APPLICATION NOTE

BAYSPEC
Pervasive Spectroscopy

Polymorph and Ingredient Analysis with High-Resolution 1064nm Dispersive Raman Spectroscopy

Superior Fluorescence Avoidance at 1064nm

Background

Polymorphs are different crystalline forms of the same pure substance in which molecules have different arrangements and/or different molecular conformation. Polymorphism is crucial in the pharmaceutical industry because different polymorphs have different physical and chemical properties, such as chemical reactivity, solubility, stability, dissolution rate and excipient compatibility in the formulation of medicines. After all, the different properties of polymorphs would affect the bioavailability and storage of the active pharmaceutical ingredient (API) in the medicine. Due to the importance of polymorphism and the fact that many drugs receive regulatory approval for only a single crystal form or polymorph, screening of polymorphs becomes necessary for drug research and development.

Owing to technological improvements spurred on by the telecommunications boom of the last decade, Raman spectroscopy has become much more accessible to users in all fields. The combination of improved technology and the technique's molecular sensitivity has led to a surge in Raman usage in a myriad of application areas, including pharmaceutical, biomedical, and forensic, etc. In all of these applications, however, there remains a struggle to extract useful Raman spectra from fluorescent and luminescent samples.

Fluorescence, a type of broad emission thousands times stronger than Raman effects, is very common in pharmaceutical samples such as API and final drug. It is much more likely and intense when illuminated by short wavelengths. For users who require longer wavelengths such as 1064nm as a fundamental way to avoid the fluorescence, the only available option has been FT-Raman, which is typically more complicated and slower than dispersive Raman systems. But now, BaySpec's new dispersive 1064nm Raman spectrometer family of instruments offers users a turn-key solution that combines the speed, sensitivity, and rugged design of dispersive Raman instruments with same fluorescence avoidance of traditional FT-Raman. In addition, the dispersive geometry permits diffraction-limited optical performance, enabling confocal microscopic Raman configuration at 1064nm.

Results and Discussion

Ranatadine Hydrochloride, the major API of Zantac®, usually can exist in two distinct polymorphic forms and several other pseudo-polymorphic forms. After the expiration of the patent restrictions, many generic drugs based on Ranatadine HCl appear on the market for the treatment of peptic ulcers.

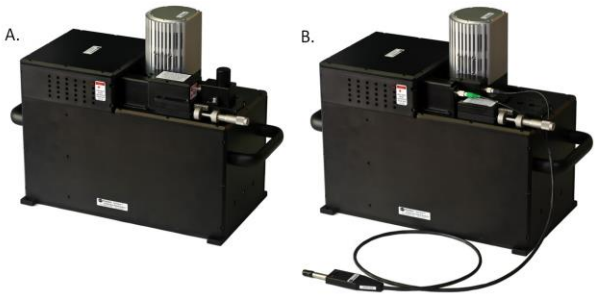

Figure 1: *BaySpec's RamSpec™-HR High-Resolution 1064nm Raman Spectrometer. Two exchangeable sample interfaces are provided: (A) direct sampling for higher optical efficiency and (B) fiber probe for flexibility.*

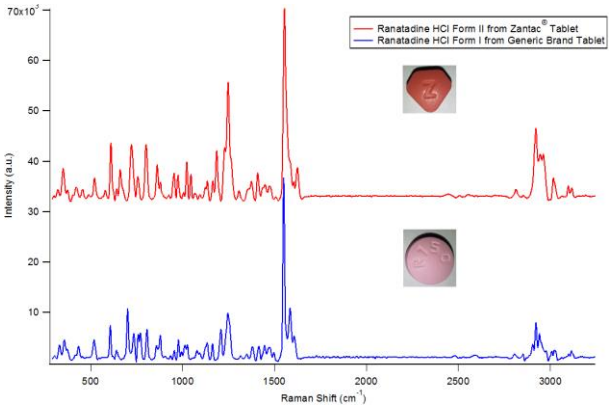

Figure 2: *1064nm Raman Spectra of different Ranatadine HCl forms contain in Zantac® tablet and generic brand tablet.*

Zantac 150® tablet and one generic brand tablet were purchased from local pharmacy and both Raman spectra of both Zantac® tablet and generic brand tablet were acquired with BaySpec's RamSpec™-HR High-

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Resolution 1064nm Raman Spectrometer as in **Figure 1**, which provides turn-key solutions designed for best-in-class performance and resolution for dispersive 1064 nm Raman spectroscopy. As an alternative for bulky, slow and expensive FT-Raman system, the RamSpec™-HR 1064nm Raman spectrometer can cover full spectral range (100-3200 cm^{-1}) as well as reach high resolution up to 4 cm^{-1} for providing more detail in the Raman spectrum for further analysis. As shown in **Figure 2**, the Raman Spectra of the core of two tablets are acquired and based on the Raman features, it can be concluded that the API for the Zantac 150® is in form II while the generic brand contains form I.

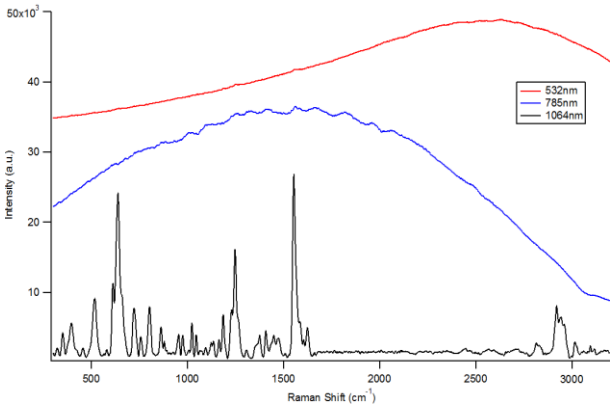

Figure 3: *Raman spectra of the Zantac® tablet collected through the coating by 532nm, 785nm and 1064nm Raman Spectrometers.*

One of the major advantages for Raman technology comparing with other analytical methods is non-destructive measurement which requires minimal sample preparation but provides fast spectral acquisition. As many of other drugs, Zantac® tablets have colorful coatings covering the core. 1064nm Raman Spectroscopy is provides a fast, non-contacting method to measure the API through the coating, even the packaging material (usually glass or thin polymer) for achieving quality assurance or counterfeit detecting. **Figure 3** shows the Raman spectra of the Zantac® tablet collected through the coating by 532nm, 785nm and 1064nm Raman Spectrometers. Even for 785nm, the fluorescent from the pigments in the coating dominated the whole spectrum and no distinguishable Raman features can be found. But with the advantages of superior fluorescence avoidance and minimal signal loss through the coating for 1064nm dispersive Raman, a clear Raman spectrum is generated.

Comparing the Raman spectra collected from the core of the tablet without coating and through the coating (Blue and Red spectra in **Figure 4**), most of the Raman features through the whole spectral range match with each other. However, three distinguishing Raman peaks center at 405, 515 and 637 cm^{-1} appear in the Raman spectrum collected through the coating on the tablet. As referenced with a Raman spectrum of pure TiO_2, it can be concluded these peaks are from the TiO_2 coating.

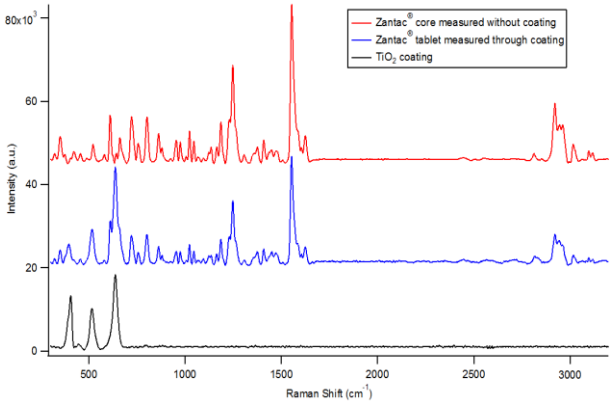

Figure 4: *Comparison of the 1064nm Raman spectra acquired directly from the tablet core and through the coating.*

Conclusion

Based on these experiments, 1064nm dispersive Raman is demonstrated as a viable new option and non-destructive method to identify polymorph and enable further component analysis on the pharmaceutical tablets. With automatic measurement accessories, a 96-well micro-plate Raman reader as an example (**Figure 5**), fully automatic Raman spectra measurement and identification can be easily applied for R&D or quality assurance purpose. Further, chemometrics tools such as principal component analysis (PCA) and partial least squares regression (PLS) based on the high-resolution Raman spectra acquired with BaySpec's RamSpec™-HR 1064nm Raman Spectrometer can provide an accurate and precise method of identification and quantification of the chemical compositions automatically. Moreover, the instrument and methodology can be easily adapted to many other R&D areas in pharmaceutical industry.

Figure 5: *96-well micro-plate sampling accessory for automatic Raman acquisition. Inset: software interface during an automated measurement with Identification Mode on.*

References

1) Pratiwi, D., et al., *Eur J Pharm Biopharm,* **2002**, 54, 337-341.
2) Chieng, N., et al., *J Pharmceut Biomed Anal*, **2009**, 49, 18-25.

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