Assessment of Laser Directed Infrared (LDIR) Imaging for a Physicochemical Approach to In Vitro Characterization of Pharmaceutical Tablets

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Abstract

Laser direct infrared spectroscopy (LDIR) is an emerging technology for rapid, non-destructive spectroscopic imaging. LDIR spectroscopic imaging can reduce data collection time to minutes without losing critical physicochemical information such as chemical identity, particle size and shape, and distribution of components. LDIR could be an ideal technique for the characterization of complex generic drugs. However, LDIR technology is still in its infancy and thus this work will focus on optimizing method development for LDIR imaging and comparing the technique to more conventional spectroscopic imaging approaches such as Raman mapping. Midodrine HCl, prepared in-house as tablets with different proportions of API and two excipients (microcrystalline cellulose and corn starch) were evaluated and assessed with LDIR spectroscopic imaging and Raman mapping. Methods for evaluation of pharmaceutical tablets were developed and parameters were assessed including pixel-size, classification and multi-peak methods. Methods were verified from point spectra and compared to the representative library. Additionally, an OTC product (Excedrin®) consisting of three different APIs was imaged and evaluated. LDIR images of a Midodrine HCl tablet showed good agreement with the Raman mapping. Nonetheless, LDIR method depends on the selection of peaks and baseline point/points which needs to go through careful method development and validation by the analyst. Important data such as API/excipient particle size, shape and distribution could also be extracted from the resulting spectroscopic images from both techniques. LDIR shows potential as a spectroscopic imaging technology for pharmaceutical analysis. A detailed LDIR reflectance library of the excipients is necessary for a better understanding of the physicochemical characteristics of the drug product. Future work will evaluate LDIR imaging for other dosage forms such as extended-release tablets/capsules, topicals or transdermals.

Introduction

Vibrational spectroscopic imaging techniques allow for visual assessment and chemical identification of compounds within a wide variety of sample types and dosage forms. Non-destructive high resolution spectroscopic images can be collected by Raman mapping which can be a lengthy process for data collection with sufficient resolution. Near infrared (NIR) microscopy can improve the data collection times to minutes however has very low spatial resolution. Conventional IR microscopy can provide high resolution but suffers from very long acquisition times. Quantum cascade lasers (QCL) are a new advance in laser technology that emit all their output power in a single narrow range of wavenumbers with tunability of the laser. QCLs coupled with IR microscopy have resulted in an emerging technology known as LDIR imaging that overcomes these challenges and allows for collection of spectroscopic images in minutes with high spatial resolution over large surface areas.

LDIR reflectance imaging can be a viable option to analyze complex drug products rapidly in comparison to other spectroscopic imaging technologies without losing any physicochemical information. However, generalized LDIR imaging reflectance spectral libraries, methods, and data analysis are not yet well established for pharmaceutical applications. Here method development was done on a well-understood in-house prepared tablet as well as on a common OTC product and data was validated with Raman mapping.

Materials and Methods

An in-house prepared pharmaceutical tablet, Midodrine HCl, was formulated with two of the excipients (microcrystalline cellulose (MCC) and corn starch (CS)) with two formulations (66% CS, 32% MCC, and 2% API as tablet A; 10% CS, 88% MCC, and 2% API as tablet B) . Over-the-counter (OTC) pharmaceutical tablet Excedrin was purchased. Comparative assessment of both tablets were carried out with LDIR and Raman imaging to evaluate surface physicochemical characteristics (chemical identity, particle size and shape, and distribution of excipients).

Figure 1 shows the instrumentation for LDIR imaging (left) and Raman mapping (right). QCL based Agilent 8700 was used for LDIR imaging which offers rapid analysis of samples. Renishaw inVia Raman Microscope was used for Raman mapping. LDIR imaging methods for tablets were carefully assessed and developed with the pure ingredient spectra and the role of pixel-size was evaluated:

Midodrine HCl contains MCC and CS with the API (Figure 2, left), Excedrin contains three API (acetaminophen, aspirin, and caffeine) with two excipients (MCC and CS) (Figure 2, right).

Collected images from both techniques were analyzed with imageJ software for the physicochemical properties: Feret diameter, particle distribution, and area coverage of the API in the tablet. Feret diameter is the size of any particles in a specific (longest distance between any two points of the particle boundary) direction which is generally used to analyze particles in microscopic imaging.

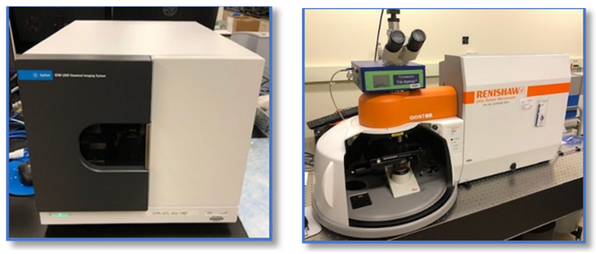


Figure 1. Instrumentation for the comparative pharmaceutical tablet analysis: LDIR imaging by Agilent 8700 (left) and Raman mapping by Renishaw inVia Raman Microscope (right).

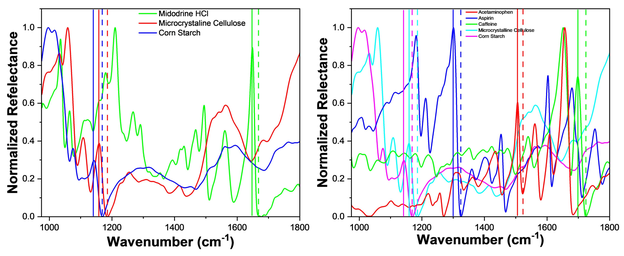


Figure 2. IR reflectance spectra library of Midodrine HCl ingredients (left) and Excedrin ingredients (right)

Results and Discussion

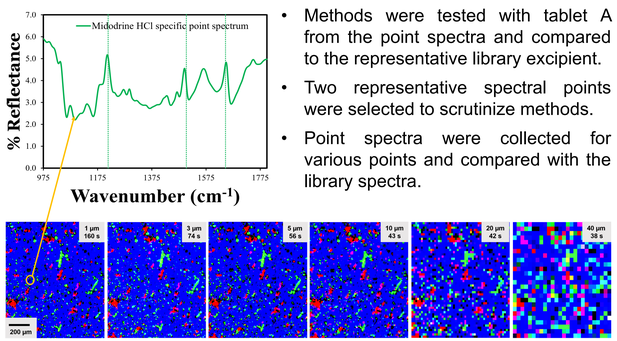


Figure 3. Effect of pixel-size(1 to 40 µm resolution) in LDIR imaging

- Effect of pixel-size were tested with tablet A for the most suitable method (Figure 3).
- Tablet was analyzed with two-point baseline method for three components.
- ≤10 µm pixel-size of resolution detects the component clearly.
- However, acquisition time and pixel-size needs to be adjusted based on the expected size of the API/excipients.

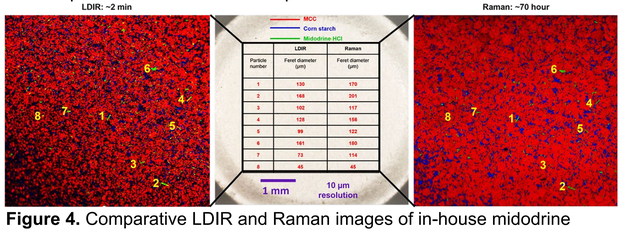


Figure 4. Comparative LDIR and Raman images of in-house midodrine HCl tablet B.

- LDIR imaging can detect particles comparable to Raman mapping (Figure 4)
- Feret diameter of specific particles were smaller in LDIR imaging than Raman (Figure 4).
- LDIR was able to detect more # of domains than Raman.
- Percent area coverage by the API was found the same by both LDIR and Raman techniques for in-house midodrine HCl tablet.
- Particle sizes of API showed smaller in LDIR imaging than Raman mapping(Figure 5).
- Overall, LDIR showed similar capability to image in-house Midodrine HCl tablet in compared to Raman imaging.

Table 1. ImageJ analysis of midodrine HCl in-house tablet for API.

Total Statistics		
Properties	**LDIR**	**Raman**
Total number of particles	235	185
% area covered	1.33	1.33

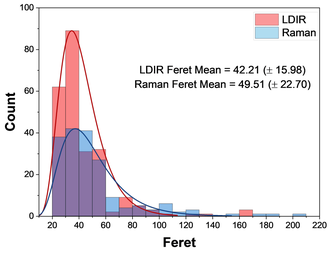


Figure 5. ImageJ analysis results for feret diameter comparison of API in in-house midodrine HCl tablet by LDIR and Raman.

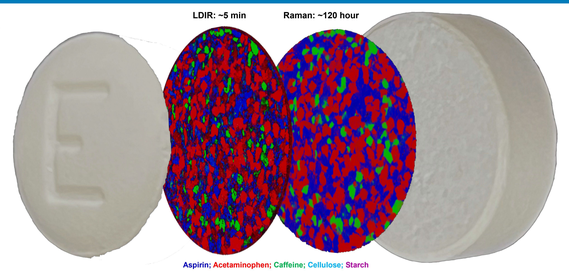
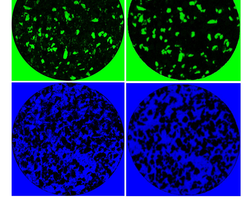


Figure 6. Comparative LDIR and Raman images of OTC Excedrin® tablet

Table 2. ImageJ analysis of Excedrin® OTC tablet

Properties	LDIR	Raman
Acetaminophen		
Total number of particles	292	302
Feret diameter (µm)	505	640
% area covered	**44.06**	**44.56**
Caffeine		
Total number of particles	204	99
Feret diameter (µm)	261	539
% area covered	**9.89**	**9.30**
Aspirin		
Total number of particles	357	322
Feret diameter (µm)	446	631
% area covered	**43.53**	**46.08**



- There were no significant differences in surface morphologies observed between LDIR and Raman images(Figure 5). LDIR was able to detect more # of domains than Raman for caffeine and aspirin.
- Feret's diameter for the 3 APIs was smaller in LDIR than Raman imaging.
- Particle analysis demonstrated similar % area coverage in both techniques

Conclusions

- LDIR imaging can detect both APIs and excipients in pharmaceutical products
- Pixel-size of LDIR imaging can be selected based upon the expected size of particles.
- LDIR provided high resolution images comparable to Raman imaging, but with collection times on the order of minutes rather than the hours or days needed for Raman collection.
- LDIR has potential as a rapid spectroscopic imaging technology for pharmaceutical analysis.

Acknowledgements

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