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Drug–Excipient Interactions in Ketoprofen: A Vibrational Spectroscopy Study

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Abstract: *Ketoprofen (3-benzoyl-α-methylbenzeneacetic acid) is a widely used nonsteroidal anti-inflammatory drug (NSAID), always administered in the form of* drug–excipient physical mixtures *(PMs). The occurrence of possible interactions between ketoprofen and two commonly used excipients—lactose (LAC) and polyvinylpyrrolidone (PVP)—was evaluated, through vibrational spectroscopy techniques [both Raman and Inelastic Neutron Scattering (INS)]. Spectral evidence of drug:excipient close contacts, which were enhanced by aging, was verified for the (1:1) (w:w) (ketoprofen:PVP) and (ketoprofen:LAC) PMs, both by Raman and INS. These interactions were found to involve mainly the central carbonyl and the terminal methyl-carboxylic moieties of the ketoprofen molecule, this being reflected in particular vibrational modes, such as the methyl torsion, the out-of-plane C−OH bending, and the inter-ring C=O stretching.* © 2006 Wiley Periodicals, Inc. Biopolymers 82: 420–424, 2006

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INTRODUCTION

Ketoprofen (3-benzoyl-α-methylbenzeneacetic acid, Figure 1) is a nonsteroidal anti-inflammatory drug (NSAID), widely used in medicine as an analgesic and an antipyretic, mainly for the treatment of rheumatoid arthritis, osteoarthritism and ankylosis spondylitis,[1–3] but also for nonrheumatoid diseases.[4] Although the therapeutic action of ketoprofen is known to be mainly associated with inhibition of

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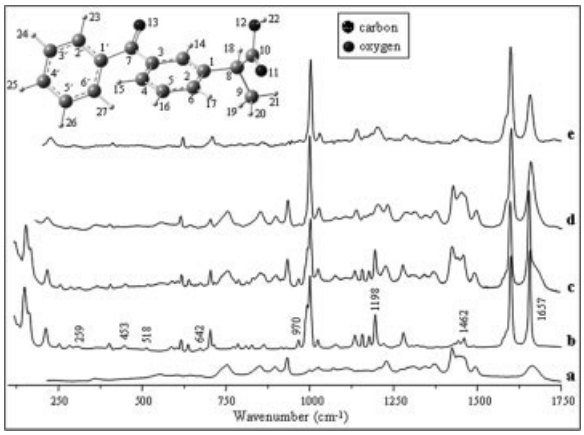

FIGURE 1 Experimental Raman spectra for PVP (a), ketoprofen (b), ketoprofen:PVP (1:1) fresh PM (c), ketoprofen:PVP (1:1) aged PM (d), and [ketoprofen:PVP (1:1) aged PM–PVP] (e). The calculated (B3LYP/6-31G*[15]) lowest energy geometry for ketoprofen is also represented (including the atom numbering).

prostaglandin and leukotrien synthesis,[5] the mechanisms underlying this activity are still poorly understood and have been the subject of vigorous research. It is generally accepted, however, that a controlled release of the drug greatly enhances its activity. In fact, one of the challenges facing drug delivery is to achieve a steady concentration of the pharmacophore, instead of the dramatic variations that usually result from traditional administration. These may be rather beneficial, as they allow the maintenance of therapeutic plasma levels with only one daily intake of the drug, leading to an improved patient compliance. Ketoprofen's short half-life in blood plasma (2–3 h),[6] coupled to its poor solubility in water, renders this NSAID a very good candidate for the formulation of controlled-release dosages.[7,8]

The successful formulation of a stable and effective solid dosage form depends on the careful choice of the excipient. Lately, the use of hydrophilic polymers [e.g., cellulose derivatives, polyvinylpyrrolidone (PVP), either isolated or in blends] has attracted considerable attention,[10] due to their ability to form gels in an aqueous medium. Because the in vivo drug release profile, and consequently the bioavailability of the therapeutic agent, may be affected by the occurrence of close contacts with these polymeric compounds, the evaluation of possible drug–excipient interactions is of the utmost importance for the preparation of effective controlled-release formulations. However, current research in this direction is formulation driven, with no underpinning or understanding of the microscopic mechanisms or interactions within the mixtures. The presence of such interactions, however, does not necessarily imply an incompatibility, as the pharmacological action of the drug may remain unchanged in the presence of the polymer, and can even be enhanced. The occurrence of drug–excipient close contacts in solid matrices is presently the object of some controversy, and despite evidence of either synergistic or negative effects,[11–13] there are no conclusive results to be reported. Thus, further study is needed in order to clarify this matter.

Drug–excipient interactions may involve intermolecular hydrogen bonds or more subtle intermolecular interactions, e.g., van der Waals contacts. Vibrational spectroscopy, long established as a noninvasive method, is particularly appropriate to investigate this kind of systems.[14] It is especially useful for disordered systems where diffraction techniques falter, and it allows the detection and characterization of both intra- and intermolecular interactions. No special preparation of the sample is required, thus avoiding mechanical influences that might alter the physicochemical properties of the drug–excipient pair. Inelastic neutron scattering (INS), in particular, is quite suitable for the study of interactions involving hydrogen atoms, as the ones under study.

The present work aims to evaluate ketoprofen–excipient interactions, through Raman and INS spectroscopy. Physical mixtures (PM) of the two solids, drug:excipient (1:1 w:w), are studied, using lactose (LAC) and polyvinylpyrrolidone (PVP) as excipients. The complementarity of the Raman and INS spectroscopic techniques is exploited, with the intention of gaining a better knowledge of the conformational relationships within the systems investigated. The results obtained are interpreted in the light of a previously reported conformational analysis of ketoprofen,[15] in order to better understand how its structural preferences may be affected by the presence of different excipients.

EXPERIMENTAL

Preparation of the Drug–Excipient Mixtures

The drug:excipient (1:1 w:w) PMs were obtained by lightly hand grinding a mixture of the two solid constituents, without temperature variation. This method, which minimizes the influence of sample preparation on the possible interactions between the components, is the one used in the pharmacological industry.

Raman Spectroscopy

The Raman spectra were obtained at room temperature on a triple monochromator Jobin-Yvon T64000 Raman system, as previously described.[15] The laser power was set to

40 mW at the sample position. An integration time of 10 s and 20–30 scans were used.

INS Spectroscopy

INS spectroscopy is a technique well suited for the study of hydrogenous materials. Indeed, because neutrons have a mass similar to that of the hydrogen atom, an inelastic collision between them involves a significant transfer of both momentum, Q (Å^{-1}), and energy to the irradiated sample. The scattering cross-section, σ, which is a characteristic of each element and does not depend on its chemical environment, is 80 barns for hydrogen as opposed to 5 barns for most other elements. Therefore, the modes involving a significant hydrogen displacement will dominate the spectrum. The intensity of each molecular vibrational transition (S_i) follows the equation

$$S_i \propto Q^2 U_i^2 \exp(-Q^2 U_{\text{total}}^2) \cdot \sigma \qquad (1)$$

where for each vibrational mode, i, U_i stands for the amplitude of vibration of the atoms in this mode and U_{total} represents the total amplitude of the atom in all the modes. The exponential term, $\exp(-Q^2U_{\text{total}}^2)$ is the well-known Debye–Waller factor; in order to reduce its impact on the observed intensity, the samples are cooled below 20 K.

The spectra were obtained in the Rutherford Appleton Laboratory (United Kingdom), at the ISIS pulsed neutron source, on the TOSCA spectrometer. This is an indirect geometry time-of-flight, high-resolution [($\Delta E/E$) ca. 2%], broad-range spectrometer.[16] Between 4 and 5 g of sample (wrapped in aluminium foil) was placed in the beam, and it was cooled to ca. 20 K before collecting the spectra. Data were recorded in the energy range from 16 to 4000 cm^{-1} and converted to the conventional scattering law, $S(Q,\nu)$ vs. energy transfer (in cm^{-1}), through standard programs.

Chemicals

Ketoprofen (99.9+%) and polyvinylpyrrolidone were obtained from Sigma-Aldrich Chemical Co. (Sintra, Portugal). Lactose monohydrate Granulac® 200 was purchased from Meggle (Wasserburg, Germany).

RESULTS AND DISCUSSION

The excipients studied—LAC and PVP—are among those most commonly used in controlled-release formulations, and for which some indication of interactions with ketoprofen (e.g., by H-bonding) has been reported.[17–20] Raman spectra of freshly prepared ketoprofen:PVP and ketoprofen:LAC PMs are represented in Figures 1(c) and 2(c), respectively. Both vibrational patterns can be interpreted as almost the direct sum of the pure ketoprofen and excipient spectra, allowing us to assume an absence of noteworthy intermolecular interactions in the newly prepared

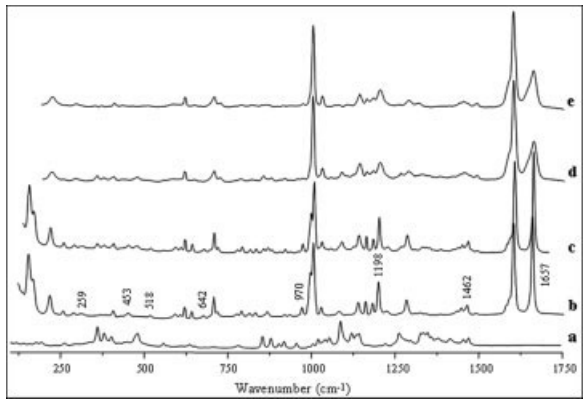

FIGURE 2 Experimental Raman spectra for LAC (a), ketoprofen (b), ketoprofen:LAC (1:1) fresh PM (c), ketoprofen:LAC (1:1) aged PM (d), and [ketoprofen:LAC (1:1) aged PM–LAC] (e).

PMs. Nevertheless, when Raman spectra of these same samples were obtained 24 h after preparation [Figures 1 (d) and 2 (d)], remarkable spectral changes were observed. Sample degradation is ruled out by stability studies on both components of the PMs.[20] Therefore, the present vibrational results should be taken as a clear evidence of the occurrence of ketoprofen–excipient close contacts upon aging, for both ketoprofen:PVP and ketoprofen:LAC (1:1). The spectral modifications presently detected comprise changes to both the band intensity and width (full width at half maximum, FWHM). In the light of the vibrational assignments previously performed for ketoprofen, in the solid state,[15] it is possible to identify the groups involved in the intermolecular drug:excipient interactions, as well as to characterize these close contacts.

Figures 1(e) and 2(e) display the difference spectrum between the aged ketoprofen:excipient PMs [Figures 1(d) and 2(d)] and the pure excipients [Figures 1(a) and 2(a)], for PVP and LAC containing mixtures. The bands at 759 and 480 cm^{-1} (from the excipient) were used as reference for Figures 1 and 2, respectively, as they appear in a spectral region where ketoprofen does not display any signals. The almost generalized increase in the bandwidths in the difference spectrum indicates a significant loss of crystallinity of ketoprofen in the PMs. There are several other noticeable changes that are common to both ketoprofen:PVP and ketoprofen:LAC: some vibrational bands are missing (at 259, 453, 518, and 642 cm^{-1}) and others display significantly lower Raman intensities (at 970, 1462, and 1657 cm^{-1}).

The disappearance of the Raman bands at 259 cm^{-1}, assigned to the $\tau(C^9H_3)$ and $\delta[C^9H_3—C^8(C^{10}=O)]$ ketoprofen modes, and at 453, 518, and

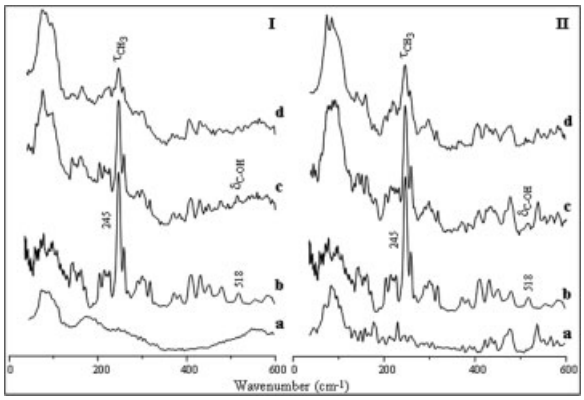

FIGURE 3 Experimental INS spectra. I: PVP (a), ketoprofen (b), ketoprofen:PVP (1:1) fresh PM (c), and ketoprofen:PVP (1:1) aged PM (d). II: LAC (a), ketoprofen (b), ketoprofen:LAC (1:1) fresh PM (c), and ketoprofen:LAC (1:1) aged PM (d).

642 cm^{-1}, due to $C^{10}—O—H$ out-of-plane bending vibrations, is a clear evidence of the involvement of the $CH_3CHCOOH$ terminal moiety of the drug (Figure 1) in the contacts established with the excipient molecules. Moreover, the intensity changes detected for the bands at 970 and 1462 cm^{-1} (ascribed to CH_3 rocking and antisymmetric deformation modes, respectively) are in accordance with that hypothesis, attending to the proximity of this methyl group to the interaction site. They clearly indicate that a new environment is created for CH_3 by the drug–excipient interaction. Furthermore, the band at 1657 cm^{-1}, arising from the stretching vibration of the inter-ring ketoprofen carbonyl [$\nu(C^7{=}O^{13})$], undergoes a marked peak intensity decrease (coupled to an increase in FWHM) in the aged PMs. The absence of any frequency shift for this signal, however, seems to rule out the formation of H-bonds with the excipient involving this C=O group, the spectral variations detected at 1657 cm^{-1} being suggested to arise from an amorphization of ketoprofen in the presence of the excipient. This amorphization is also reflected in the broadening of the bands due to the ring CH in-plane bendings (e.g., 1198 cm^{-1}).

In the analysis of the experimental INS data, particular attention was paid to characteristic spectral regions—namely, the low-frequency one comprising torsional modes that are hard to detect by optical methods. The main modifications detected in the ketoprofen INS spectral pattern due to the occurrence of interactions with both the PVP and LAC excipients upon cogrinding were (Figure 3) (i) a clear intensity decrease of the $\tau(C^9H_3)$ vibration, at ca. 245 cm^{-1}, upon aging of the samples, and (ii) a slight frequency shift of the $\delta(C^{10}—O^{12}H)$ bending mode, from 518 to 514 cm^{-1}. These variations are in accordance with those detected by Raman for the same drug:excipient PMs.

The spectral changes observed by both INS and Raman for the ketoprofen:excipient aged PMs, as compared to isolated ketoprofen, seem to involve two particular regions of the molecule—the methyl-carboxylic moiety ($C^9H_3—C^8H—C^{10}OOH$) and the inter-ring $C^7{=}O^{13}$ group (Figure 1). This is probably indicative of an interaction with the PVP and LAC excipients through hydrogen-type bonds with the ketoprofen terminal carboxylate group, coupled to a decrease of the crystalline state of the drug. The cogrinding process is thus proposed to initiate a slow dissolution-like process of the ketoprofen into the excipient, leading to an amorphization of ketoprofen and giving rise to new drug–excipient H-bonds.

The assessment of these drug–excipient close contacts, via a putative hydrogen bonding, will hopefully lead to an understanding of their effect on the drug-release process. This will provide a basis for the beginnings of an understanding of the microscopic mechanisms and interactions occurring within these mixtures, such that tomorrow's drug formulations might couple a higher efficacy and lower toxicity to a better patient compliance.

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