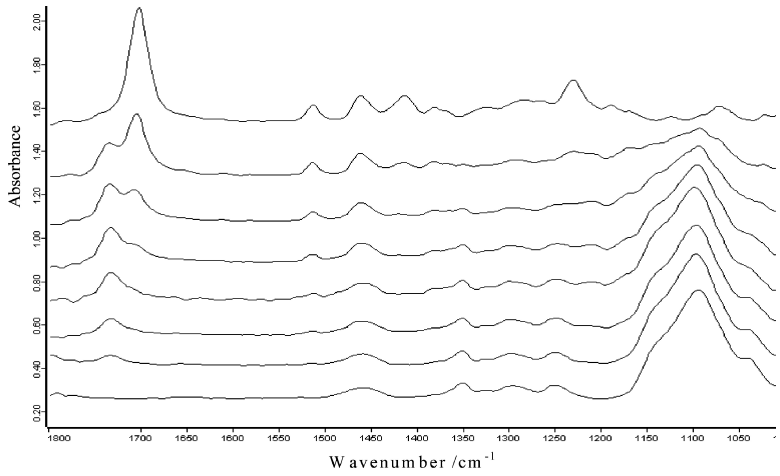
Article

High-Throughput Study of Poly(ethylene glycol)/Ibuprofen Formulations under Controlled Environment Using FTIR Imaging

K. L. Andrew Chan, and Sergei G. Kazarian

J. Comb. Chem., **2006**, 8 (1), 26-31• DOI: 10.1021/cc050041x • Publication Date (Web): 08 December 2005



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 5 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

High-Throughput Study of Poly(ethylene glycol)/Ibuprofen Formulations under Controlled Environment Using FTIR Imaging

K. L. Andrew Chan and Sergei G. Kazarian*

Department of Chemical Engineering, Imperial College London, SW7 2AZ UK

Received March 30, 2005

Simultaneous analysis of many samples under identical conditions improves the effectiveness of research and accelerates product design. A novel spectroscopic imaging approach using a multichannel detector has been developed for parallel analysis of pharmaceutical formulations under controlled environments. Samples of formulations of ibuprofen in poly(ethylene glycol) have been prepared with ibuprofen concentrations ranging from 0 to 100% using a microdroplet deposition approach. The concentration of ibuprofen in PEG at which dimerization of ibuprofen molecules can be avoided has been determined via simultaneous measurement of all samples using in situ FTIR spectroscopic imaging. FTIR spectra from all samples have been analyzed to assess the molecular state of the drug and the degree of polymer swelling as a function of drug concentration. The effect of elevated temperature on the stability of all formulations was also studied. This high-throughput approach identified the concentration range for stable formulations and provided evidence that hydrogen bonding between ibuprofen and the polymer is responsible for enhanced stability at higher temperatures. This high-throughput imaging approach, based on a miniature sampling system, significantly reduces the experimental time by allowing many (potentially a few thousand) experiments to be run in parallel and increases the accuracy by minimizing variations between experiments.

Introduction

The research and development of pharmaceutical formulations often involves the measurement and analysis of a large number of samples. This can be very laborious and time-consuming because of the large number of variables that can influence the performance and stability of the final product. Therefore, there is currently a significant interest in the development of high-throughput screening and experimentation platforms for studying small amounts of pharmaceutical substances in parallel.[1] The current status of applications of high-throughput technology (HTT) for the discovery and analysis of physical forms of drugs is provided in a comprehensive review by Morissette at al.[2] with a focus on drug crystallization, polymorphism, co-crystals, and solvates of pharmaceutical solids. Integration of HTT in pharmaceutical processing is becoming an important feature in industrial applications.[3,4]

Recently, we introduced a new high-throughput approach for parallel analysis of pharmaceutical formulations under controlled humidity utilizing a combination of FTIR-ATR (attenuated total reflection) imaging with a focal plane array (FPA) detector.[5] In this approach, spectroscopic imaging HTT was combined with the microdroplet device for preparation of ∼100 samples directly on the surface of the ATR crystal. The whole imaging area for all samples was relatively small (a few square millimeters), with the size of each sample ∼200 μm, thus minimizing the amount of sample material used for each experiment. The feasibility of screening many different pharmaceutical formulations under controlled humidity was demonstrated in that work.[5] In this paper, we apply this novel approach to analyze the effect of drug concentration and the effect of temperature on the stability of the drug (ibuprofen) in the formulation. The chemical specificity of FTIR spectroscopy has been employed to study the molecular state of ibuprofen under controlled environment as a function of concentration.

The FPA detector contains thousands of small detectors, arranged in a square array, allowing the simultaneous measurement of many spectra from different locations within the sample area.[6−11] The key idea of HTT with FTIR imaging is to utilize the advantage of FPA detectors to measure FTIR spectra of many different samples simultaneously. Combining FTIR imaging with the controlled humidity cell provides an opportunity to study in situ water sorption into different domains of the sample and the behavior of the sample under controlled humidity[12] or to study the sorption of water in many different samples simultaneously. [5]

High-throughput analysis with FTIR imaging can be carried out in either transmission,[13−16] reflection,[17] or ATR modes.[5] ATR spectroscopy has the advantage of having an inherently small path length of a few micrometers, which is found to be suitable for the measurement of many materials, including medical tissues[19]and pharmaceutical tablets.[18]

HTT spectroscopic imaging offers an opportunity to reveal conditions at which the drug may exhibit crystallization. This is possible because IR spectra provide direct evidence of a presence or absence of H-bonding between ibuprofen and the polymer matrix. In one of our previous studies[20] using conventional ATR-IR spectroscopy, it was shown that the

* To whom correspondence should be addressed. E-mail: s.kazarian@imperial.ac.uk.

10.1021/cc050041x CCC: $33.50
Published on Web 12/08/2005

IR spectra in the ν(C═O) spectral region provided evidence for the presence of H-bonding between ibuprofen and poly(vinyl pyrrolidone), which explained the absence of crystalline ibuprofen in this polymer matrix.[20] The absence of crystalline drug may be beneficial for its bioavailability because the presence of crystalline drug impedes the dissolution for the poorly soluble drug.

Experimental Section

FTIR Imaging. The FTIR imaging system consists of a step-scan spectrometer coupled with a macrochamber extension and a 64 × 64 FPA detector. Spectra were measured with 8 cm^{-1} spectral resolution and a spectral range of 1850−900 cm^{-1}. Twenty frames co-addition were used, and the total acquisition time was ∼180 s. Images were acquired using an ATR accessory with an inverted ZnSe pyramid crystal (Specac, Ltd.), which was originally designed for single element detector measurements. The ZnSe ATR accessory can be heated from room temperature to 110 °C to control the temperature of the samples which are attached to the crystal. The size of the FPA 64 × 64 detector is 3.8 × 3.8 mm^2. The size of the imaging area when using the ZnSe inverted pyramid is 3.8 × 5.3 mm^2 due to the geometry of the crystal.[10]

Microdroplet Device. The microdroplet-on-demand device (AutoDrop, MicroDrop) consists of a dispensing control unit, two heated dispensing heads, an in-built computer, an $x-y-z$ positioning system and an $x-y-z$ control unit. The sample container can be heated to a maximum temperature of 160 °C to enable the deposition of molten samples that are solid at room temperature. The dispensing control unit controls the droplet size and the number of droplets to be dispensed at each specific location. The possible single droplets' diameter ranges between ∼30 and 70 μm (corresponding to a volume of 14−180 pL). A number of these single droplets have been combined to form one larger droplet; each of these larger droplets formed an array of samples used in imaging measurements.[5]

Sample Preparation and Methodology. Poly(ethylene glycol) (PEG, M_w = 1500) was purchased from Sigma and was used as received. Ibuprofen was supplied by Whitehall International. The pattern of the sample deposition was programmed by using the macro software, and the deposition was carried out automatically with the $x-y-z$ motorized robot arm. Ibuprofen and PEG 1500 were melted at 80 and 120 °C, respectively, during the dispensing of samples. The dispenser head was heated and maintained at 100 °C to control the viscosity of the liquid being dispensed. The microdroplet device was set to dispense a total number of seven drops from the two dispenser heads to form samples of various ibuprofen concentrations on the ATR crystal. The samples were arranged in an array format following the approach presented earlier.[5] The sample drops remained as liquid throughout the whole deposition process. The samples were deposited directly on the surface of the ZnSe crystal for the FTIR imaging experiment. The vapor-generating instrument (VGI, Surface Measurements Systems) was modified such that it could be integrated with the ZnSe ATR accessory. The uniformity and accuracy of the controlled humidity inside the modified ATR cell were evaluated by comparing the amount of water absorbed in PEG 1500 in the modified cell with the same polymer exposed in the controlled humidity cell in its normal operation mode (the reliability of which has been verified by the manufacturer). All samples were exposed to a controlled humidity and temperature. The system was allowed to reach equilibrium before the image acquisition; equilibrium was verified by the absence of changes in measured spectra.

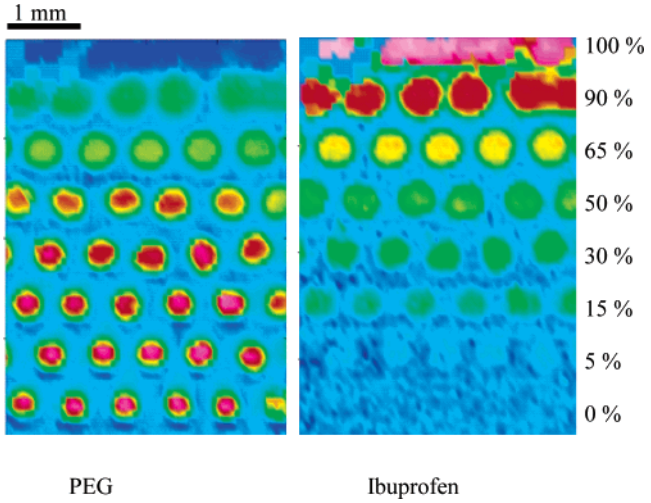


Figure 1. FTIR images of the sample array at 22 °C and 20% RH showing the distribution of PEG on the left and the distribution of ibuprofen on the right. The percentages on the right indicate the calibrated concentration of ibuprofen in PEG for each row of samples.

Results and Discussions

FTIR imaging of samples with known concentrations of ibuprofen deposited on the ATR crystal has been performed under a controlled environment. The diameter of the droplets deposited on the surface of the ATR crystal was estimated to be between 200 and 400 μm (using an optical microscope), depending on the surface tension of the molten sample. The spacing between the centers of each sample was ∼700 μm, giving a total number of samples analyzed in a single image of ∼40. Figure 1 shows the FTIR images of the samples at ambient conditions (22 °C and 20% RH). The top row has been labeled as row 1, and the row numbers increase downward. The FTIR image of PEG was generated by plotting the value of the integrated area of the PEG characteristic band between 1170 and 1020 cm^{-1} for all of the spectra measured by each pixel over the imaged area. The absorbance between 1760 and 1663 cm^{-1} was used to present the distribution of ibuprofen in the imaging area. The integrated absorbance values for the band of ibuprofen have been calibrated with samples of known concentration. A number of formulations of PEG and ibuprofen with different ibuprofen concentrations were created, and the concentrations of ibuprofen in each sample have been represented by a different color. The top row shows the samples of pure ibuprofen and the bottom row shows the samples of pure PEG. Between these two extremes are different mixtures of the two components. The concentration of ibuprofen in each sample was verified spectroscopically using a calibration

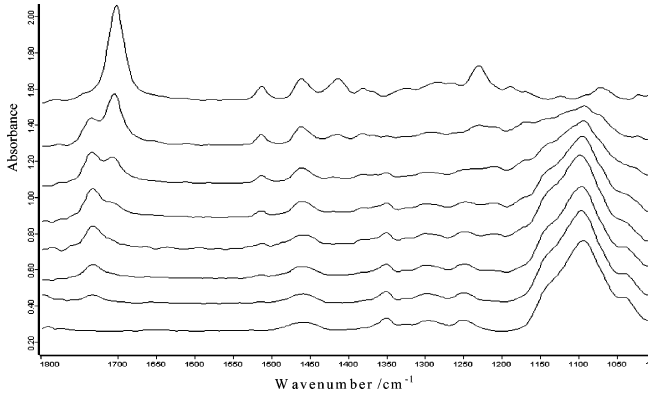


Figure 2. Extracted spectra from each row of the sample array starting from the top with pure ibuprofen to the bottom with pure PEG.

relationship presented in our previous study.[5] The samples within each row were identical which could serve as repeated experiments for specific concentrations to validate the reproducibility. It is important to stress that the samples within the same row could be modified with the addition of a third variable, for example, a variable amount of a third component along each row. This example has demonstrated the opportunity to obtain chemical information of many samples quickly, quantitatively, and simultaneously.

Representative FTIR spectra of the samples from each row have been extracted and are shown in Figure 2. When the concentration of ibuprofen was low (<50 wt %), the maximum of the carbonyl band was at 1732 cm^{-1}, demonstrating that the ibuprofen was molecularly dispersed in the PEG.[21] It also demonstrates that good mixing had been achieved between the PEG and ibuprofen after the deposition. However, as the ibuprofen concentration increased to 50 wt %, a second carbonyl band appeared as a shoulder at 1705 cm^{-1}; this is similar to the absorption of the carbonyl group of pure ibuprofen at the top row of the image. This has been interpreted as the dimerization of the ibuprofen molecules, which is the precursor for crystallization of the drug. The shift of the ν(C═O) band to the lower wavenumber region is caused by the H-bond formed between the carbonyl group and the OH group of two ibuprofen molecules (see Figure 3a). A heating experiment has been performed to confirm that ibuprofen undergoes dimerization. A small amount of ibuprofen was melted at 78 °C, and the IR spectrum showed a strong absorbance at 1705 cm^{-1} and a small shoulder at ∼1750 cm^{-1} (see Figure 3b). The small shoulder has been interpreted as the absorption of free (not dimerized) ibuprofen molecules. When the pure ibuprofen sample was heated further to 160 °C, the absorbance at 1750 cm^{-1} increased, indicating that a higher proportion of the ibuprofen molecules were released from dimers at a higher temperature. The actual position of the ν(C═O) band corresponding to the "free ibuprofen" was estimated from spectral subtraction of the spectrum measured at 78 °C from the spectrum measured at 160 °C; the resultant band was found at 1750 cm^{-1}. The wavenumber of this band is higher than the carbonyl band of the ibuprofen dispersed in PEG, suggesting that there could be interaction, such as hydrogen bonding, between the carbonyl group of ibuprofen and the PEG. In this case, the

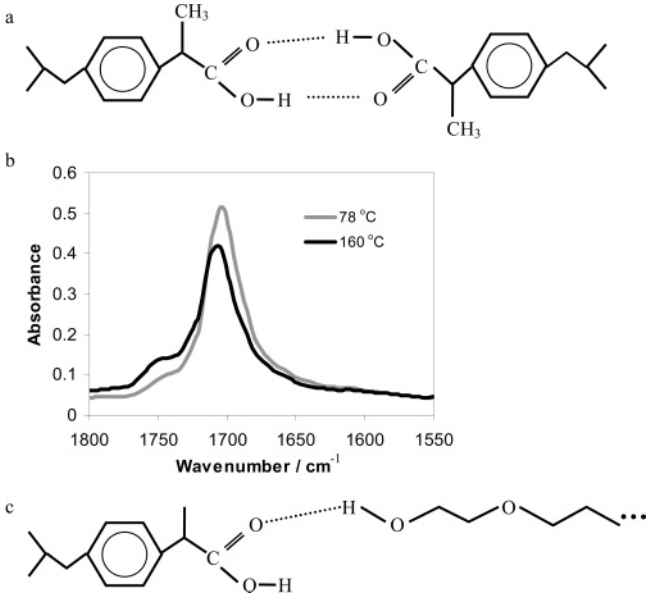


Figure 3. (a) Schematic diagram showing the dimerization of two ibuprofen molecules. (b) FTIR spectra of ibuprofen in the ν(C═O) band region at different temperatures. (c) Schematic diagram showing the hydrogen bonding between the carbonyl group of ibuprofen and the terminal hydroxyl group of PEG.

interaction presumably occurs with the terminal groups of PEG (see Figure 3c), since each PEG chain contains two OH groups that are available for H-bonding. The molecular weight of ibuprofen is 206 g/mol and that of PEG is ∼1500 g/mol; therefore the ibuprofen/PEG ratio above which all hydrogen bonding sites will be occupied is estimated to be 412/1500. This corresponds to ∼27.5 wt % of drug loading. The results presented in Figures 1 and 2 clearly indicate that the weight fraction of ibuprofen in PEG should not exceed 30 wt % in the formulation to avoid dimerization of ibuprofen. This also confirms the importance of H-bonding between ibuprofen and PEG to prevent drug dimerization or crystallization.

The Effect of Controlled Humidity. In these experiments, the ATR crystal was covered with the controlled environment cell shortly after the deposition of the samples. The temperature was maintained at 25 °C while the relative humidity was increased to 80% for a duration of 20 h. FTIR images were measured in situ with 30-min intervals. Spectroscopic images, presented in Figure 4, show the distribution of the relative concentration of water and PEG during the experiment. The images show that water is preferably absorbed in the samples with the lower ibuprofen concentration. Ibuprofen is a hydrophobic substance, and it absorbs a small amount of water, whereas PEG is more hydrophilic. Therefore, the amount of water absorbed should be proportional to the PEG concentration. These results are similar to the initial feasibility study;[5] however, in this paper, the interesting effect of different humidity levels on ibuprofen/PEG formulations is reported.

The bottom row of samples (pure PEG) has the highest PEG concentration at room temperature and humidity (∼22 °C and 20% RH). However, when the whole system was equilibrated at 80% RH, the middle row appeared to contain the greatest PEG concentration. Figure 5 clarifies this finding

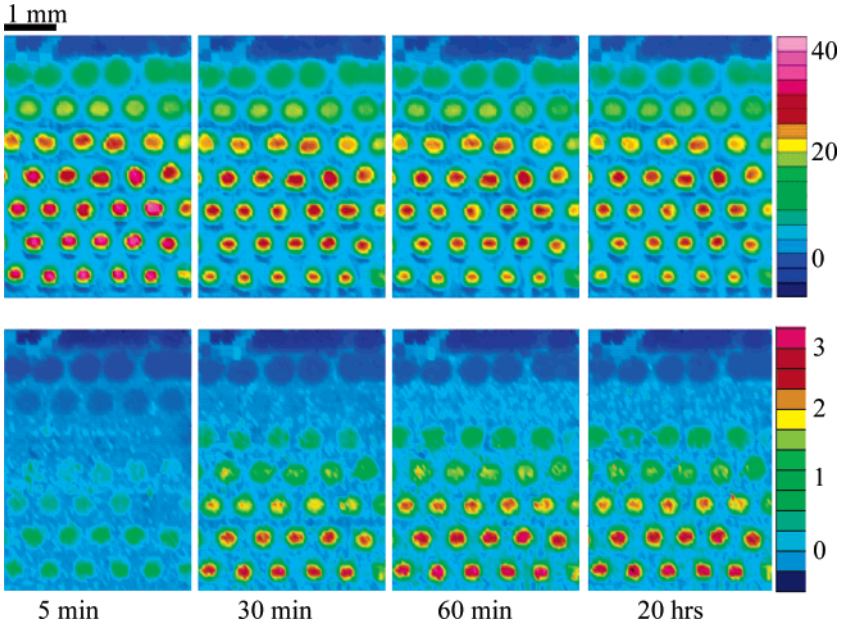


Figure 4. FTIR images of PEG (top row) and water (bottom row) measured at different times after the introduction of 80% relative humidity to the samples. The color represents the value of the integrated absorbance of the corresponding component, which is indicated on the scale bar on the right.

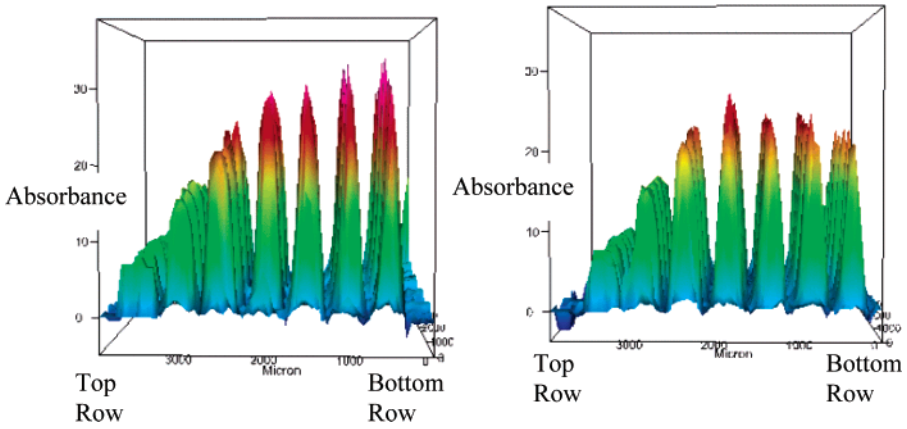


Figure 5. 3D representation of FTIR images of PEG at 20% RH (left) and 80% RH (right).

by presenting images in the format that the relative amount of PEG can be assessed from the height of the corresponding images. The explanation for this is that because of the hydrophilic nature of PEG, a significant amount of water at high RH was absorbed, thus diluting the PEG concentration (measured from ATR spectra), whereas the ibuprofen in the middle row prevents water's being absorbed into the PEG and, hence, reduces the degree of dilution of the PEG. After 20 h of exposure time, the samples in row 5, corresponding to an original ibuprofen concentration of 30 wt %, contained the highest PEG concentration. This is an interesting observation which is important for further application of this HTT approach to study formulations under controlled humidity.

The Effect of Elevated Temperature. A new array of samples was produced with the same range of PEG and ibuprofen concentrations as the experiment described above. The temperature of the ATR crystal was increased to 55 °C, and the samples were exposed to a relative humidity of 80%. The purpose of this experiment was to evaluate the effect of heat on the stability of different formulations with different drug loadings. The samples remained at these conditions for 18 h, and FTIR images were measured at 1-h intervals. A series of images showing the distribution of the concentration of ibuprofen at different times are shown in Figure 6. Under these conditions, ibuprofen undergoes sublimation, and the ibuprofen concentration in PEG decreases with time. However, the relative reduction in ibuprofen concentration in those samples that originally had a lower concentration was much smaller. Table 1 summarizes the percentage changes of the amount of ibuprofen after 18 h of heating in the controlled environment unit. Pure ibuprofen (row 1) was totally sublimed after 5−9 h of heating, according to Figure 7. The sample with a significant amount of the dimerized ibuprofen (rows 2−3 in Figure 4) has shown a larger percentage reduction of ibuprofen concentration, whereas the reduction for the samples with molecularly dispersed ibuprofen is relatively smaller. Furthermore, the samples containing only dispersed ibuprofen have shown a similar percentage reduction in ibuprofen concentration. This suggests that the H-bonding between PEG and ibuprofen in the formulation with molecularly dispersed drug increases the

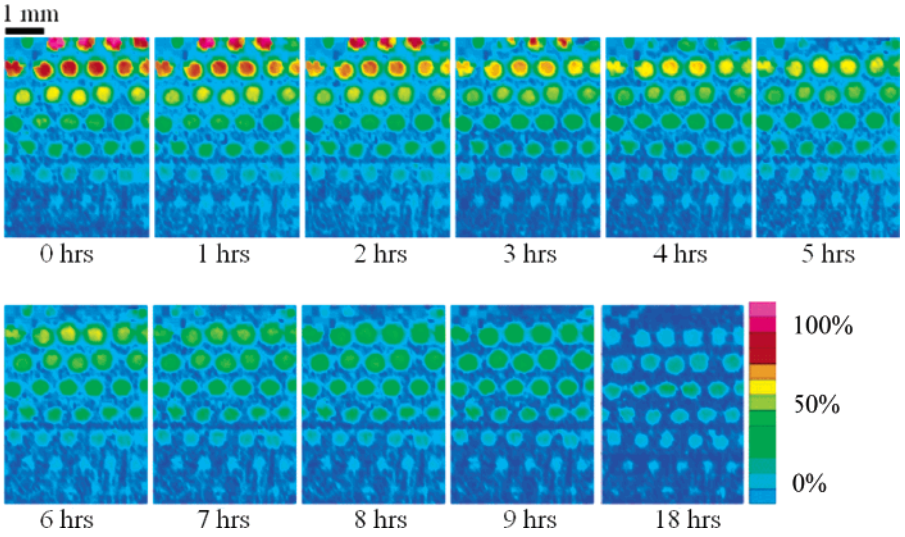


Figure 6. FTIR images of ibuprofen with samples heated to 55 °C. The percentages on the right of the color scale indicate the calibrated concentration of ibuprofen in PEG for each row of samples.

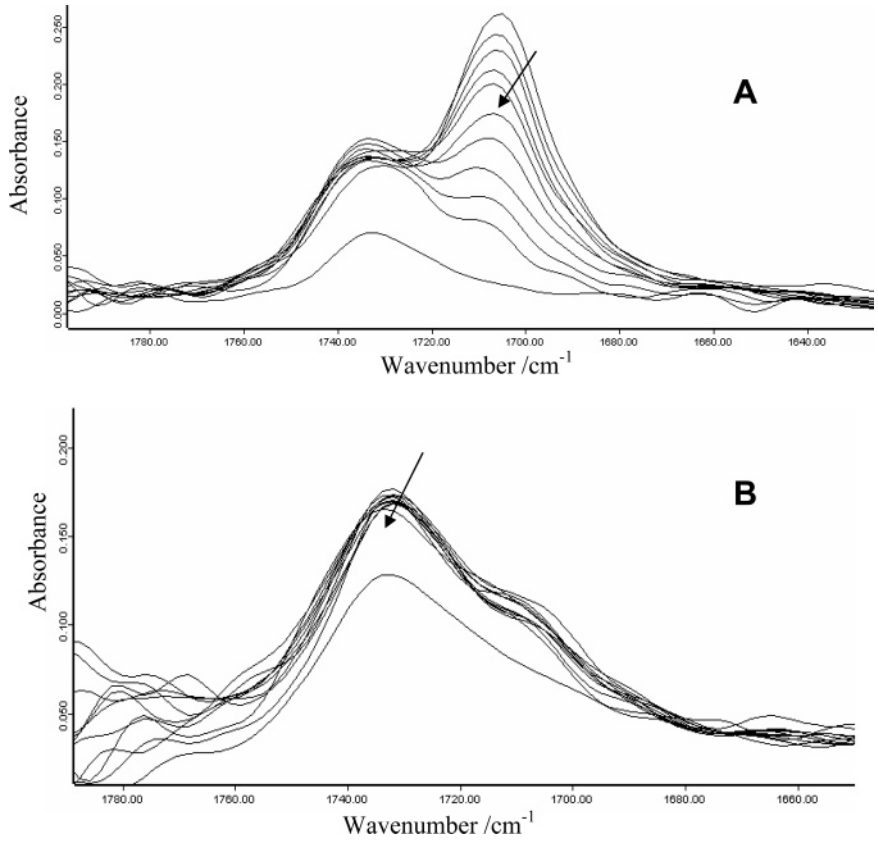


Figure 7. A and B show the FTIR spectra extracted from the sample in rows 2 and 4, respectively, at 55 °C and 80% RH as a function of time in the ν(C═O) band region of ibuprofen. Arrows show changes in the spectra with time.

stability of ibuprofen and retards the sublimation process. The dimerized or crystallized ibuprofen molecules are less affiliated with the PEG chains, as compared to dispersed ibuprofen molecules, thus supporting the proposal that the dispersed ibuprofen molecules were bound to the PEG chain through H-bonding. Spectra of the samples in row 2 during the heating have been extracted and are shown in Figure 7A. The ν(C═O) band at 1705 cm^{-1}, which represents the dimerized ibuprofen molecule, decreased dramatically in the first 9 h, while the peak at 1735 cm^{-1}, which represents the dispersed ibuprofen, did not change. These spectra show that most of the dimerized ibuprofen, which accounted for more than half of the initial ibuprofen concentration, sublimed in the first 9 h of heating. Comparing this to the spectra extracted from the sample at row 4, most of the ibuprofen molecules were dispersed as confirmed by the position of the carbonyl band. Figure 7B shows that for the samples in row 4, there are minor changes in ibuprofen concentration for the first 9 h, which is much less than the sample in row 2. These results infer that dispersed ibuprofen molecules were

Table 1. Summary of the Effect of Temperature and Humidity on the ν(C═O) Band of Ibuprofen

integrated absorbance of the ν(C═O) band of ibuprofen			
row	before	after	% change
1	10.83	−0.64	−106
2	9.13	0.86	−91
3	6.67	1.92	−71
4	5.09	3.00	−41
5	3.10	1.71	−45
6	1.77	1.02	−42
7	0.31	0.40	28
8	−0.77	0.03	103

more stable than those of the dimerized ibuprofen. Rows 7 and 8 have shown a slight increase in ibuprofen concentration, which could be due to the absorption of the sublimed ibuprofen vapor during the experiment. However, the absolute amount of absorption was very small. More sophisticated data analysis, such as principle component analysis (PCA) and classical least-squares (CLS), could be applied to improve the accuracy of data interpretations; this is left for further studies. Nevertheless, it is clear that the HTT approach is a fast and effective way to identify a specific drug loading at which the drug will be the most stable in a formulation under a specific environment and at a specific temperature. This is especially important when the active pharmaceutical ingredient has a high vapor pressure. The results of the presented HTT approach have demonstrated the opportunity to optimize a formulation with the correct drug loading, thus reducing the waste of expensive ingredients in pharmaceutical formulations.

Conclusions

FTIR imaging was successfully applied in a novel way to study in situ 40 samples of ibuprofen/PEG formulations simultaneously at a controlled humidity and temperature. This high-throughput approach provided information about a specific weight fraction of ibuprofen in PEG (∼30 wt %) which should not be exceeded in the formulation to avoid dimerization of ibuprofen. It was also found that 50 wt % of ibuprofen loading is the maximum drug/polymer ratio under which the drug is most stable. This effect was particularly pronounced at elevated temperatures when formulations with the higher ibuprofen loading lost a significant amount of drug due to sublimation while the amount of ibuprofen in molecularly dispersed formulations changed significantly less.

The number of samples being measured in this setup is far less than the number of detector elements (4096 for a 64 × 64 array) present in the FPA. There is a possibility to increase the number of samples further to the total number of detector elements. Work left for future studies includes exploring opportunities to increase the number of samples via the introduction of a grid on the surface of the ATR crystal to gain direct control of the sample size and to reduce the separation between samples, modifying the surface properties of the crystal, and expanding the field of view with optical lenses.

The demonstrated FTIR spectroscopic imaging HTT approach can contribute to significantly shorter production cycles for pharmaceutical formulations because it allows one to rapidly identify specific formulations that exhibit drug crystallization or polymorphism. This method also enables one to assess the molecular state of the drug in many formulations simultaneously and to study the stability of formulations at different environments. It is also possible to analyze relative concentrations of the different polymorphs in many formulations in a broad range of environmental conditions; this will be investigated in our future studies.

Acknowledgment. We thank EPSRC (Grant GR/T08746/01), Pfizer, and Surface Measurement Systems, Ltd for support.

References and Notes

(1) Gardner, C. R.; Walsh, C. T.; Almarsson, O. *Nat. Rev. Drug Discovery* **2004**, *3*, 926.
(2) Morissette, S. L.; Almarsson, O.; Peterson, M. L.; Remenar, J. F.; Read, M. J.; Lemmo, A. V.; Ellis, S.; Cima, M. J.; Gardner, C. R. *Adv. Drug Delivery Rev.* **2004**, *56*, 275.
(3) Storey, R. A.; Docherty, R.; Higginson, P. D. *Am. Pharm. Rev.* **2003**, 100.
(4) Gardner, C. R.; Almarsson, O.; Chen, H.; Morissette, S.; Peterson, M.; Zhang, Z.; Wall, S.; Lemmo, A.; Gonzalez-Zugasti, J.; Monagle, J.; Marchionna, J.; Ellis, S.; McNulty, C.; Johnson, A.; Levinson, D.; Cima, M. J. *Comput. Chem. Eng.* **2004**, *28*, 943.
(5) Chan, K. L. A.; Kazarian, S. G. *J. Comb. Chem.* **2005**, *7*, 185.
(6) Koenig, J. *Adv. Mater.* **2002**, *14*, 457.
(7) Miller-Chou, B. A.; Koenig, J. L. *Macromolecules* **2002**, *35*, 440.
(8) Rafferty, D. W.; Koenig, J. L.; Magyar, G.; West, J. L. *Appl. Spectrosc.* **2002**, *56*, 1549.
(9) Kazarian, S. G.; Higgins, J. S. *Chem. Industry* **2002**, *issue 10*, 21.
(10) Chan, K. L. A.; Kazarian, S. G. *Appl. Spectrosc.* **2003**, *57*, 381.
(11) Kidder, L. H.; Haka, A. S.; Lewis, E. N. Instrumentation for FT-IR Imaging. In *Handbook of Vibrational Spectroscopy*; Chalmers, J. M., Griffiths, P. R., Eds.; John Wiley & Sons: Chichester, 2002; Vol. 2; p 1386.
(12) Chan, K. L. A.; Kazarian, S. G. *Vib. Spectrosc.* **2004**, *35*, 45.
(13) Snively, C. M.; Oskarsdottir, G.; Lauterbach, J. *Catal. Today* **2001**, *67*, 357.
(14) Snively, C. M.; Oskarsdottir, G.; Lauterbach, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 3028.
(15) Hendershot R. J.; Vijay, R.; Feist, B. J.; Snively, C. M.; Lauterbach, J. *Meas. Sci. Technol.* **2005**, *16*, 302.
(16) Hendershot, R. J.; Snively, C. M.; Lauterbach, J. *Chem.—Eur. J.* **2005**, *11*, 806.
(17) Kubanek, P.; Busch, O.; Thomson, S.; Schmidt, H. W.; Schuth, F. *J. Comb. Chem.* **2004**, *6*, 420.
(18) Chan, K. L. A.; Hammond, S. V.; Kazarian, S. G. *Anal. Chem.* **2003**, *75*, 2140.
(19) Colley, C. S.; Kazarian, S. G.; Weinberg, P. D.; Lever, M. J. *Biopolymers* **2004**, *74*, 328.
(20) Kazarian, S. G.; Martirosyan, G. G. *Int. J. Pharm.* **2002**, *232*, 81.
(21) Kazarian, S. G.; Chan, K. L. A. *Macromolecules* **2003**, *36*, 9866.

CC050041X