

Raman Spectroscopy for PAT in Pharmaceutical Manufacturing

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Raman Spectroscopy for Process Analytical Technology (PAT)

Raman spectroscopy is emerging as a powerful Process Analytical Technology (PAT) tool for pharmaceutical manufacturing, enabling rapid, non-destructive, and real-time monitoring of critical quality attributes throughout the production process. Its molecular fingerprinting capability allows direct assessment of raw materials, intermediates, and finished products, while providing valuable information on chemical composition, concentration, polymorphic form, crystallinity, and process-related changes. Raman-based PAT can support continuous process monitoring, reduce dependence on time-consuming laboratory analysis, and facilitate early detection of process deviations. When integrated with chemometric and multivariate data analysis, Raman spectroscopy provides actionable insights for process understanding, control, and optimization, thereby supporting consistent product quality and more efficient pharmaceutical manufacturing.



What is PAT and Why Raman is a preferred choice for PAT?

Process Analytical Technology (PAT) is a science- and risk-based approach for monitoring and controlling pharmaceutical manufacturing processes in real time to ensure consistent product quality. Raman spectroscopy is a preferred PAT tool because it provides rapid, non-destructive, molecular-specific analysis with minimal sample preparation. It can be integrated through in-line, on-line, or at-line configurations to monitor raw materials, intermediates, and finished products, while tracking critical quality attributes such as composition, concentration, polymorphic form, and process changes. Raman spectroscopy is particularly suitable as a PAT tool for Esterification because it provides molecular-level information based on vibrational transitions, allowing differentiation of reactants (alcohol, acid), products (ester), and by-products (e.g., water, methanol).

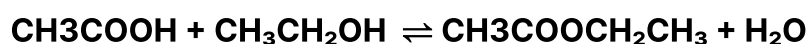
It has weak interference from water, which is advantageous since water is often a by-product in Esterification. It can be implemented in-line or on-line using fibre-optic probes directly in the reactor, enabling continuous, non-destructive monitoring.

In this study, TechnoS Instruments monitored the Esterification process in-line using the IndiRAM™ Portable Raman spectrometer.

Materials and Methods:

In-line reaction monitoring: Raman spectra were acquired using an IndiRAM Portable Raman Spectrometer, TechnoS Instruments Ltd., Jaipur, India. Fibre-optic Raman probes are inserted into batch or flow reactors to acquire spectra throughout the reaction. A laser excitation source of 785 nm emission wavelength was used with 300 mW power. A total of 500 scans were acquired with an integration time of 1.25 sec per scan and a 1 sec interval between consecutive scans. The reactants are acetic acid (CH₃COOH) and ethanol (CH₃CH₂OH).

Reaction equation



Reaction conditions:

- **Acid catalyst:** usually concentrated sulfuric acid (H₂SO₄) or dry HCl gas.
- **Heat:** reflux is commonly used to increase the rate.
- **The reaction is reversible:** to drive it toward ester formation, one can use **excess** ethanol or remove water (e.g., using a Dean–Stark apparatus or molecular sieves).

Results & Discussion

Figure 1 (a,b,c) shows the Raman spectra of the reactant, the reaction and the product, respectively.

Raman peak of the reactant

- **Ethanol:** CH₃CH₂OH (*ref 1, 2*)
- ~ **880-890 cm⁻¹**: C–C symmetric stretch (often used as the main ethanol marker).
- Additional bands: ~**1045–1095 cm⁻¹** (C–O stretch), ~**14500-1460 cm⁻¹** (CH₂/CH₃ bending).
- **Acetic acid:** CH₃COOH (*ref 2*)
- ~ **618-622 cm⁻¹**: O=C–O bending; ~**893 cm⁻¹**: C–C symmetric stretch and bands in the **1320–1460 cm⁻¹** region are associated with O–H bending/carboxylic vibrations.

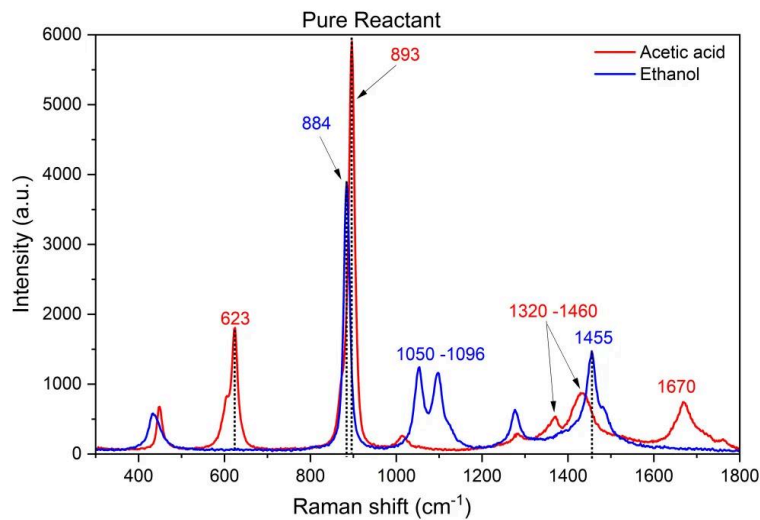


Figure 1a: Raman spectra of pure reactant

Real-Time Process Monitoring (PAT)

Each Raman spectrum is collected after 1 sec. The representative Raman spectra are shown below: ~1 sec, 50 sec, 100 sec, 150 sec, and 200 sec. The conversion point is observed at ~200 sec.

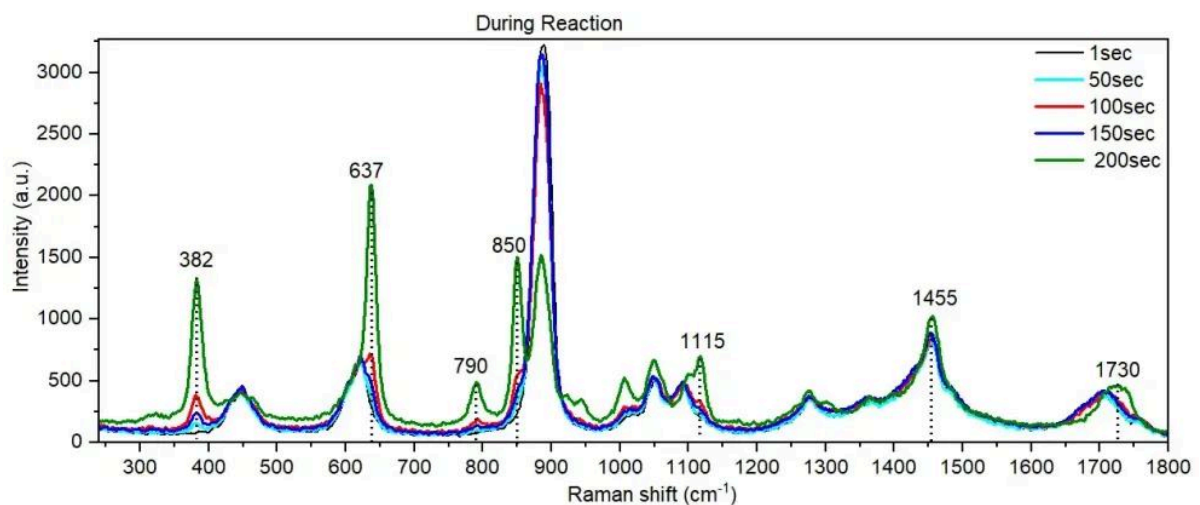


Figure 1b: Monitored during Reaction

Raman peak of Product

Ethyl acetate: $\text{CH}_3\text{COOCH}_2\text{CH}_3$

- **$\sim 789 \text{ cm}^{-1}$** : CH_2 rocking.
- **$\sim 847 \text{ cm}^{-1}$** : C-C symmetric stretch (strong, often used as the main ethyl acetate marker).
- **$\sim 1115 \text{ cm}^{-1}$, $\sim 1454 \text{ cm}^{-1}$, $\sim 1736 \text{ cm}^{-1}$** : C-O and C=O related modes.
- The **$\sim 1736 \text{ cm}^{-1}$** band corresponds to the ester C=O stretch and is very characteristic of ethyl acetate.

Characteristic Raman bands are tracked, such as:

- C=O stretching region (**$\sim 1740\text{--}1750\text{ cm}^{-1}$**), which shifts or changes intensity as acid is converted to ester.
- Bands associated with alcohol (e.g., C–O, O–H) and ester (C–O–C) functional groups in the $1000\text{--}1300\text{ cm}^{-1}$ region.
- Decrease of methanol or alcohol bands as they are consumed.
- Growth of the ester C=O band (slightly different wavenumber/shape) and C–O–C bands.

NOTE

Endpoint detection and conversion tracking: The endpoint detection was observed for **$\sim 200\text{ sec}$** (e.g., when residual acid or alcohol falls below a threshold).

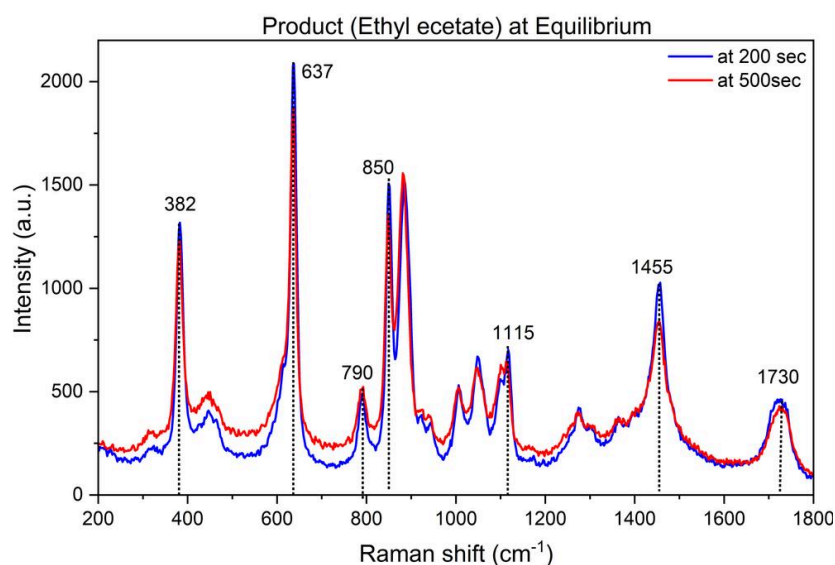


Figure 1c: Raman spectra of Product

Conclusion

In this application note, these models show real-time Estimation of **conversion at 200sec**.

Raman spectroscopy provides molecular-level information with minimal sample preparation, making it well-suited for in-line and on-line process monitoring.

Raman spectroscopy offers pharmaceutical manufacturers a powerful pathway to achieve faster, smarter, and more efficient process control. By enabling real-time, non-destructive monitoring with minimal sample preparation, Raman-based PAT can reduce reliance on time-consuming laboratory testing, minimize process variability, detect deviations early, and support consistent product quality. Its integration with chemometrics and automated process control can further improve manufacturing efficiency, reduce material and production losses, and accelerate decision-making.

Ultimately, Raman PAT helps manufacturers strengthen quality assurance while driving greater productivity, operational efficiency, and cost-effectiveness across pharmaceutical manufacturing.

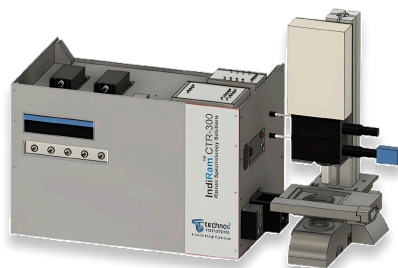
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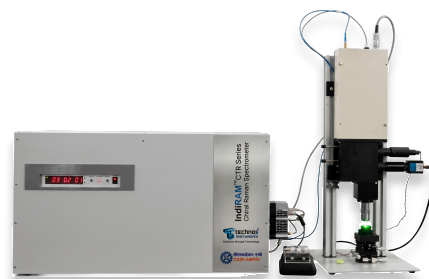
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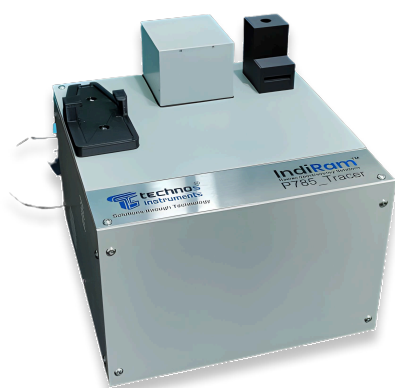
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