NOTE

FTIR Spectroscopic Study of Poly(Ethylene Glycol)–Nifedipine Dispersion Stability in Different Relative Humidities

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ABSTRACT: Solid dispersion has shown to be a promising formulation strategy to enhance dissolution for hydrophobic drugs. However, solid dispersions are often thermodynamically unstable, there is a continuous interest in studying their stabilities. In this study, attenuated total reflectance Fourier transform infrared (ATR-FTIR) was used to compare the amount of crystalline nifedipine formed in different formula of poly(ethylene glycol) (PEG)–nifedipine solid dispersions when exposed at various relative humidities (RHs) for 2 h at 40°C. The ratio of the crystalline nifedipine band and an internal reference band in the out of plane δ(C–H) region has been used to indicate the relative degree of drug crystallisation in a sample. A band ratio of ∼0.05 and 0.5 was respectively indicative of a fully amorphous or crystallised drug in the formula. Results show that increasing the RH generally increases the amount of crystalline nifedipine. Formulations with low (5%, w/w) nifedipine concentration in higher molecular weight PEG were found to be better at resisting crystallisation. Deliquescence of the 10% nifedipine in PEG 4000 was observed at 77% and 100% RH with a reduction in crystalline nifedipine. All 5% (w/w) nifedipine samples were stable at RH below 77%. Crystallisation of nifedipine occurred at all RH when drug loading was increased to 10% (w/w).
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INTRODUCTION

Nifedipine has poor aqueous solubility and, as a result, poor dissolution profile and bioavailability when orally administered. One of the methods used to enhance the bioavailability is formulating a solid molecular dispersion of the drug into a water-soluble polymer. However, this does not lead to the production of a permanently stable formulation, overtime the amorphous drug will gradually convert back to its most thermodynamically stable, least bioavailable crystalline form.

The purpose of this research was to investigate the effect of relative humidity (RH), drug loading and polymer molecular weight on the stability of the amorphous nifedipine/poly(ethylene glycol) (PEG) solid dispersion using attenuated total reflection FTIR spectroscopy (ATR-FTIR). Work has previously been carried out on nifedipine/polyvinylpyrrolidine (PVP) solid dispersions,[1–10] where it was found that a high RH led to crystallisation of the nifedipine/PVP solid dispersion. Work has also been conducted on pure nifedipine to examine the effect of RH on amorphous samples of the drug.[11,12] Studies have also been conducted on felodipine/PVP solid dispersions[13] and nifedipine/PEG solid dispersions.[14] However, little work has been conducted on examining the effects of a range of RH on nifedipine/PEG solid dispersions where the drug loading and the molecular weight of PEG is also changed.

Attenuated total reflection FTIR[15] was selected to study the morphological changes taking place. ATR-FTIR is a non-destructive, chemical (and polymorphic) specific, label-free and quantitative spectroscopic measurement. FTIR has shown to be able to clearly differentiate crystalline and amorphous nifedipine based on their spectra,[16–18] which is confirmed by the result that is in agreement with powder X-ray diffraction.[18] The proposed method therefore provides a convenient tool for the quantification of drug crystallinity in a matrix. Other advantages include relatively quick sample analysis compared with other destructive techniques like differential scanning calorimetry (DSC). The simplicity of sample preparation of ATR-FTIR allows good reproducibility of spectra between samples, which is important when analysing the changes in physical states of solid dispersions. A recent review on ATR-FTIR spectroscopy can be found elsewhere.[19] It should be noted that ATR-FTIR, whilst a convenient measuring method, detects the first few micrometres of the sample in contact with the ATR element. However, the composition on the surface layer of the sample is thought to relate to the bulk concentration of a homogeneously prepared formulation and therefore a quantitative analysis is possible with this convenient technique. Traditionally, FTIR studies of cyrstallisation of nifedipine were focused on the ν(N–H) or the ν(C=O) regions,[16,17,20] which can be interfered with the presence of water. In this work, we will focus on the ratio of the crystalline nifedipine band against an internal reference band in the out of plane δ(C–H) of the ring region and used it as a drug concentration-independent indicator for the degree of nifedipine crystallisation in samples as a function of PEG molecular weight, drug loading and RH.

EXPERIMENTAL

Solid Dispersion Preparation

Nifedipine was purchased from Santa Cruz Biotechnology (Heidelberg, Germany) and was used as received. PEG

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4000/8000/35000 was kindly donated by Professor Sergei Kazarian of Imperial College London. Different solid nifedipine/PEG dispersions were formulated with drug loading of 5% and 10% and PEG molecular weight of 4000, 8000 and 35,000 g/mol. To ensure the samples were well mixed, a batch of 100 mg of nifedipine/PEG dispersion was first prepared in a glass vial by heating the vial on a hotplate until the PEG had turned molten and the nifedipine had completely dissolved into the PEG. The vial was left on the hotplate for a further 30 s to ensure all nifedipine was dissolved which is followed by cooling on a bench for 3 min. Six repeated samples of 3 mg of the solidified nifedipine–PEG dispersion were then weighed out into the ridge of a 90 mm DSC aluminium pan with each of the samples spaced out equally. The pan was then transferred to a hotplate and the six samples were melted again to ensure the drug is molecularly dispersed in the polymer and a similar size and shape of each sample is achieved. Once molten, they were left on the hotplate for a further 30 s, after which the pan was removed from the hotplate and placed on a cool workbench for a period of 3 min where the samples re-solidified. Sample pans were then transferred to a sealed container where the RHs were controlled using saturated solutions of lithium chloride, magnesium chloride or sodium chloride which respectively produced 11%, 33% and 77% RH at 41°C. Samples were also exposed in dry environment (<5% RH, thereby labelled as 5% RH) which was created by using molecular sieve type 4A that has been dried at 160°C for a minimum of 24 h, and 100% RH environment which was created by using distilled water. The container was then transferred to an oven and maintained at 40°C–41°C for a period of 2 h, after which the dispersions were analysed using ATR-FTIR spectroscopy. At each stage of the sample preparation, the exposure of light was minimised to prevent photo-degradation of the drug. The procedure was strictly followed to ensure that all samples were prepared in the same way for a good reproducibility of results.

ATR-FTIR Spectroscopy

A FTIR spectrometer (Frontier; PerkinElmer, Seer Green, UK) with the diamond ATR accessory was used for analysis of the samples, it was set to scan between 4000 and 650 cm^{-1}, the number of accumulations was set to four scans and the spectral resolution was set to 4 cm^{-1}.

The clean diamond crystal was measured as the background. A sample of the nifedipine/PEG dispersion was then carefully removed from the aluminium pan with minimal force. The sample was then placed with the top side down on the ATR element. A moderate force of 40 N was applied to each sample onto the ATR element and it was found to produce reproducible intensities without inducing changes to the state of the sample. The sample was then scanned and a spectrum was obtained.

RESULTS AND DISCUSSIONS

Samples were exposed at 40°C, just below the T_g of pure nifedipine while the T_g of the solid dispersions are expected to be much lower, in order to accelerate the process of crystallisation allowing comparison of the stability of different formulas to be made more quickly.

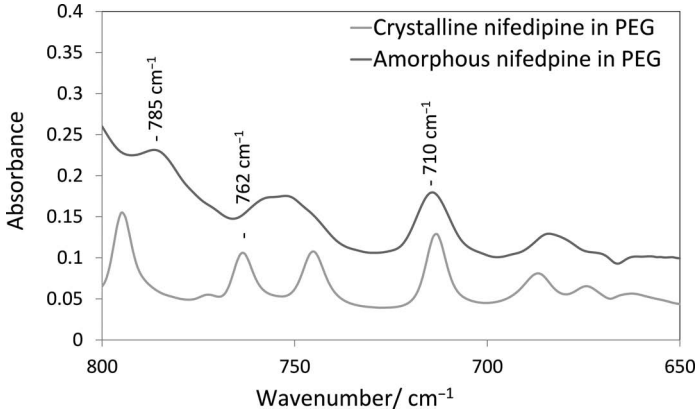

Figure 1. (a) Infrared spectra of α-crystalline (light grey) and amorphous (dark grey) nifedipine dispersed in PEG.

FTIR Spectral Analysis

Molecularly dispersed amorphous nifedipine in PEG have distinctive IR features from crystalline nifedipine in PEG with the most pronounced differences are found in the ν(N–H) region, the carbonyl region as well as the 800–750 cm^{-1} out-of-plane δ(C–H) vibration of the ring regions, where PEG also does not have strong absorbance. Previous works has utilised the shift in the ν(N–H) band to characterise the different polymorphs of nifedipine.[11] In this study, all the crystalline nifedipine formed has the ν(N–H) band at 3332 cm^{-1} meaning that all the crystalline nifedipine formed are α-crystalline, therefore the nifedpine spectral analysis of this study concerned only the α-crystalline and amorphous nifedipine spectrum. The single peak at 1700 cm^{-1} is typical of molecularly dispersed amorphous nifedipine, the peak red shifts to 1678 cm^{-1} in the crystalline dispersion which can be used as a marker for the crystallisation behaviour. However, the 1678 cm^{-1} band can be affected by the nearby water band bending mode absorbance at ~1640 cm^{-1}. The α-crystalline and amorphous nifedipine have distinct bands in the 800–750 cm^{-1} out of plane δ(C–H) region that are well separated and not affected by water absorbance. As shown in Figure 1, the band at 785 cm^{-1} is specific to amorphous nifedipine, whereas the area underneath the band at 762 cm^{-1} can be used to quantify the amount of amorphous and crystalline nifedipine present in the dispersions. An area under the peak has been calculated by carefully selecting a baseline that will result in a positive value for the target molecular state (e.g. crystalline) and a near zero value for the other molecular state (e.g. amorphous). The area of this peak was ratioed against a reference band at 710 cm^{-1} (see Fig. 1a), which does not significantly change between the amorphous and crystalline forms, to remove any variations in the data because of the slight variation in contact and drug concentration. The ratio was found to be useful as a semi-quantitative analysis of the amount of crystallisation in the dispersion where <0.05 for amorphous nifedipine dispersion and ~0.54 for fully crystalline nifedpine in PEG. Figure S1 (Supporting Information) illustrates some of the typical spectral results.

Stability of Samples With 5% Nifedipine Drug Loading

A plot of the averaged ratio of the nifedipine crystalline band at 762 cm^{-1} to the reference band at 710 cm^{-1} against the RH for the 5% (w/w) nifedipine in PEG formulations are shown in