Glassy drugs: a Raman investigation of binary dihydropyridine systems

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This paper extends an earlier vibrational spectroscopic investigation of the vitrification and polymorphism of nifedipine (Nif), a common antihypertension drug, to two more 1,4-dihydropyridines: felodipine (Fel) and nitrendipine (Ntd). FT Raman spectroscopy is employed to identify two Ntd and one Fel polymorphs. Crystalline α-Fel is found to resemble structurally one of the three nifedipine polymorphs (γ-Nif). It is demonstrated that glass formation by melt quenching is possible throughout the binary nifedipine–nitrendipine and nifedipine felodipine systems. Both the glass transition temperatures and Raman spectra of the binary systems appear additive with respect to the corresponding end members. Preliminary devitrification data of the equimolar binary glasses indicate that the Nif–Fel glass is unstable towards sub-T_g devitrification, while its Nif–Ntd counterpart is particularly stable even at temperature above T_g.

Drugs are often formulated in the amorphous state, or as one or more polymorphic forms. Quite often the thermodynamically stable crystal is difficult to produce. In other cases, the glassy state is chosen to enhance the performance characteristics of the drug, *e.g.* for dissolution enhancement, but is required to exhibit sufficient stability towards devitrification on storage.[1,2] Overall, many of structural issues related to vitrification and polymorphism in inorganic glasses[3] are clearly relevant to glassy drugs.[4]

The glassy states and the crystalline polymorphs of dimethyl 1,4-dihydro- 2,6-dimethyl–4-[2-nitrophenyl]-3,5-pyridine dicarboxylate (Nifedipine, *Nif*), ethyl methyl 1,4-dihydro- 2,6-dimethyl–4-[2,3-dichlorophenyl] -3,5-pyridine dicarboxylate (Felodipine, *Fel*) and ethyl methyl 1,4-dihydro- 2,6-dimethyl–4-[3-nitrophenyl]-3,5-pyridine dicarboxylate (Nitrendipine, *Ntd*), all common antihypertension drugs of the 1,4-dihydropyridine family, have been studied by several authors.[5–10] In a recent Raman and infrared investigation, the structure of glassy nifedipine (*g*-Nif) was found to involve conformations of the ester side chains and hydrogen bonding patterns that are not encountered in the thermodynamically stable α-Nif crystal (Figure 1) but, instead characterise two metastable β- and γ-Nif polymorphs.[11] Unfortunately, *g*-Nif with a T_g of 47±1°C is particularly unstable towards sub-T_g devitrification at 40°C, and this process is greatly accelerated in humid environments.[11]

In this work, we explore the possibility of increasing the stability of glassy dihydropyridines by developing binary Nif–Ntd and Nif–Fel glasses and studying their structure by Raman spectroscopy.

Experimental

Crystalline nifedipine, felodipine and nitrendipine in powder form have been kindly provided by Lavipharm SA. Glasses have been made by melting 2 g batches of thoroughly mixed powders at 150–200°C depending on composition, for ca. 5 min in the dark, followed by splat quenching. This procedure often leads to glasses prone to surface crystallisation. Monolithic glasses with good top surfaces can be conveniently made in open aluminium DSC pans. Melting is performed on a hot plate and quenching by transfer to a metal block.

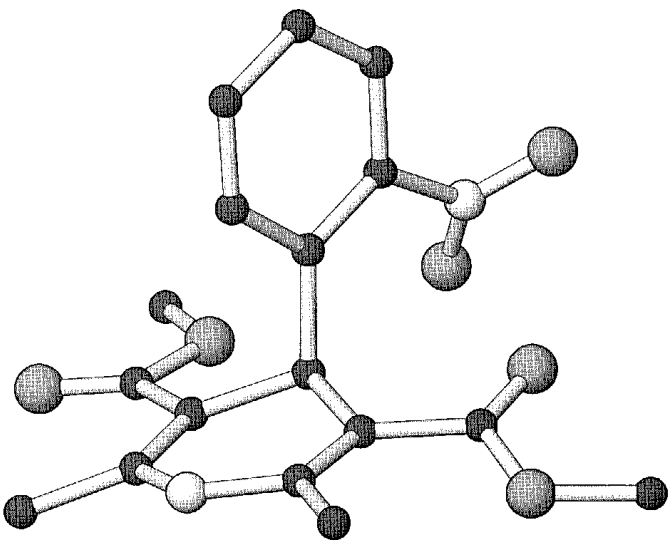

Figure 1. *Molecular conformation of nifedipine in the thermodynamically stable α-Nif form.[5] Oxygen atoms are shown in grey, nitrogen in white and carbon in black. H atoms are not shown. The ester carbonyls are in the syn-, and antiperiplanar conformation. In α-Ntd the two carbonyls are also in the syn-, anti- conformation,[6] while in α-Fel, they are both in the syn- conformation[8]*

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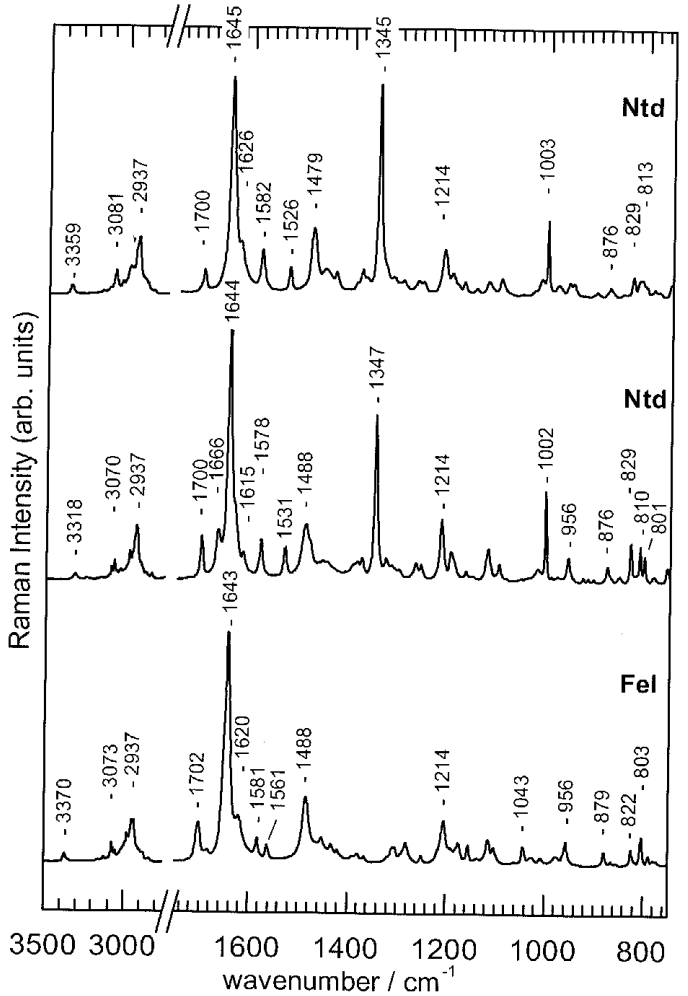

Figure 2. *FT Raman spectra of the crystalline felodipine and nitrendipine polymorphs isolated during the course of this study*

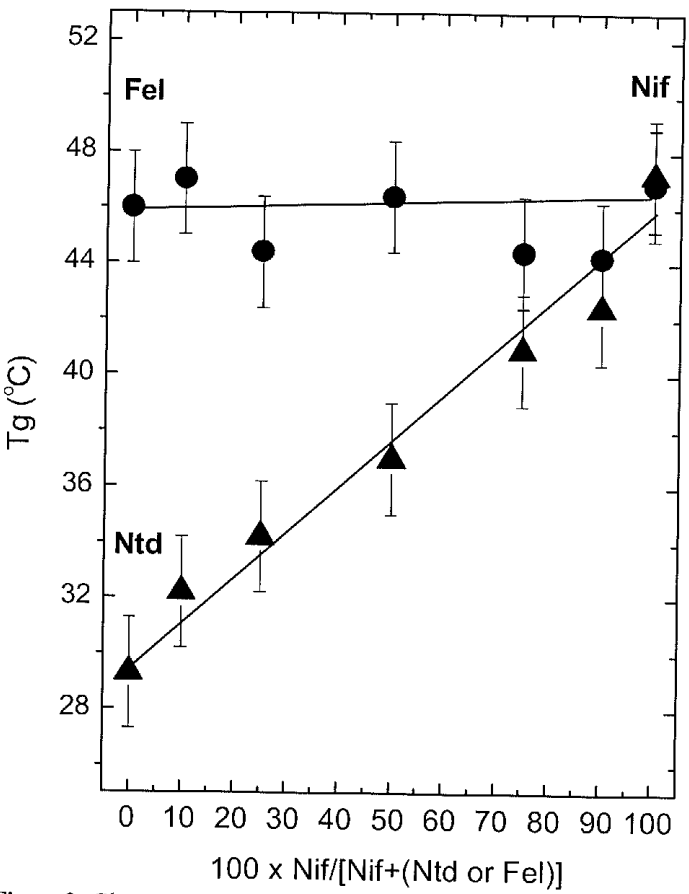

Figure 3. *Glass transition temperatures (mid-point values) along the nifedipine–nitrendipine and nifedipine–felodipine binaries. Compositions are molar and the lines are guiding the eye*

Glass transition temperatures (mid-point values) have been measured with a 2910 TA Instruments DSC, with a heating rate of 5°C/min and modulation ±0·8°C/min. The FT-Raman spectra have been obtained with a Bruker RFS 100 spectrometer with ca. 400 mW of Nd:YAG 1064 nm radiation for excitation and a back-scattering geometry. The spectra of glasses (crystals, respectively) were obtained at a resolution of 4 cm^{-1} (1 cm^{-1}) and represent averages of 100 scans (500 scans).

Results and discussion

Crystalline compounds

The FT-Raman spectra of the crystalline Ntd and Fel compounds identified in the course of this study are shown in Figure 2. α-Ntd and α-Fel are the common final devitrification products of *g*-Ntd and *g*-Fel, respectively. These compounds are spectroscopically identical to the starting crystalline materials. β-Ntd is a polymorph obtained by devitrifying monolithic *g*-Ntd samples at 42–45°C. Together with the Raman spectra of the three Nif polymorphs reported in Ref. 11, they form a database of six dihydropyridine compounds suitable for structural comparisons and the identification of devitrification products.

A detailed set of assignments for the spectral features observed in Figure 2 is beyond the scope of this paper. However, we note that the frequency of the ν(NH) stretching mode varies from 3318 cm^{-1} (α-Ntd) to 3370 cm^{-1} (α-Fel), where all Nif polymorphs exhibit this mode in the range 3330–3359 cm^{-1}.[11] The frequency of the ν(NH) mode has been correlated with the strength of the intermolecular hydrogen bonding between the hydropyridine NH group and the carbonyl of the ester.[12] A similar correlation based on the peak positions of the C=O groups (1650–1705 cm^{-1}) should also take into account at least the conformation of these groups (syn- or anti-) and the presence or absence of H-bonding. All crystalline dihydropyridines investigated (except α-Nif) exhibit their highest C=O stretching contributions in the range 1700–1705 cm^{-1}, suggesting that these should represent carbonyl species that are not involved in H-bonding. Several compounds exhibit additional C=O modes in the range 1660–1680 cm^{-1}. These should correspond to ester carbonyls involved in hydrogen bonding, but their exact frequency and bandshape does not correlate in a straightforward manner with ν(NH) or the XRD data available for the thermodynamically stable forms, presumably because it is biased by crystal symmetry effects.

Overall, both the vibrational and XRD spectra of the thermodynamically stable dihydropyridines indicate a large variety of different crystal structures, despite the fact that the main interacting entities in most of these systems, i.e. the NH group and the ester carbonyl, are common to all. Given the fact that dihydropyridines are known to exhibit rich polymorphism, it is quite possible that structures that are metastable in one system become stabilised in another, in order to accommodate variations in side alkyl chains or ring substitutions. Our data provide evidence for

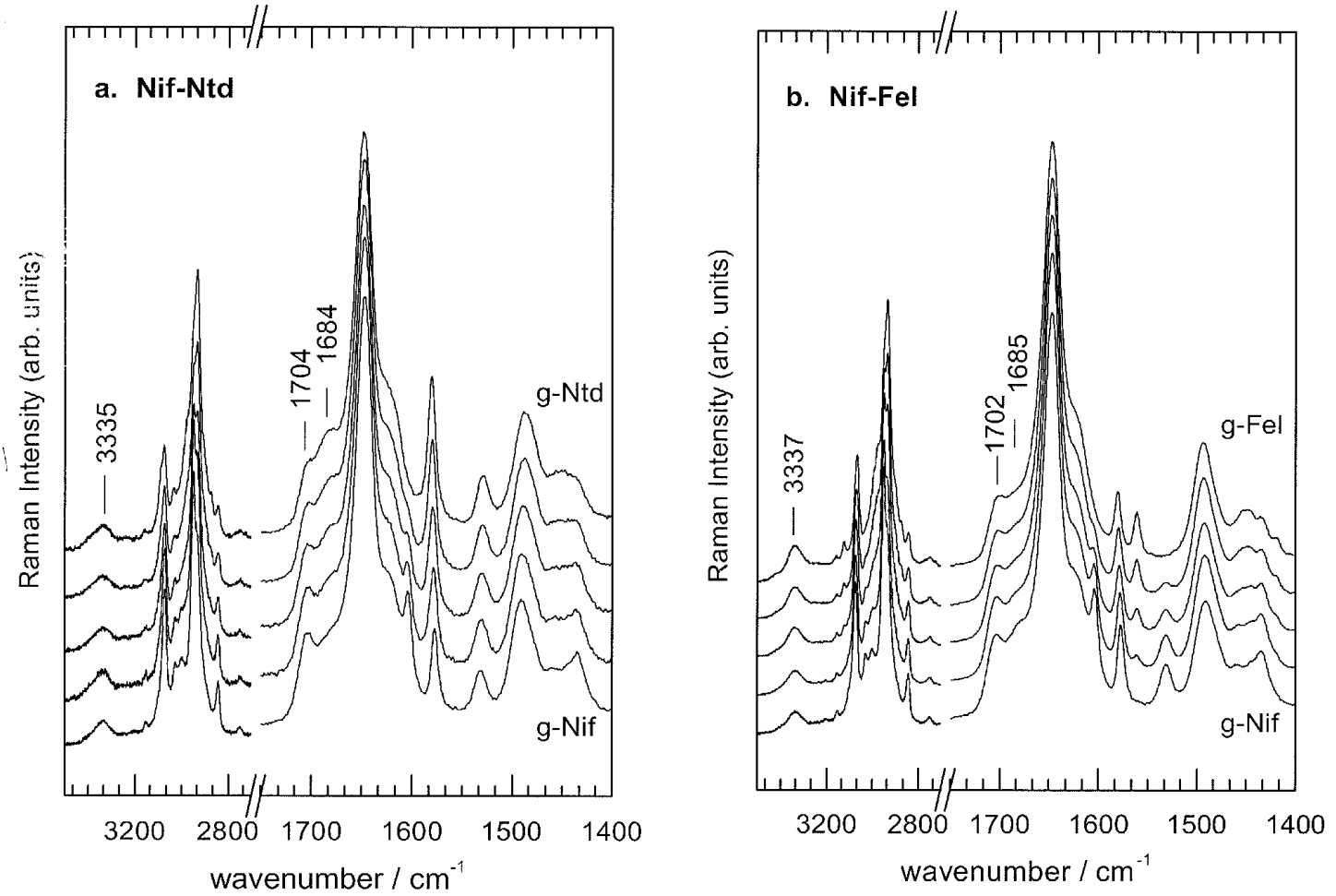

Figure 4. *Detail of the FT-Raman spectra of glasses along the Nif-Ntd (a.) and Nif-Fel (b.) binaries. From top to bottom they correspond to molar ratios of Nif equal to 0, 0·25, 0·50, 0·75 and 1. The spectra have been off-set for clarity*

one such case: a careful comparison of the Raman spectra in Figure 2 and Ref. 11 based on the high frequency of the ν(NH) mode, the ν(C=O) stretching doublet (1670–1710 cm^{-1}) as well as on the profile of the ν(C=C) modes (1620–1645 cm^{-1}), indicates that α-Fel bears structural similarities to γ-Nif in terms of both, carbonyl conformation and H-bonding pattern.

Amorphous solids

Glass formation is continuous over both the Nif-Fel and Nif-Ntd binary systems. The data compiled in Figure 3 indicate that the T_g of any binary glass falls within error on a straight line joining the end members. No broadening of the transition around the 1:1 molar composition has been observed that could be an indication of a biphasic amorphous system. A similar observation can be made on the basis of the Raman spectra of the binary glasses presented in Figure 4. All spectra are very accurately reproduced by the appropriate linear combination of the end members, and there is no sign of nonlinear variation in peak intensities or widths upon 'mixing'. Based on this two-mode behaviour, it can be concluded that in the binary glasses there are no *new* types of intermolecular interactions (e.g. ester conformations or H-bonding patterns) resulting from dihydropyridine molecules of different nature.

A close look in the spectra of *g*-Ntd and *g*-Fel (Figure 4) shows that neither can be described satisfactorily on the basis of the spectra of the corresponding thermodynamically stable crystal (α-Ntd and α-Fel, shown in Figure 2). Pronounced differences can be observed in the position of the ν(NH) mode, as well as in the complex profile of the ν(C=O) stretching modes. The situation is similar to that reported earlier for *g*-Nif, and indicates that a significant fraction of the dihydropyridine molecules becomes arrested in metastable conformations upon quenching. This implies that, in the glassy state of the single component dihydropyridines, new types of intermolecular interactions (e.g. H-bonding patterns) between conformers that do not coexist in any crystalline form become possible.

The above observation can account for the lack of non-additive variations in the Raman spectra and the T_g of the binary glasses. All, or nearly all, possible conformer structures and interaction patterns are already explored by the single component systems. As a result, the ν(NH) and ν(C=O) spectra of *g*-Nif, *g*-Ntd and *g*-Fel are very similar to each other,[12] while the mixing of different dihydropyridine molecules does not introduce additional elements of local or intermediate structure to the binary networks.

Stability towards devitrification

Monolithic glasses made in open DSC pans have been simultaneously exposed to dry heat at temperatures in the vicinity of 40°C. Crystallisation was monitored visually, as well as by Raman spectroscopy. An exploratory assessment of glass stability towards devitrification

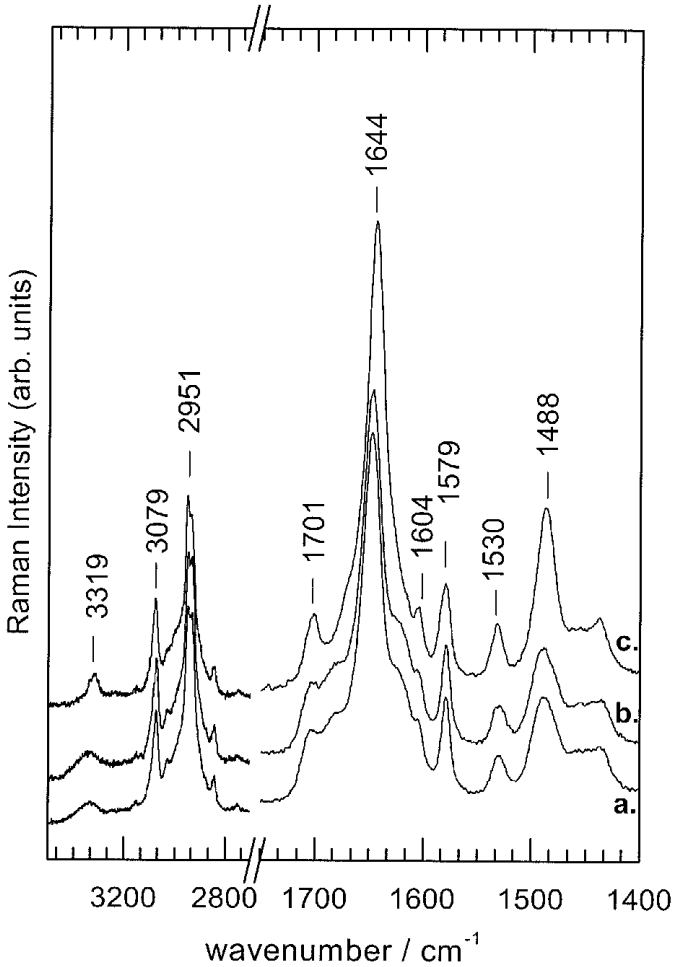

Figure 5. *Detail of the FT-Raman spectrum of an equimolar Nif-Ntd glass immediately after preparation (a), subjected to heating at 42·5°C for 6 days (b) and after an additional 40 h exposure to 75°C (c). Marked peaks correspond to spectrum (c)*

revealed significant differences between the two binary systems. In all cases, the binary glasses were found more stable than the corresponding end members. However, even the most stable glass of the Nif-Fel family (equimolar, T_g=46·2°C) was fully crystallised after ca. 48 h at 40°C. The crystallisation products were of the γ-Nif and α-Fel type, while the corresponding single component glasses crystallise to α-Nif and α-Fel. Due to the spectroscopic similarity between γ-Nif and α-Fel, and the limited spatial resolution of our technique, it is not evident whether the crystallisation of the equimolar glass yields a mixed crystal, or a mixture of the two single component polymorphs.

On the contrary, the Nif-Ntd equimolar binary glass exhibits considerably higher stability despite its lower T_g (37·5°C). This glass shows no signs of crystallisation after 6 days at 42·5°C (Figure 5). Under the same conditions, the end member glasses are fully crystallized to α-Nif, and β-Ntd. The onset of crystallisation of equimolar g-(Nif-Ntd) to α-Ntd is only observed above 70°C and is not complete after heating the glass for 40 h at 75°C.

Conclusions

Fourier transform Raman spectroscopy is an excellent tool for the structural evaluation of polymorphism in pharmaceutical compounds of the 1,4-dihydropyridine family. Metastable structures can be studied more conveniently than by XRD, in a manner that allows for the identification of different molecular conformations and hydrogen bonding networks.

Melting and quenching of mixed dihydropyridine systems produces glasses that are considerably more stable towards devitrification than their single component counterparts. The highest stability is observed for equimolar glassy nifedipine–nitrendipine, i.e. for a system where the crystallisation of the end members yields polymorphs of dissimilar structures. On the contrary, the structural similarity between the thermodynamically stable form of felodipine (α-Fel) and one of the metastable nifedipine compounds (γ-Nif), renders the equimolar nifedipine–felodipine glass unstable towards devitrification at sub-T_g conditions.

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