Understanding solid state interactions of co-amorphous indomethacin and naproxen with the use of quantum mechanical calculations and infrared spectroscopy

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ABSTRACT

Co-amorphous drug systems have recently shown to be a potential new strategy in stabilizing the amorphous state of a drug and increasing its apparent dissolution. The improved properties of these systems, when compared to the single amorphous drug, were attributed to molecular interactions between the drug and its co-amorphous partner. In this regard, vibrational spectroscopy presents a useful tool to analyse these interactions because changes in the molecular arrangement may be reflected in shifts in the vibrations of functional groups involved in such interactions, e.g. hydrogen bonding. However, even with single amorphous compounds this analysis can be challenging because changes are often minor or get lost in the complexity of the spectra. In case of materials with more than one compound, this becomes even more complicated. The purpose of this study was to investigate the molecular near range order of the co-amorphous blend of naproxen (NAP) and indomethacin (IND) (1:1 molar ratio) using quantum mechanical calculations together with FT-infrared (IR) spectroscopy. Initially, both drug molecules were optimized as monomers, homodimers and a heterodimer using density functional theory. In a second step the respective IR spectra were calculated. Comparison of the calculated and experimental spectra of the individual drugs revealed that both molecules exist as homodimers in their respective amorphous states. A detailed analysis of the theoretical heterodimer and experimental co-amorphous spectra revealed that the changes of vibrational modes were similar in both, when compared to the single amorphous or homodimer spectra. This indicates that both drugs form a heterodimer when prepared as a co-amorphous 1:1 molar blend.

KEYWORDS

density functional theory, quantum mechanical chemistry, co-amorphous, naproxen-indomethacin, infrared spectroscopy

INTRODUCTION

In the past few years, single phase amorphous blends containing two small molecular compounds were introduced to overcome problems associated with amorphous materials (Chieng et al., 2009; Allesø et al., 2009; Löbmann et al., 2011). These co-amorphous systems showed improved dissolution and physical stability when compared to the respective single amorphous drugs. In this regard, intermolecular interactions between the co-amorphous partners in the blends were suggested to explain the improved behaviour.

In order to probe the molecular arrangement of compounds and amorphous solids, a spectroscopic method such as infrared (FTIR) spectroscopy is often used. Changes in H-bonding or π-π interactions of functional groups are usually reflected in altered vibrations thereof and may thus be detectable. However, the analysis and interpretation of these peak shifts can be a significant challenge even for single amorphous compounds because the impact of these changes can sometimes only be minor or lost in the complexity of the spectra. This becomes even more pronounced when a second compound is added and contributes to the overall spectrum.

In order to overcome challenges in the analysis of vibrational spectra, quantum mechanical calculations have been investigated recently in the pharmaceutical field and shown to be a useful tool in guiding interpretations (Gordon et al., 2007). However, the use of this technique so far only concentrated on single drug molecules and their different molecular arrangements in polymorphic forms or the amorphous solid state.

The purpose of this study was to combine FTIR spectroscopy and quantum mechanical calculations in order to gain a better understanding of the molecular near range order in amorphous blends containing two different molecules. In this regard, the co-amorphous blend of indomethacin (IND) and naproxen (NAP) in a 1:1 molar ratio was investigated.

MATERIALS AND METHODS

Materials

Indomethacin (IND) and naproxen (NAP) were obtained from Sigma Aldrich, USA and Divis Laboratories Ltd., USA, respectively. Both drugs were used as received.

Sample preparation

NAP and IND alone and a binary mixture of both drugs in a 1:1 molar ratio were melted at 168 °C, kept isothermal for 5 min and subsequently quench cooled with liquid nitrogen in order to obtain the amorphous systems. Samples were stored over phosphorus pentoxide to prevent moisture sorption.

Attenuated Total Reflectance FT-Infrared Spectroscopy (ATR-FTIR)

FTIR spectra were collected with a Varian 3100 FTIR (Excalibur series) using an attenuated total reflectance accessory (GladiATR, Piketech, WI, USA). Spectra were recorded over a range of 4000 – 400 cm^{-1} with an average of 64 scans and a resolution of 4 cm^{-1}.

Computational Studies

Quantum mechanical modelling was conducted on the single drug molecules, the homodimers NAP-NAP and IND-IND and the heterodimer NAP-IND (Figure 1) using the Gaussian 09 Suite of programs. In a first step, an optimization calculation of the conformations of the monomer and dimer structures was conducted. In a second step, the optimized structures were used to calculate the vibrational IR frequencies using density functional theory (DFT; B3-LYP functional, 6-31G(d) basis set). Before plotting the calculated IR spectra, the

recommended scaling factor of 0.9614 (Scott et al., 1996) was applied to the predicted vibrational modes.

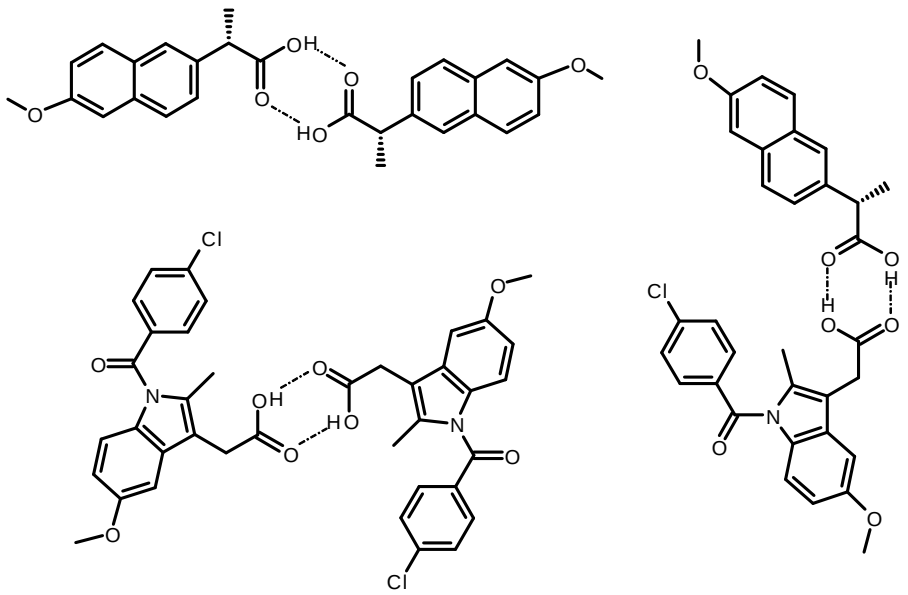

Fig. 1 Molecular structures of (a) the NAP and (b) the IND homodimer and (c) the NAP-IND heterodimer.

RESULTS AND DISCUSSION

Conformational Analysis

Geometry calculations were conducted based on the crystallographic data of the two drugs IND (Kistenmacher et al.; 1972) and NAP (Kim et al.; 1987). The resulting optimized bond parameters, angles and dihedral angles in the single drug molecules were then compared to those of the respective crystalline drug. It could be shown that the geometry of the calculated structures (monomer and homodimer) was similar to those in the respective crystalline drug (data not shown). Therefore, the optimized structures were suitable for the calculation of vibrational IR spectra.

Spectroscopic Analysis

In general, the intensities of strong and weak bands in the calculated spectra were in good agreement with those found in the experimental spectra. This suggests that the predicted spectra display a good model. Furthermore, it was found that the H-bonded homodimer structures resulted in a prediction close to the experimental spectra (Figure 2) when compared to the monomer calculations (data not shown). Vibrational modes could be matched with bands from the experimental spectra of the respective amorphous drugs and it is suggested that IND and NAP also exist as homodimers in the amorphous state.

Upon the formation of a co-amorphous NAP-IND mixture, major peak shifts and changes in peak intensity were detected in the experimental IR spectra when compared to the individual amorphous spectra (Figure 3). In particular, the carboxylic acid vibration appeared at an intermediate wavenumber and with increased intensity in the co-amorphous spectrum. In this

regard, the respective band of the amorphous NAP at 1697 cm^{-1} and IND at 1708 cm^{-1} merged into a single vibration at 1703 cm^{-1} in the co-amorphous blend (Figure 3).

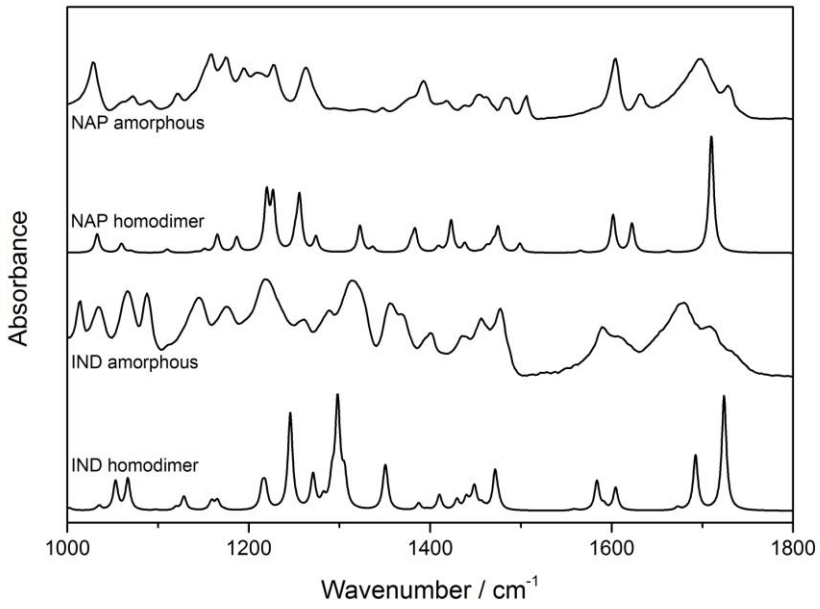

Fig. 2 IR spectra of experimental amorphous and predicted homodimer of NAP and IND, respectively

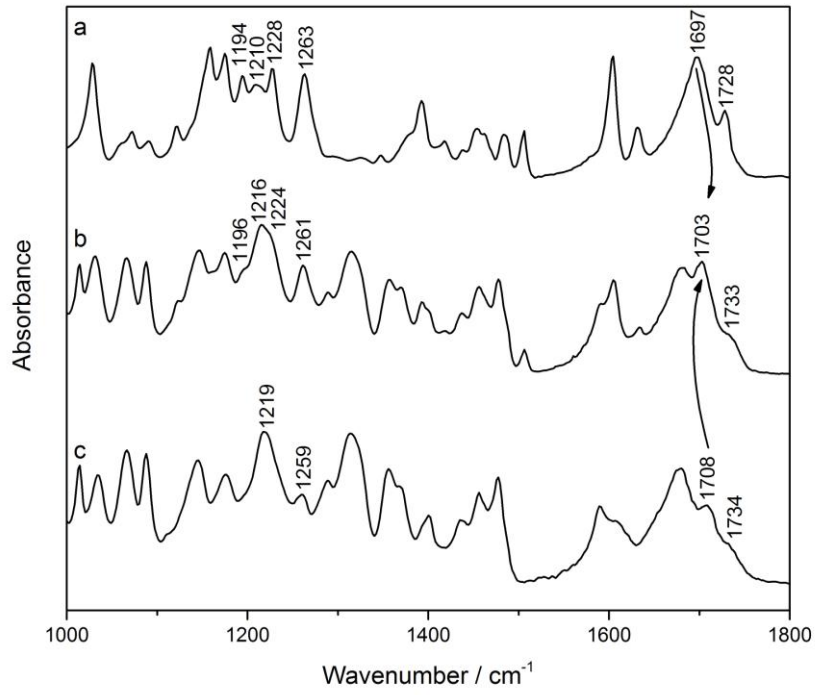

Fig. 3 Experimental IR spectra of (a) amorphous NAP, (b) coamorphous NAP-IND and (c) amorphous IND

Quantum mechanical calculations of the individual homodimers and the heterodimer revealed the same trend. The carboxylic acid modes for the IND and NAP homodimer were predicted at 1723 cm^{-1} and 1710 cm^{-1}, respectively, and a single and synchronized vibration of both acid groups was predicted for the heterodimer at 1718 cm^{-1}, thus, intermediate to the homodimer vibrations (Figure 4). The similar behavior in both experimental and calculated spectra strongly suggests the presence of a heterodimer upon the formation of a co-amorphous mixture in a 1:1 molar ratio.

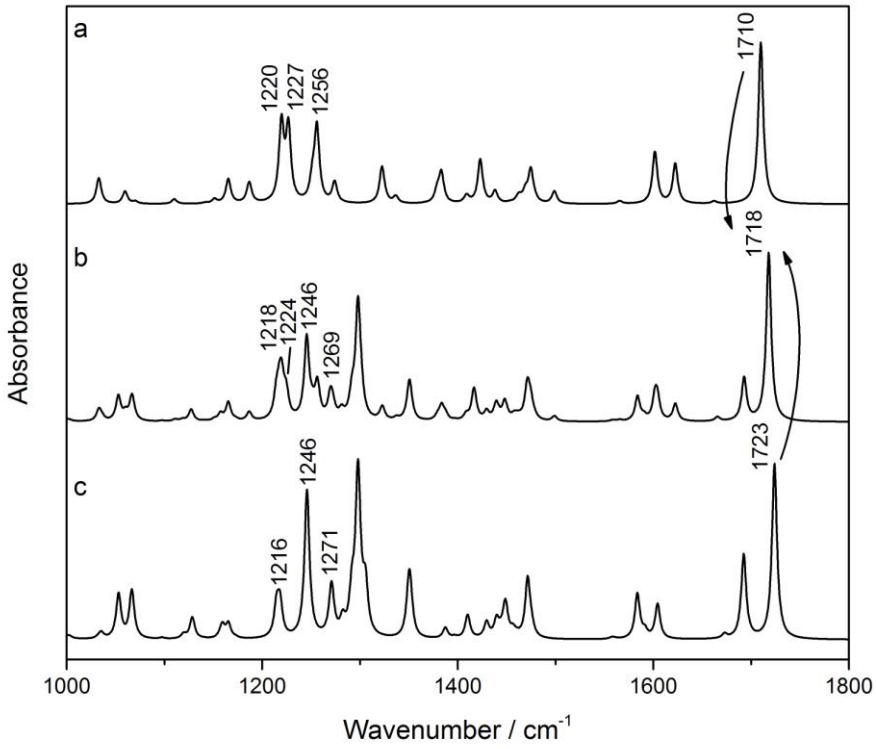

Fig. 4 Predicted IR spectra of (a) the NAP homodimer, (b) the NAP-IND heterodimer and (c) the IND homodimer

In addition, several peak shifts in the experimental spectra could also be found for aromatic ring vibrations in the region from 1194 to 1263 cm^{-1}. This outcome indicates that changes in the molecular environment and potential interactions also occur between the aromatic ring systems of both drugs upon formation of the co-amorphous mixture.

CONCLUSION

In this study, density functional theory was succesfully applied to predict IR spectra of IND and NAP monomers, homodimers and a heterodimer of both drugs through hydrogen bonding of the respective two carboxylic acid groups. The quantum mechanical calculations approach was then used for the interpretation and analysis of experimental infrared spectra of individual amorphous IND and NAP as well as a 1:1 molar co-amorphous blend thereof. It could be shown that both drugs form homodimers in their single amorphous state and rearrange to form a hydrogen bonded heterodimer upon the formation of a co-amorphous blend when quench cooled together.

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