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Original Research Article

Opportunities and Challenges: Process Raman for the Real-Time Release Testing (RTRT) of Extended-Release Formulations

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Abstract

The use of a process analytical technology has been demonstrated using near-infrared spectroscopy for continuous manufacturing of pharmaceutical formulations and is within the scope of the U.S. Food and Drug Administration's real-time release testing initiative. While effective for simple formulations, this preliminary study investigates whether such a spectroscopic surrogate application can replace pharmaceutical dissolution testing for extended-release formulations. In this study, we will assess the use of process Raman spectroscopy for real-time dissolution testing. Extended-release tablet formulations often accomplish the release rate delay through the addition of gelling agents. In this work, hydroxypropyl methylcellulose (HPMC) polymers were used to formulate extended-release niacin tablets. Process Raman spectroscopy was evaluated as a tool to effectively model dissolution profiles to determine if the optical technique has the ability to differentiate HPMC polymers from the background and be selective for the polymer type employed. Our preliminary work indicates that while Raman can effectively detect and monitor the niacin response of the tablet formulations, there are not enough unique spectral features between the different HPMC polymers to selectively resolve their responses. Additional measurements and chemometric analysis might suggest otherwise. Thus, for extended-release tablet applications with continuous manufacturing, further dissolution surrogate development is needed.

Keywords

Raman spectroscopy, process analytical technology, PAT, process Raman spectroscopy, niacin, dissolution testing

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Introduction

In an attempt to lower manufacturing costs and improve efficiency, the pharmaceutical industry is moving to wider applications of continuous manufacturing and rapid-release testing.[1,2] This rapid testing has successfully modeled dissolution testing for continuous manufacturing applications for simple formulations.[1–7] The Food and Drug Administration recognizes this capability and cites examples of real-time release testing (RTRT), which includes "multivariate analysis models as a surrogate for dissolution."[8] Use of such models is not as simple as submitting a traditional method and validation. Submission of such a model would require (i) a full description of data collection, pretreatment, and analysis, (ii) justification of the model building approach, (iii) statistical summary of results, (iv) verification using data external to the calibration set, and (v) a discussion of approaches to model maintenance and updates.

Raman spectroscopy, a vibrational spectroscopic technique is a process analytical technology (PAT) that is quickly being implemented and deployed in the pharmaceutical manufacturing and testing process. The technique is attractive primarily due to the rich, real-time compositional data generated, the ease of implementing it in a process, and the minimal response to water. Raman spectroscopy has been used as an in-line PAT tool with continuous manufacturing testing.[9–13] and traditional pharmaceutical dissolution testing.[14–19] There are other PAT spectroscopic tools that have also been used for dissolution applications but due to the transparency to water, Raman spectroscopy has become the tool of choice. This investigation is the first in the literature to apply Raman spectroscopy for rapid-release dissolution modeling of extended-release tablets.

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A representative extended-release matrix was chosen for evaluation. Successful implementation of this capability would directly impact many products both in development and in the market. Typically, tablet manufacture of extended-release formulations requires critical parameter controls to be set up within a dissolution design space. To model the extended-release capability of the formulation, and thus the resulting dissolution profile, the spectroscopic technique employed must be able to reliably detect the release profile change from each formulation design. Thus, if a Raman library could distinguish between, dissolution release changes due to hardness, lubricants, particle sizes, etc., the spectroscopic tool could serve as a surrogate for lengthy dissolution testing similar to the earlier work using near-infrared for continuous manufacturing.[3,4] Such modeling would require a much larger body of data for the spectral library.

The challenge is that dissolution studies for extended-release matrices often take several hours to execute. The application and transfer of methods using USP Apparatus I and II,[20,21] Apparatus III,[21–23] and Apparatus IV[24–26] could be replaced with rapid spectroscopic evaluation models that require only a few minutes. In addition, all samples going to the clinic could be effectively modeled. Once the dissolution model was determined the Raman model could also potentially yield drug potency and content uniformity,[27] as well as crystallinity determination for enabling amorphous formulations.[28–31] The notion of using Raman spectroscopy in this regard is appealing for an extended-release formulation. Perhaps, Raman spectroscopy could be the missing tool for in vivo/in vitro correlations for the pharmaceutical industry.[32,33]

Experimental

Materials and Methods

Niacin used in this investigation was ≥98% from Sigma. All excipients were commercial grade from warehouse vendors. Hydroxypropyl methylcellulose (HPMC) polymers Methocel K100LV and K15M were used as received from Dow. Mannitol was Pearlitol 100 SD grade from Roquette. Microcrystalline Cellulose was Avicel PH 102 grade from FMC Biopolymer. Colloidal silicon dioxide was from Cabot Corporation and the magnesium stearate used was compendial grade from Mallinckrodt Pharmaceuticals. Standard industry practices were used to control particle uniformity in the raw materials.

Dissolution Testing

Dissolution evaluation of the extended-release formulations was run using an ultraviolet (UV) fiber optic system based on USP ⟨711⟩ guidelines.[34] The extended-release determination use profiled using 50 mM pH 6.8 phosphate buffer at 50 rpm in a Sotax AT7smart Dissolution Apparatus (Westborough, Massachusetts). Niacin release was monitored using a Pion Rainbow Fiber Optic Dissolution Monitor operating with Pion Indigo v.4.0.0.0 software (Billerica, Massachusetts).

Raman Instrument

A MarqMetrix All-In-One (AIO) process Raman system was used to measure niacin and HPMC samples. The AIO instrument (Model: M785C) houses a 785 nm laser (5–450 mW power) and the spectrometer has a spectral window of 100–3250 cm^{-1} with a spectral resolution of 6.5 scm^{-1}. A fiber optic probe (300 Series) with a 1.27 cm (0.5 in.) outside diameter sampling optic (20.32 cm/8 in. length Performance BallProbe) was used to collect Raman spectra of the samples. A pair of excitation and collection fiber optic cables (100 and 200 μm, respectively) carry the laser light to the sample and Raman scattered light from the sample back to the spectrometer. The spherical lens of the sampling optic is made with UV-grade ultrapure sapphire that has minimal Raman response and does not interfere with the sample Raman signal. The instrument comes calibrated from the factory and the calibration has been proven stable by the vendor for over four years of use (and running).[35]

Results and Discussion

Scope of Work

Extended-Release Niacin Tablets. One classical way for drug release to be controlled is using gel-forming polymers of HPMC.[36] The HPMC K100LV polymer is a low molecular weight HPMC thickener that has a viscosity of 100 cP at a 2% addition rate in water. The HPMC K4M and K15M polymers have moderate hydroxypropyl substitution. The K4M polymer has a viscosity of 4000 cP at 2% in water and the K15M has a viscosity of 15 000 cP at 2% in water. Non-proprietary extended-release formulations of niacin were developed for this study based on internal experience with HPMC and literature procedures.[37–39]

The niacin concentration for all the formulated tablets was maintained at 200 mg. By rationing slower-releasing HPMC polymers with the K100LV polymer, the release rate of niacin can be slowed. The tablets investigated in this study ranged from 95% K100LV/5% K15M to 25% K100LV/75% K15M. A representative formulation for the K100LV/K15M extended-release tablet design is listed in Table I.

The ability to control the release of niacin from the HPMC-based formulations is demonstrated in Figure 1 for the K100LV/K15M formulations. As the tablet dissolves, the K15M polymer in the tablet gels and releases the drug much more slowly than the K100LV polymer. Thus, the release profile is expected to slow down with increasing K15M content. Figure 1 illustrates the formulations used for this study have significantly different release rates and

times to release 80% of the niacin. Thus, by knowing the tablet formulation content of each polymer in the tablet, the resulting dissolution profile can be modeled. This model can then ideally be used to develop a surrogate dissolution determination for RTRT and continuous manufacturing of extended-release tablet formulations. The key, however, is the development of a selective technique to discriminate the HPMC polymer content in the tablets.

Table I. Representative extended-release niacin formulation.

Excipient	w/w (%)	mg/tablet
Niacin	40.0	200.0
HPMC K100LV	19.0	95.0
HPMC K15M	1.0	142.5
Avicel PH102	28.5	50
Mannitol	10.0	2.5
Colloidal silicon dioxide	0.5	5
Sum	100	500

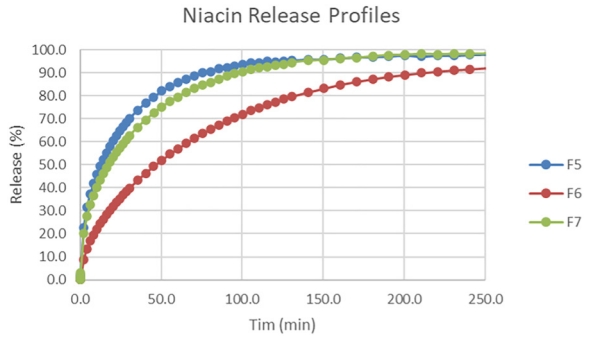

Figure 1. Representative niacin dissolution profiles. Formulation: F5 (blue): 95% K100LV/5% K15M. F6 (red): 25% K100LV/75% K15M. F7 (green): 50% K100LV/50% K15M.

Raman Profiling

The MarqMetrix AIO instrument was set to 300 mW laser power and all measurements were acquired at this setting. Electronic background (dark spectrum) was subtracted from each spectrum by selecting dark subtract and auto new dark. Raman spectra of pure niacin (Figure 2), HPMC LV (Figure 3a), and HPMC K15M (Figure 3b) were measured by directly touching the sapphire lens of the BallProbe to the sample. The integration time for each sample was chosen to maximize the signal without saturating the detector (<~65 000 counts). Niacin is a stronger Raman scatterer than the different types of HPMC presented and hence, a spectral acquisition time of 150 ms was chosen, whereas an acquisition time of 2000 ms was chosen for analysis of the HPMC polymers. Ten spectra were collected for each sample and averaged to improve the signal-to-noise ratio of the pure component spectrum. Figures 2 and 3 show the fingerprint region (100–2000 cm^{-1}) of the averaged Raman spectra of niacin, HPMC LV, and HPMC K15M.

Raman spectra of the different extended-release tablets were acquired at 200 ms acquisition time. Spectra from five random spatial points on each extended-release sample were collected and averaged to get a spectrum that best represents the chemical composition of the tablet. Figure 4a shows the full Raman spectra of pure niacin, HPMC LV, HPMC K15M, and the three extended-release formulated tablets. Figures 4b and 4c show the zoomed-in fingerprint

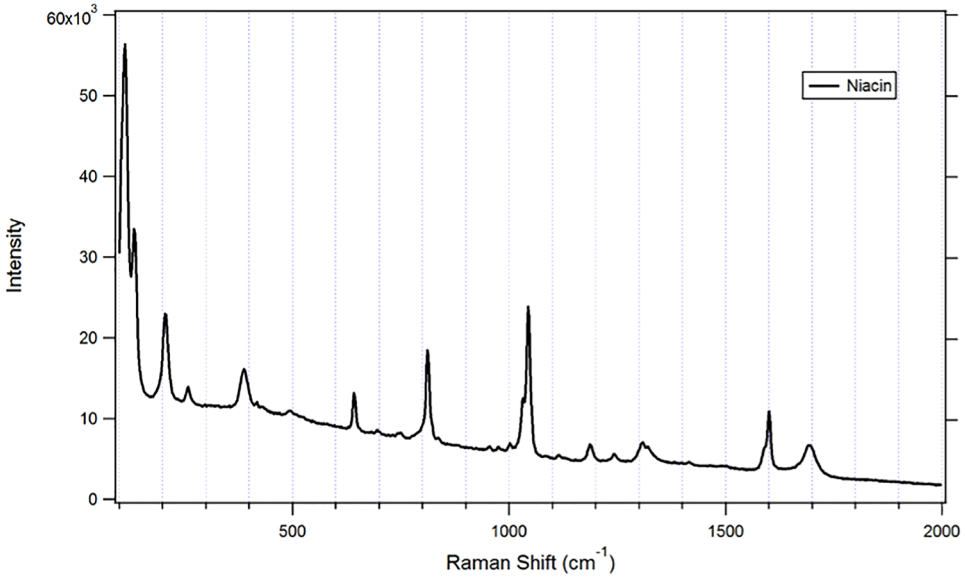

Figure 2. Raman spectrum of niacin. Spectral window: 100–2000 cm^{-1}. Laser power: 300 mW. Spectral acquisition time: 150 ms.

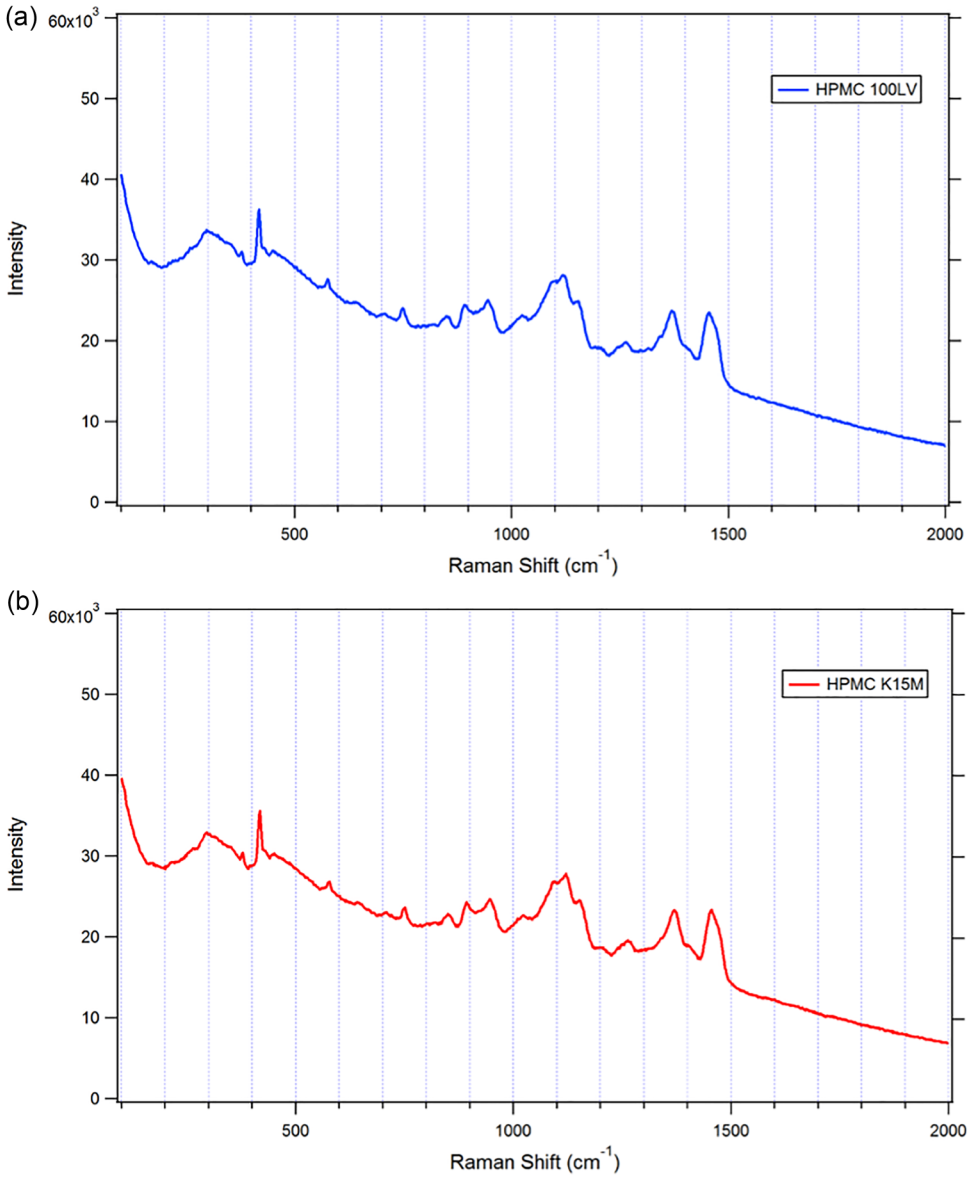

Figure 3. Raman spectrum of HPMC polymers: (a) K100LV, (b) HPMC K15M. Spectral window: 100–2000 cm^{-1}. Laser power: 300 mW. Spectral acquisition time: 2000 ms.

(100–2000 cm^{-1}) and C–H stretch (2000–3250 cm^{-1}) regions, respectively.

Mechanism of Release

As mentioned, any potential capability of a spectroscopic technique for the RTRT of extended-release formulations must effectively model the mechanism of drug release. In this study, this entails resolving and quantifying the high-performance liquid chromatography polymers used. A previous study in the literature has shown that Raman spectroscopy can be used to discriminate between 44E and 41K series of HPMC.[40] This work was able to discriminate grades through small differences in the stretching and bending of the methyl and hydroxypropyl substituents. For our formulation, all the components, except silica, have a strong Raman signal. As illustrated in Figure 5, Raman spectroscopy could distinguish between the K100LV and K15M polymers of HPMC in this matrix. However, this came at the cost of long acquisition times due to the similarities of the polymers. Small spectral differences are observed for the two polymers in the spectral ranges 800–1100 and 2800–2900 cm^{-1}. The maximum relative signal difference between the polymers achieved was <0.3%.

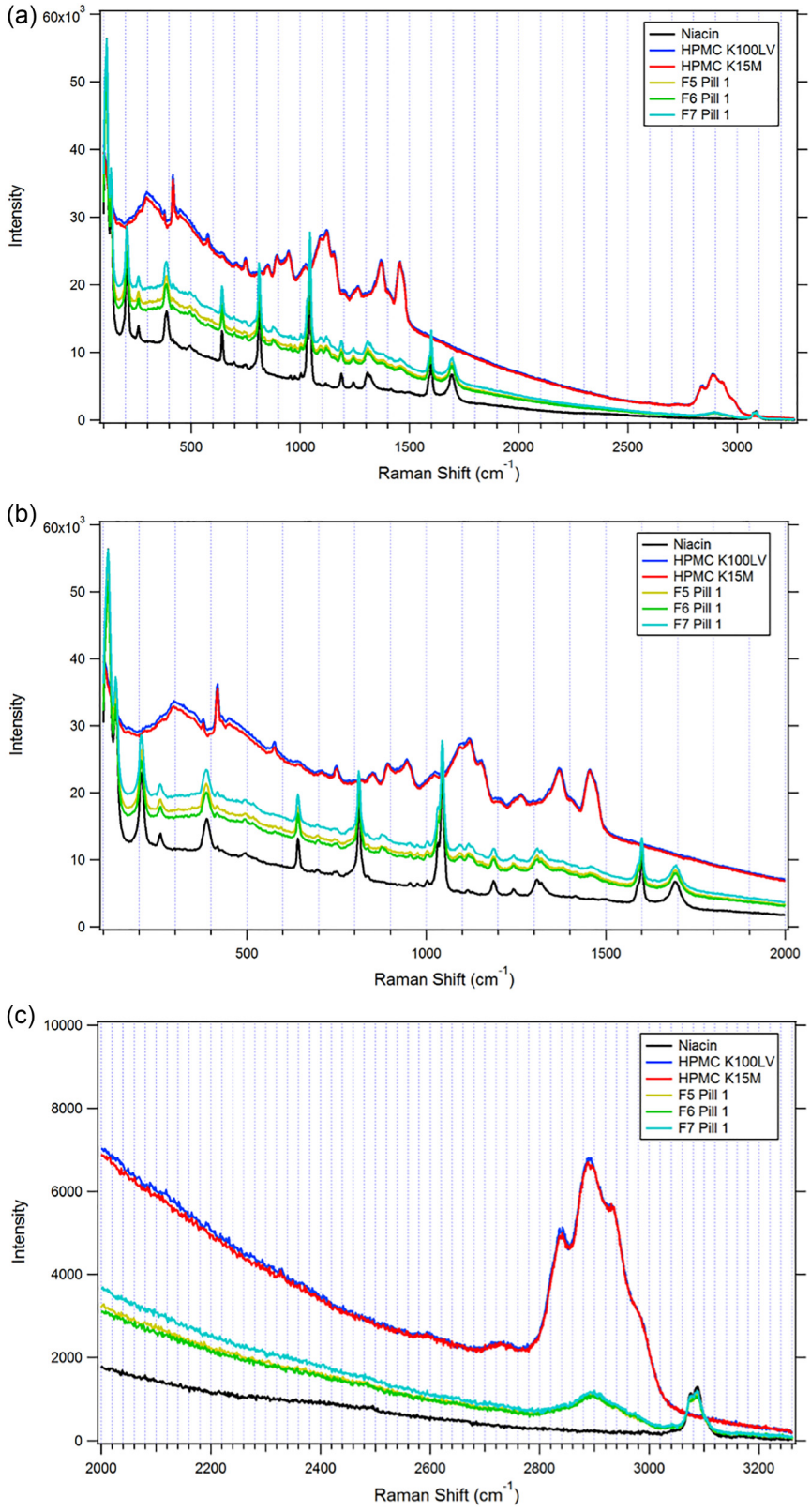

Figure 4. Raman spectra overlay of extended-release tablets: (a) Spectral window 100–3250 cm^{-1}, (b) spectral window 100–2000 cm^{-1}, and (c) spectral window 2000–3250 cm^{-1}.

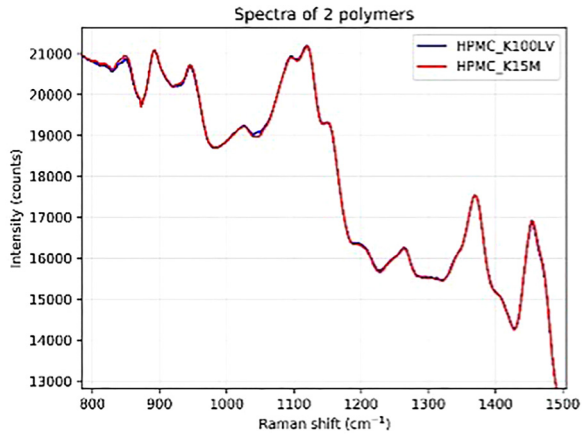

Figure 5. Similarity of HPMC polymers. Small differences are observed between 800–1100 and 2800–2900 cm^{-1}.

Sampling/Tablets

Several Raman sampling interfaces from the Raman supplier were assessed to optimize the tablet signal for this study. The BallProbe interface was not optimal for the analysis of the solid tablets due to the small optical sampling volume of the heterogeneous tablet. The probe did not sample/illuminate enough tablet volume to effectively determine a difference in the spectra of the two polymers. Many laboratories use transmission Raman to achieve representative sampling of tablets as Raman photons are generated from the bulk volume of a sample as light travels through the tablet.[41,42] Applying transmission Raman in this study we found was not optimal due to the low signal intensity and very long analysis times per tablet. The low signal was likely due to the tablet thickness and the absorption/scattering of photons within the tablets.

Finally, a volume excitation and collection MarqMetrix Proximal BallProbe HV with a 3 mm wide excitation spot was evaluated for this application. The large volume sampling Raman probe was the best-performing interface for this application. The results from the volume sampling analysis were more representative of the tablet composition (or tablet surface) and the analysis time was greatly improved.

The chemometric models applied to the spectra for the study tablets were homogeneous in yielding differing dissolution profiles but were heterogeneous in terms of spectral chemical composition. The dissolution variability between tablets within the same group is very strong, much stronger than the spectral variance within any tablet. Thus, our ability to build a successful model was not limited by the Raman signal intensity, but by the complexity of tablet-to-tablet variations. The large area sampling probe was the most effective in analyzing the tablets and greatly improved the sampling precision between tablets. However, this came at the cost of reduced signal intensity. It is clear that the Raman spectra from these preliminary studies have too much variance between tablets, which is not directly correlated to the ratio of polymers. This is not an uncommon occurrence. It has been shown previously that powder blend uniformity strongly depends on the effective sample size of the instrument being used.[43] Differing sample volumes can yield significant effects on the analysis of homogeneity.[44]

Not only does the Raman technique need to be optimized to achieve HPMC polymer resolution, suitable sensitivity, and sample spectral homogeneity, but this investigation must also incorporate content uniformity and dissolution studies to determine whether acceptable uniformity in tablet dissolution is achieved prior to seeing spectral chemical homogeneity. Content uniformity and dissolution are "whole tablet" techniques while the spectroscopic technique tends to use a sampling window. If the spectroscopic sampling window is not representative of the whole tablet profile, spectroscopic RTRT studies for extended-release formulations will be too discriminating to be applied to pharmaceutical manufacturing.

Chemometric Analysis

All chemometric analysis was performed using both proprietary homebuilt and open-source Python libraries such as Scipy and Scikit-learn. A similar analysis can be performed using multivariate data analysis software such as The Unscrambler, Solo, or VektorDirektor. To understand how well a mixture of pure component spectra describes the tablet spectra, we split the Raman spectral range into three regions: phonon (100–300 cm^{-1}), fingerprint (300–1800 cm^{-1}), and CH-stretch (2600–3200 cm^{-1}) as shown in Figure 6.

Each of these regions contains information relevant to the crystalline and amorphous structures as well as the chemical composition of the tablets. Extended multiplicative scatter correction preprocessing was used to correct for additive, multiplicative, and wavelength-dependent baseline variation. A classical least squares (CLS) model was created for each of these regions and applied to the new Raman spectra of the pure niacin and the model residuals were examined. The results indicate that the CLS model works well for the fingerprint and the stretch regions with low residuals. However, the phonon region has a lot of unexplained variation shown in the model residuals. The phonon variation is most likely due to differences in the intermolecular interactions and changes in the crystalline structure from the pure niacin spectrum used as a reference for the CLS.

Next, the CLS model was applied to Raman spectra collected from each of the tablets, and the component composition for niacin and Avicel was analyzed. Again, three tablets from three different batches were selected. The

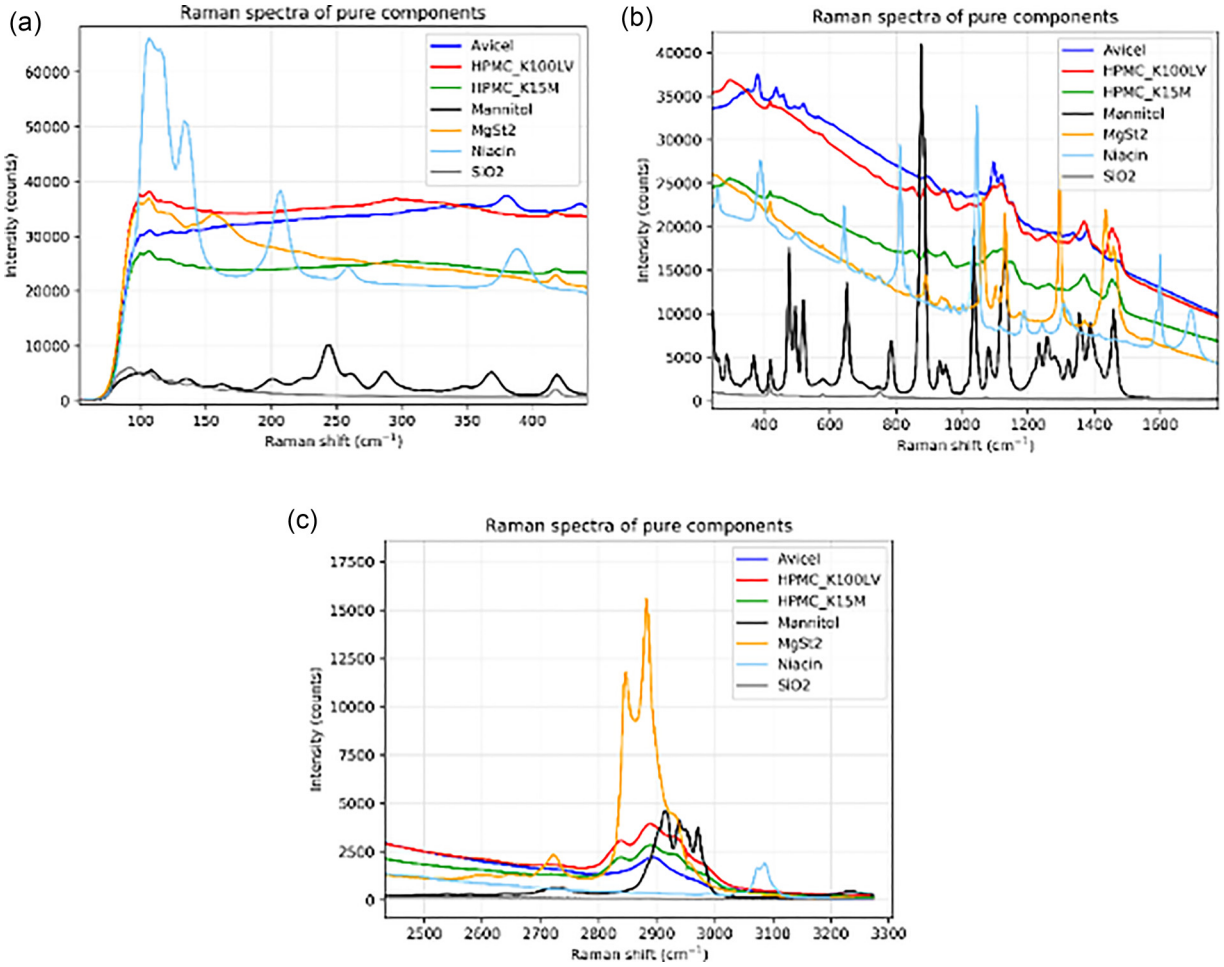

Figure 6. The Raman spectra were divided into three regions before analyzing using CLS. (a) The phonon region from 100 to 300 cm^{-1}. (b) The fingerprint regions are from 300 to 1800 cm^{-1}. (c) The stretch region from 2600 to 3200 cm^{-1}.

tablets within the same group should have the same composition of all ingredients. However, the CLS analysis revealed unexpectedly high variation in concentration of niacin and Avicel between tablets within the same group. This variation was unexpected since the concentration of the two components in all tablets was constant. Furthermore, the variation measured in the content of the polymers using Raman did not correlate well with that described in the formulation.

A medium-level data fusion approach was applied to further investigate the variation identified by the CLS model. The data fusion approach yielded a single model from interrelated datasets that contain complementary information about the sample set.[45,46] The medium level refers to concatenating the data matrix after feature selection. Since the variation in the CLS prediction did not correlate with the group activity, separate principal component analysis (PCA) models for the three spectral regions were applied to the residuals of the CLS model and then the results were combined yielding a single model. Figure 7 shows the schematic of the data fusion approach. The data fusion approach yielded a single model from the data sets that contained information about the sample sets.

The fused data was split into calibration and validation blocks. Out of three tablets in each group, one was randomly chosen for validation keeping the other two as calibration sets. This random split was repeated many times. A PLS-1 model was created on the calibration data set and validated using the validation set. Because of the presence of six independent components, the possible interaction between them, sample warmup during laser illumination, and other unknown factors, having a model with as many as 10 latent variables was considered reasonable.

The errors in the cross-validation of the model were found to be extremely sensitive to the random split of the data into calibration and validation. The results demonstrate the impact of the compositional variation between tablets in the small sample set. In all cases tested, the cross-validation errors were unsatisfactory and were not dependent on the number of latent variables.

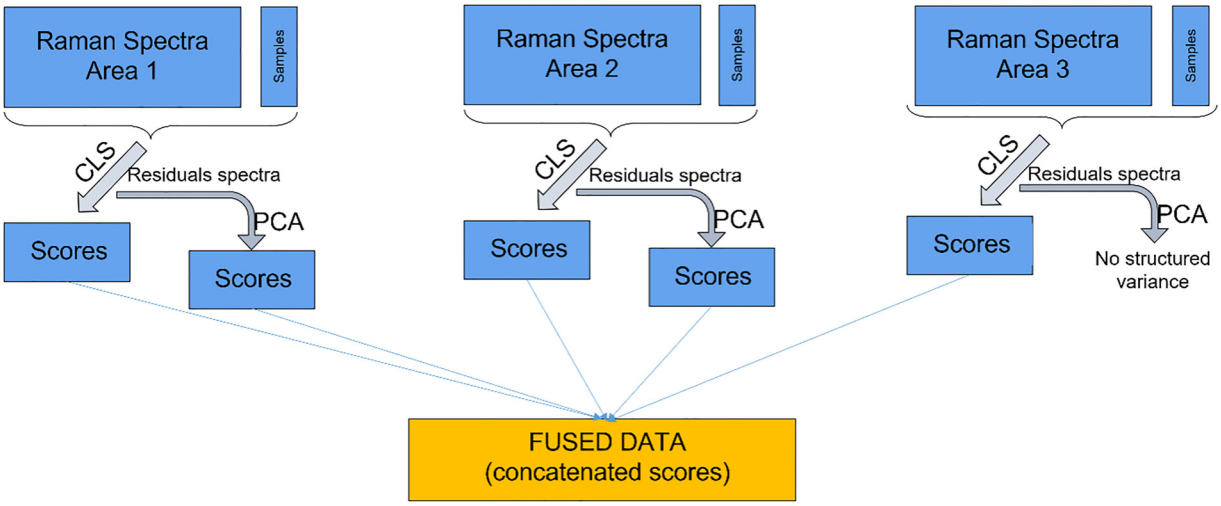

Figure 7. The schematic of a medium-level data fusion approach. Raman spectra were split into three regions (areas) and the CLS model was applied to each region. PCA was performed on the residual spectra from each region and the scores from both approaches were combined.

Conclusion

The use of Raman spectroscopy can easily detect the differences in niacin content in the extended-release tablet formulations. The overlay of the spectra (Figure 4) shows varying amounts of fluorescence (broad background) in all the spectra, with the greatest amount in the HPMC samples and the least in the niacin spectra. There are strong Raman features that allow chemical composition classification of both niacin and HPMCs. Throughout this study, it was observed that the Raman spectra of the different extended-release tablets have strong Raman spectral features of niacin and weak Raman features from HPMC and other components. Raman spectroscopy can be used to easily distinguish niacin from HPMC background and perhaps even be used to distinguish the purity of niacin with more experimentation.

However, while Raman spectroscopy could be used for RTRT in continuous manufacturing for potency and content uniformity determinations, it was incapable here of modeling the mechanism of extended-release of the niacin from the formulation. This was due to the inability to selectively resolve and distinguish the individual HPMC polymer content of the tablet formulations used to control drug release. While the polymers could be distinguished in individual sets, there was not enough spectral difference between the two samples of HPMC to effectively model them in the dissolution study. Further chemometric analysis such as PCA followed by discriminant analysis could possibly be used to distinguish between the two types of HPMC samples with further investigation and a larger sample set.

This study was limited to a small sample size and further work is required to expand on the sample size and the use of chemometric tools to distinguish between the HPMC types. For extended-release tablet applications with continuous manufacturing, further development of dissolution surrogate profiling by spectroscopic techniques is needed.

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Declaration of Conflicting Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article: G.K. Webster is an employee of AbbVie and may own AbbVie stock. B. Mankani is an employee of PPG Inc. S. Mozharov is an independent contractor. B. Marquardt is an employee of MarqMetrix, Inc. AbbVie sponsored and funded the study, contributed to the design, participated in the collection, analysis, and interpretation of data, and in writing, reviewing, and approval of the final publication.

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