRV.**

**Sample Preparation:** The pharmaceutical product (cream, gel, ointment, or syrup) is carefully prepared and placed in the measuring system of a rheometer. The sample must be at controlled conditions, such as specific temperature and humidity, to simulate actual usage environments.

**Test Selection**

**Rotational Test:** For liquid formulations like syrups, this test measures the flow behavior (viscosity). The rheometer rotates a measuring bob (or plate) within the sample at varying speeds, applying shear forces. The instrument measures the resistance (shear stress) and calculates viscosity, ensuring the product flows smoothly during manufacturing, packaging, and application.

**Oscillatory Test**: For semi-solids like creams and gels, this test evaluates viscoelastic properties. The rheometer applies oscillating (back-and-forth) motion to the sample, assessing how the material deforms and returns to its original structure (elasticity) or flows (viscosity). This is critical for determining spreadability, stability, and the product's feel during application.

**Data Collection:** Shear Stress and Shear Rate are recorded in rotational tests. Storage Modulus (G') and Loss Modulus (G") are measured in oscillatory tests, revealing the material's solid-like or liquid-like behavior.

**Result Analysis:** Rheological data, such as viscosity, shear stress, and moduli, are calculated. This information helps refine product formulation to ensure consistent texture, stability, and drug delivery.

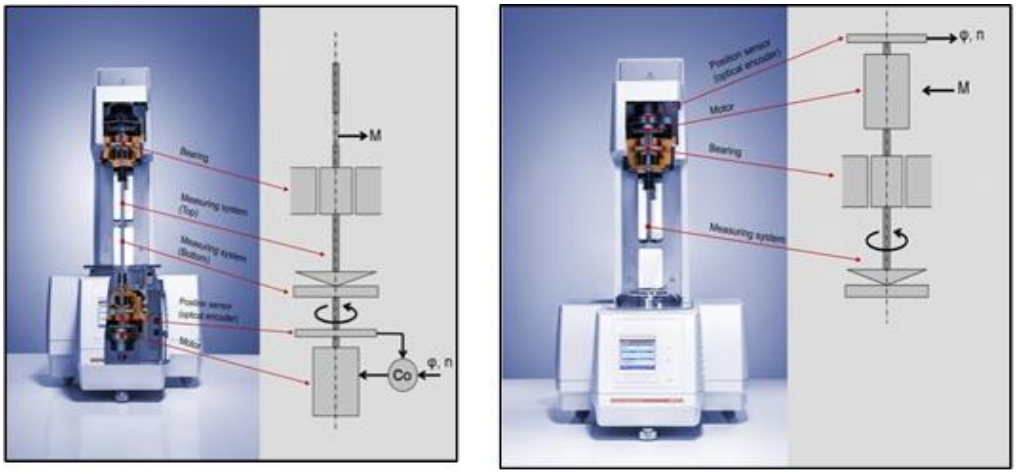



**Figure No. 09: Inbuilt Mechanism of Anton Par MCR 302 and MCR 502.**

**SRV: Wide-range inline process Viscometer**

This advanced viscosity measurement sensor is designed for simplicity and reliability, featuring a compact form factor that allows for easy installation in various setups. It provides real-time, stable, repeatable, and reproducible measurements, making it suitable for both Newtonian and non-Newtonian fluids. With the capability to track viscosity changes across a wide range using a single sensor, it ensures versatility and efficiency. Constructed entirely from 316L stainless steel, the sensor offers exceptional durability and corrosion resistance, and its performance is completely unaffected by mounting conditions. It also integrates built-in fluid temperature measurement for added functionality and operates reliably under extreme conditions, withstanding pressures up to 500 bar (7500 psi) and temperatures as high as 300°C (575°F). Available with threaded, flanged, and sanitary process fittings, the sensor is easy to clean, requires no maintenance, and eliminates the need for reconfigurations, ensuring long-term convenience and cost-effectiveness. In-line, online, real-time fluid viscosity.

**Figure No. 10: SRV wide range inline process viscometer.**

In thixotropy determination, the SRV sensor helps in understanding how a material's viscosity decreases under shear (like mixing or pumping) and recovers over time, which is crucial for the processing and handling of various pharmaceutical products. The Rheonics SRV viscosity sensor is widely used in the pharmaceutical industry, particularly for inline and at-line viscosity measurements, which are crucial for real-time quality control. A key application of the SRV sensor is in monitoring the thixotropic properties of non-Newtonian fluids, such as those found in pharmaceutical formulations. The sensor's high repeatability and ability to provide real-time data make it ideal for scaling from pilot production to full-scale manufacturing, ensuring consistent product quality across different production lines.[25,26,27]

**DXR3 Raman Microscope**

The DXR3 Raman Microscope by Thermo Fisher is an advanced, high-performance tool designed to provide detailed molecular and structural analysis in various fields, including thixotropy determination. Thixotropy refers to the property of certain gels or fluids that become less viscous when stressed and recover their viscosity after the stress is removed. The DXR3 is particularly suitable for studying such behaviors due to its capabilities in confocal Raman microscopy, which provides real-time insights into material properties on a microscopic level.

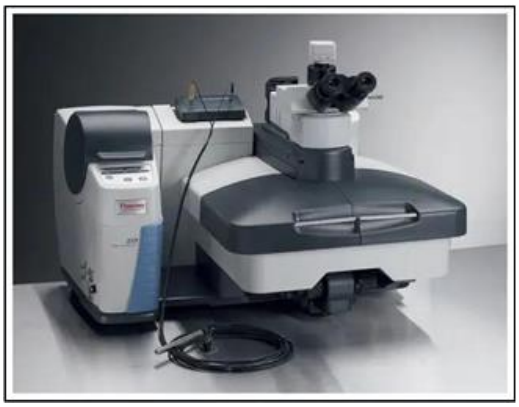


**Figure No. 11: DXR3 Raman Microscope Mechanism.**

The methodology behind the DXR3 Raman Microscope involves several core steps, all designed to provide accurate molecular and structural analysis. The microscope utilizes Raman spectroscopy, a technique based on inelastic scattering of photons, which provides detailed information about molecular vibrations that can be used to identify chemical compositions. Step-by-Step mechanism includes.

**Sample Preparation:** Samples can be solid, liquid, or gas, and minimal preparation is required as the Raman technique is non-destructive. Thixotropic materials, the sample is typically placed on a microscope slide, and no additional treatment like staining is necessary since the technique uses laser-induced scattering.[28,29]

**Laser Excitation:** The DXR3 Raman Microscope uses a variety of laser wavelengths (455 nm, 532 nm, 633 nm, 785 nm) to excite the sample molecules. Laser interacts with the molecular bonds in the sample, and the scattered light is analyzed to determine the chemical structure of the sample.[29,30]

**Confocal Raman Microscopy**: The microscope utilizes confocal optics to ensure precise focus on a specific region of the sample, enabling depth profiling and 3D imaging. This is particularly useful in thixotropy studies, where the behavior of a material at different depths under stress is important. Confocal imaging is essential for ensuring high spatial resolution, with the DXR3 achieving resolutions as fine as 540 nm and depth resolutions of 1.7 μm.[28]

**Data Acquisition and Correction**: The system automatically corrects for fluorescence (common in some samples), and cosmic ray interference, and ensures the optimal laser exposure for consistent sample excitation. Real-time previews allow users to monitor the analysis and adjust parameters, if necessary, before capturing final data.[29]

**Spectral Analysis:** The scattered light is collected by the spectrometer, and the resulting Raman spectra are analyzed. The spectral data represents molecular vibrations, with unique fingerprints corresponding to different chemical compounds. The DXR3 employs patented data optimization tools, including multi-component searching algorithms, which help decode complex samples and provide precise identification of materials.[28,30.31]

**Data Interpretation**: After acquiring the Raman spectra, data interpretation is facilitated by software like OMNIC Spectra, which allows for rapid analysis and identification of materials. For thixotropy studies, the software can generate maps showing how molecular structures change under stress.[29,32]

## CONCLUSION

From this review, it was concluded that advancements in thixotropy determination have revolutionized the thixotropy determination of pharmaceutical products. Modern techniques like Small Amplitude Oscillatory Shear (SAOS) and the Three-Interval Thixotropy Test (3ITT) allow precise analysis by separating breakdown and recovery phases. PAT tools, including in-line rheometers and Raman spectroscopy, provide real-time monitoring of viscosity and structural recovery during manufacturing, enabling process optimization, quality control, and regulatory compliance. Future advancements, integrating traditional and modern methods with real-time monitoring, promise greater precision and innovation in thixotropy determination. These developments will improve product stability, manufacturing efficiency, and patient outcomes, reinforcing thixotropy's critical role in pharmaceutical science.

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