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FTIR Spectroscopic Imaging of Dissolution of a Solid Dispersion of Nifedipine in Poly(ethylene glycol)

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Abstract: FTIR imaging was applied to study solid dispersions of a poorly water-soluble drug in poly(ethylene glycol) (PEG) and dissolution in water. It has been shown that initially amorphous nifedipine crystallizes within PEG-8000 for formulations with a drug loading of at least 10 wt %. The formation of a significant amount of crystalline drug within the polymer matrix reduces the rate of dissolution of the drug. This FTIR spectroscopic imaging in the ATR mode provides novel insight into the mechanism of dissolution of nifedipine from solid dispersions in water-soluble polymers, which is valuable in optimization of manufacturing these formulations.

Keywords: FT-IR imaging; spectroscopy; crystallization; poly(ethylene glycol); drug dissolution

Introduction

Solid dispersions of poorly water-soluble drugs in water-soluble polymers are usually used to enhance drug dissolution rates.[1−4] However, significant questions remain with regard to polymer dissolution and drug release, and these are often difficult to answer without spatially resolved chemical information about the dissolution process. These questions are as follows. How does drug release proceed, primarily via diffusion or via polymer degradation? How do the drug loading and its distribution in the polymer matrix affect the drug dissolution? Does the morphology of drug change during the dissolution process? In this paper, we demonstrate that FTIR imaging is the method of choice for answering these questions.

FTIR imaging is based on the use of infrared array detectors initially developed for military applications.[5−7] FTIR imaging offers a possibility of simultaneously measuring spectra from many different locations in the sample. These FTIR spectra provide information about the concentration of a specific compound and its chemical structure and morphology. This is particularly important in the case of drugs which may have a complex morphology or exhibit polymorphic changes upon contact with the dissolution medium. Therefore, FTIR imaging offers a unique method of analyzing the distribution of a drug and its molecular structure as a function of time during dissolution. We suggested the term "chemical photography" to describe the role of FTIR imaging in studying such processes.[8] Our approach is based on the attenuated total reflection (ATR) method, which allows analysis of aqueous solutions and samples in contact with water, due to a low degree of penetration of infrared light into the sample. Transmission FTIR imaging was also used recently as an analytical tool to study drug delivery systems and dissolution processes, but it required the use of D_2O and also necessitated the use of very thin samples.[9] FTIR imaging in transmission was also used recently to study a formulation of griseofulvin in PEG under controlled humidity.[10]

Nifedipine is a poorly water-soluble drugs, and many different approaches to enhancing its dissolution rate have

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been explored. These include preparation of solid dispersions using various techniques, the use of inclusion complexes, etc.[4,11−14]

Forster et al.[12] have studied the effect of different methods of preparation of solid dispersions of nifedipine on the drug molecular state via FTIR spectroscopy. They have studied preparation through melt extrusion to produce a glass solution (which results in amorphous dispersion of a drug in a polymer) and mechanical mixing of a drug and polymer. It was found that an amorphous dispersion of a drug in the polymer matrix exhibits a faster dissolution rate than formulations prepared with the crystalline drug. This paper reports the application of FTIR imaging to the study of dissolution of solid dispersions of nifedipine in poly(ethylene glycol) and will also demonstrate the effect of drug loading on the morphological stability of the drug and its implication for drug dissolution.

Experimental Section

The drug α-crystalline nifedipine [1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-3,5-pyridinedicarboxylate] was kindly supplied by G. Chryssikos (National Hellenic Research Foundation, Athens, Greece). PEG (MW = 8000) was purchased from Sigma. Three different samples with 5, 10, and 20 wt % drug loading in PEG were prepared by dissolving different amounts of the crystalline drug in molten PEG at ca. 70 °C according to their weight percentage. The mixture was allowed to cool at room temperature until it solidified. The sample was then powdered with a spatula. A small amount of sample was transferred to the surface of the ATR crystal (inverted ZnSe prism) where it was heated to 60 °C to melt again. A cover glass slide was placed over the molten sample with a spacer to create a gap of a few hundred micrometers between the cover glass and the ATR crystal surface. The sample was then allowed to cool to 40 °C to solidify before water was added from the side of the film to study dissolution of the polymer/drug formulation. The water reaches the formulation by capillary action. Once water is added, consecutive FTIR images are acquired at ca. 5 min intervals with a spectral resolution of 8 cm^{-1} and in the spectral range from 1800 to 900 cm^{-1}. The experimental setup was the same as that described previously.[8]

The FTIR imaging system consists of an IFS 66/s step scan infrared spectrometer (Bruker) with a macro chamber extension (IMAC, Bruker). The ZnSe ATR accessory was situated in the sample compartment of the macro chamber. The position of the accessory was adjusted so that a good focused image was obtained. A focal plane array (FPA) detector consists of 64 × 64 detector elements, with each element collecting a single spectrum, and is used to capture FTIR images. The sample spectra were ratioed against background spectra, which were measured without any sample. Five frames were co-added, giving a total acquisition time of approximately 90 s per image. The image size is approximately 3.8 mm × 5.3 mm.

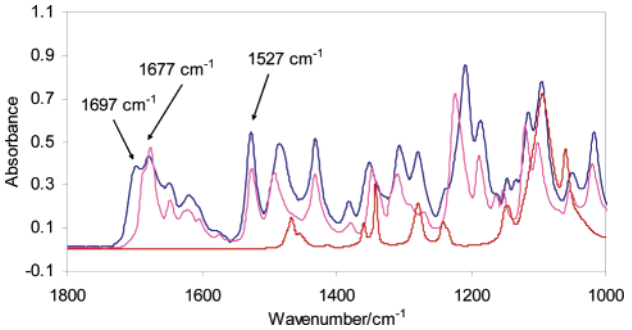

Figure 1. Representative ATR-IR spectra (with a spectral resolution of 4 cm^{-1}) of amorphous (blue) and α-crystalline nifedipine (pink) and PEG (red).

Results and Discussion

First, we compare IR spectra of amorphous and crystalline nifedipine since the integral absorbances of their IR bands were used to generate corresponding spectroscopic images. The representative spectra are shown in Figure 1 along with the spectrum of PEG for comparison. Amorphous nifedipine has a number of absorption bands in the region of the ν(C═O) band at ca. 1697 cm^{-1}. The drug has a rather complicated morphology with a number of possible polymorphs, and this has been studied in greater detail using conventional FTIR and Raman spectroscopy.[15] The pink spectrum shown in Figure 1 represents the α-crystalline form of nifedipine which can be distinguished from that of its amorphous form by the noticeable shift of the carbonyl band to the lower-wavenumber region. Our previous study has shown that with a high moisture content (e.g., at a high relative humidity) the amorphous form of nifedipine changes to its most stable α-crystalline form.[15] The ν(C═O) band of nifedipine may appear as an obvious choice for generating spectroscopic images. However, the proximity of this band to the band corresponding to the water bending mode makes the use of this band difficult in imaging experiments of dissolution of nifedipine in water. Therefore, the absorption band of nifedipine at 1527 cm^{-1} [$\nu_{as}(NO_2)$] was used quantitatively determine the distribution of this drug in the sample. The ν(C═O) band of nifedipine was still useful in assessing the molecular state and morphology of the drug.

The dissolution study of the nifedipine/PEG formulation is represented as a series of spectroscopic images of the formulation in contact with water. These images are generated by plotting the distribution of the integral absorbance of corresponding bands of the drug and polymer with a baseline drawn between the limits of integration as a function

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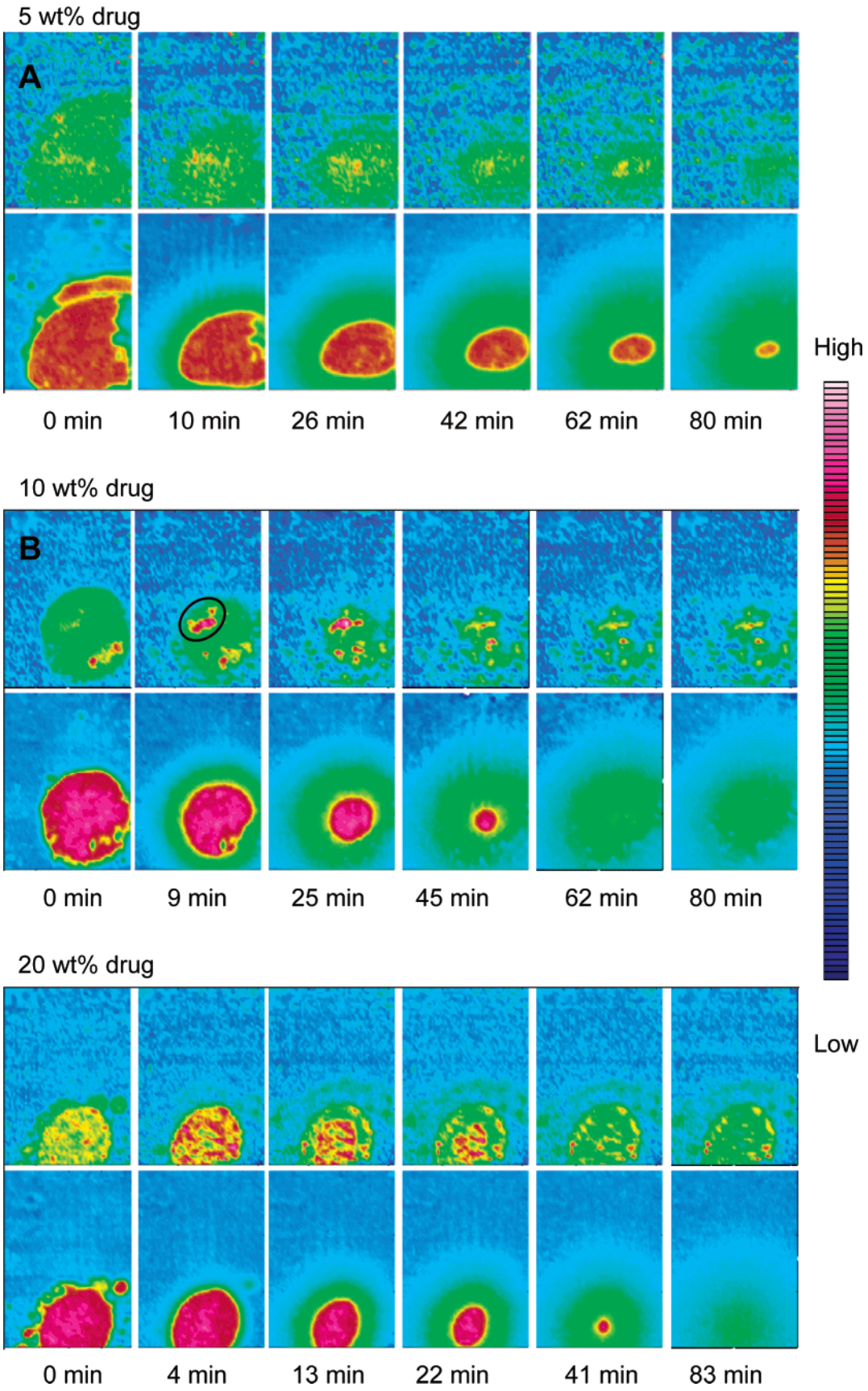

Figure 2. ATR-IR images of nifedipine/PEG formulations at different drug loadings dissolved in water. The top and bottom rows of each image set represent the distribution of the drug and polymer, respectively, as a function of time. The image size is ca. 3.8 mm × 5.3 mm.

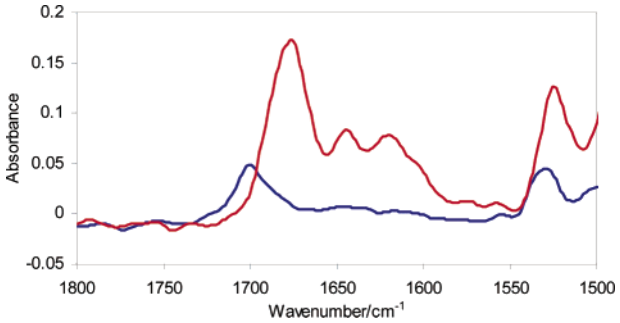

Figure 3. ATR-IR spectra of nifedipine in the ν(C═O) region extracted from selected locations in the sample from images A and B of Figure 2. The red and blue lines represent the non-normalized spectra extracted from the red and green areas of the images, respectively.

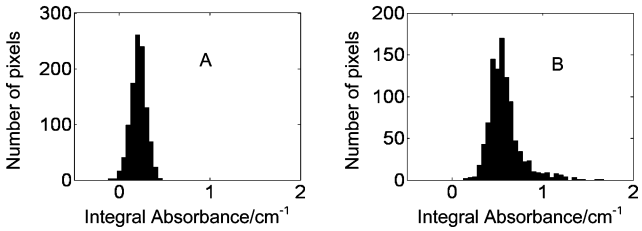

Figure 4. Histograms of nifedipine distribution in PEG with drug loadings of 5 wt % (A) and 10 wt % (B).

of time. Figure 2 shows images based on the $\nu_{as}(NO_2)$ of nifedipine (top row) and images based on the band of PEG (bottom row) between 1170 and 1020 cm^{-1} which represents the coupled stretching ν(C−O), ν(C−C), and deformation $\delta(CH_2)$ modes. Different colors in these images correspond to different relative concentrations of each component (drug and polymer) during the dissolution of the prepared formulation. Thus, the top row of each set of the images represents the distribution of nifedipine and the bottom row the PEG distribution as a function of time as dissolution proceeds. The color scales of each row of images have been adjusted so that the color represents the same range of integral absorbance within the row, which can be used for direct comparison within each row. The images of PEG (bottom rows) show a continuous and smooth dissolution profile which is evidenced by the symmetrical decrease in the concentration of PEG due to contact with water surrounding the sample. Qualitative comparison of the PEG dissolution process based on the presented images shows that it was not significantly affected by the amount of drug loading. However, analysis of the acquired images of the drug (top rows) shows that drug dissolution is a more complex phenomenon.

The image based on the distribution of the drug in the formulation containing 5 wt % nifedipine, measured prior to addition of water, shows the absence of drug crystallites in the sample. This is evidenced by the spectra extracted from the green areas in the top left image of Figure 2, which show that the position of the maximum absorbance of the drug's carbonyl band is at 1697 cm^{-1}, which indicates that the drug is amorphous. The extracted spectra are shown in Figure 3. The absence of the absorption band at 1677 cm^{-1} of the dispersed nifedipine shown in Figure 3 as compared to pure amorphous nifedipine shown in Figure 1 indicates molecular dispersion of nifedipine in PEG. However, as the drug loading increases to 10 wt %, not all of the nifedipine particles are dissolved in the molten PEG during the sample preparation and some crystalline particles remain in the polymer matrix. The nifedipine image of the formulation with a drug loading of 10 wt % before the addition of water (left image in the corresponding row) shows that most of the drug in the formulation is amorphous (green area). However, the images show that there are also small domains with high concentrations of the drug within the sample. Spectra extracted from these red areas show a shift in the carbonyl band from 1697 to 1677 cm^{-1} (see Figure 3). This is indicative of the drug in its α-crystalline form.[15,16] More crystalline drug was found in the formulation prepared with a drug loading of 20 wt %. The relative increase in the absorbance of the drug band without the apparent decrease in the absorbance of the PEG band (reflected by the rather uniform color in the images) could be due to the fact that the change in the overall amount of the PEG during the drug crystallization is relatively small.

The homogeneity of the nifedipine distribution in each of the samples (before the addition of water), apart from plotting color maps, can also be compared by plotting the integral absorbance of the drug band as a histogram. For a homogeneous mixture, the histogram will show a narrow distribution of absorbance values detected at each pixel of the array detector, while a more heterogeneous mixture will show a broader distribution of absorbance values. Since the sample size is smaller than the image field of view, the images have been masked such that only the data in the area of the sample are plotted on the histogram. Images A and B of Figure 2 have been plotted as histograms A and B in Figure 4, respectively. The peak of the histogram is shifted to a higher value for the sample with a higher drug concentration. Histogram A shows a relatively narrow distribution with little variation in absorbance across the sample. On the other hand, histogram B shows a broader distribution range. The small shoulder on the right-hand side of histogram B represents the small domains of the high drug concentration as shown in image B of Figure 2. The histograms indicate that the drug distribution is more homogeneous when the drug loading is 5 wt %. The heterogeneity of the nifedipine distribution in the high drug loading range is caused by the presence of the nondissolved crystalline particles within the polymer matrix. In one of the studies, Chutimaworapan et al. speculated that nifedipine forms hydrogen bonds with PEG.[11] Indeed, formation of H-bonds between drug molecules and a polymer may be beneficial in preventing drug crystallization.[17]

In Figure 2, the images of drug distribution for the formulation with a drug loading of 5 wt % after addition of water show that the nifedipine disappears as the polymer dissolves. No drug crystallization has been observed in this

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case upon contact with water, unlike the case of the ibuprofen/PEG formulation which was reported earlier.[8] However, a sudden increase in the drug concentration was observed in certain locations in the sample of the formulation with a drug loading of 10 wt % after contact with water for 9 min. These locations are encircled by the black line. The spectra extracted from these new locations of the high drug concentration demonstrate that the drug is transformed into the α-crystalline form in these areas of the sample. This observation is interesting because spectra also showed that liquid water has not reached those areas yet, and the spectra from the sample of the surrounding areas show nondissolved semicrystalline PEG. This phenomenon is even more pronounced in the case of the 20 wt % drug experiment. Crystallization of the drug takes place within the polymer matrix well before liquid water reaches the corresponding areas in the sample. This phenomenon is different from that reported for ibuprofen/PEG formulations in contact with water. It is known, however, that amorphous nifedipine converts to its crystalline form upon exposure to water vapor.[15,18,19] Apparently, some amount of water vapor was absorbed into the sample through the microchannels within the formulation and initiated the crystallization of the amorphous drug within the polymer matrix. This small amount of water was apparently below the detection limit of ATR spectroscopy used to generate the images. The initial presence of very small α-crystalline particles inside the formulation with drug loadings of 10 and 20 wt % may have acted as nucleation sites for the rapid growth of the drug crystals. Drug crystallization within the polymer matrix has significant implications for the overall dissolution process. Indeed, for the formulation with a drug loading of 10%, most of the drug is dissolved after 80 min; however, some drug crystallites remained close to their original locations. The formulation with a drug loading of 20% has shown an overall drug concentration reduction after 80 min, but the drug crystallites remain in their original locations.

These imaging results demonstrate that for a relatively low drug loading the polymer matrix helps to stabilize the morphology of the drug such that the drug remains amorphous upon contact with water. Consequently, drug dissolution is enhanced since the amorphous drug is more soluble in water. This enhancement was reported in several studies,[11−13] but it the first time that direct insight into the dissolution process was obtained via spectroscopic imaging. The drug release rate for the low drug loadings is controlled by the rate of polymer dissolution. This can be optimized by changing the polymer molecular weight. Our observations provide a plausible explanation of recent results published by Emara et al.,[13] who reported that an increase in the molecular weight of PEG from 5000 to 6000 improved dissolution possibly due to PEG-6000 being more effective in preventing drug crystallization. On the other hand, our results indicate that increasing the drug loading in PEG-8000 to >5 wt % causes drug crystallites to form. This shows that in such cases the mechanism of drug release becomes more complex and, therefore, more difficult to predict and control. Apparently, for PEG with a certain molecular weight, there is a maximum drug/polymer ratio limit that allows one to avoid the formation of drug crystallites, which is a drug loading of ca. 5 wt % in the case of PEG-8000. Alternative routes to improving dissolution of nifedipine by preventing drug crystallization are found in inclusion complexes with cyclodextrins, which have also been explored but not analyzed yet by spectroscopic imaging methods with the exception of a recent study of dissolution of the ibuprofen formulation.[8] Finally, multivariate analysis such as PCA (principal component analysis) or MCR (multivariate curve resolution) could be useful in a further qualitative analysis of our imaging data, and this will be the subject of our future work.

Conclusions

We have studied dissolution of solid dispersions of nifedipine in PEG using FTIR imaging in the macro-ATR mode. It has been shown that this imaging approach is particularly well-suited to studying pharmaceutical formulations in contact with water. This spectroscopic imaging approach allowed us not only to differentiate changes in the morphology of the drug upon contact with water but also to analyze changes in the spatial distribution of both the drug and polymer as a function of time. FTIR imaging allowed us to detect formation of the crystalline nifedipine within the polymer matrix upon exposure of the formulation to water but prior to liquid water reaching locations where the drug was crystallized. This crystallization was observed at drug loadings of 10 wt %, and was much greater at drug loadings of 20 wt % which resulted in the formation of large amounts of crystalline nifedipine within the PEG matrix. This observation was different compared to that with ibuprofen crystallization,[8] which occurs upon direct contact with the dissolution medium. The crystallization of nifedipine within the polymer matrix significantly inhibits the drug dissolution process since the crystalline drug does not dissolve despite the dissolution of PEG. This observation leads to the conclusion that an increase in nifedipine loading does not improve the drug dissolution rate but, in fact, results in an opposite effect due to the formation of the crystalline drug with low solubility. Dissolution of the formulations with low nifedipine loadings (ca. 5 wt %) provides an opportunity to control drug release via the rate of dissolution of the polymer. This study demonstrates the tremendous potential of FTIR spectroscopic imaging in studying dissolution and drug release due to the intrinsic chemical specificity and enhanced visualization capability of this method.

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