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Analysis of the acid–base reaction between solid indomethacin and sodium bicarbonate using infrared spectroscopy, X-ray powder diffraction, and solid-state nuclear magnetic resonance spectroscopy

Xiaoming Chen [a,1], Ulrich J. Griesser [b], Ruth L. Te [a,2], Ralph R. Pfeiffer [a], Kenneth R. Morris [a], Joseph G. Stowell [a,3], Stephen R. Byrn [a,*]

[a] *Department of Industrial and Physical Pharmacy, School of Pharmacy and Pharmacal Sciences, Purdue University, s 575 Stadium Mall Drive, West Lafayette, IN 47906-2051, USA*
[b] *Institute of Pharmacognosy, University of Innsbruck, Innrain 52, A-6020 Innsbruck, Austria*

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Abstract

Indomethacin was used as a model compound to investigate acid–base reactions of solid materials, a common type of drug–excipient interaction. In a typical experiment, 500 mg of pure α-form indomethacin were mixed with 500 mg of sodium bicarbonate. The mixture was kept at 40 °C and at several relative humidities. The reaction was monitored by IR spectroscopy, X-ray powder diffraction, and solid-state NMR. At 40 °C and 80% RH, the reaction is nearly complete after 300 h. As observed by IR spectroscopy, the characteristic peaks of α-indomethacin disappear during the course of the reaction with the appearance of the characteristic peaks of the salt product, sodium indomethacin trihydrate. Solid-state NMR spectra and X-ray powder diffraction patterns of the reaction mixtures confirm the transformation of the mixtures to sodium indomethacin trihydrate; the reduced peak intensities in the diffraction patterns of the product relative to the initial mixtures indicate the formation of a microcrystalline product. A change in the reaction rate of sodium bicarbonate with α-indomethacin is observed when the mixtures are stored at different relative humidities. At 40 °C and 66% RH, the reaction of sodium bicarbonate with α-indomethacin is about 86% complete after 500 h. No detectable reaction was observed for sodium bicarbonate with the α form of indomethacin at 40 °C and 11% RH after 15 months. The combination of these solid-state characterization techniques is demonstrated to be essential to detect and monitor acid–base reactions in solid materials, which are impossible to monitor using solution-chemistry methods. The reaction kinetics at 66% RH fits the Jander equation very well, which is consistent with a diffusion-controlled mechanism.

Keywords: Solid-state; Acid–base reaction; Diffusion-controlled; Humidity; IR; Solid-state NMR; XRPD; Indomethacin

1. Introduction

Most pharmaceuticals are either weak acids or bases. According to Wells, about 75% of pharmaceuticals are weak bases while another 20% are weak acids [1]. It is estimated that about 45–50% of the marketed drugs are salts, the majority of which are either weakly basic or weakly acidic [2]. Proton-transfer reactions between active pharmaceutical ingredients and excipients in a solid-dosage form will result in the conversion of the salt to the free form, which is very undesirable since both the safety and the efficacy of the drug will be compromised. For instance, it was reported that the dissolution rates of some sodium salts are several orders of magnitude greater than the weak-acid counterparts [3]. The effect of such a conversion on the drug pharmacokinetic profile, such as AUC, T_{max}, and C_{max},

* Corresponding author. Tel.: +1 765 494 1460; fax: +1 765 494 6545.
E-mail address: sbyrn@pharmacy.purdue.edu (S.R. Byrn).
[1] Present address: Schering-Plough Research Institute, 2000 Galloping Hill Road, K-11-2 J-4, Kenilworth, NJ 07033-1328, USA.
[2] Present address: GlaxoSmithKline, 1250 Collegeville Road, Collegeville, PA 19426-2990, USA.
[3] Present address: The Chao Center for Industrial Pharmacy & Contract Manufacturing, 3070 Kent Avenue, West Lafayette, IN 47906-1075, USA.

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cannot be discounted. However, there is little understanding of how to control such interactions, much less even to detect them.

In a traditional drug–excipient compatibility study, drug and excipients are mixed in binary or complex mixtures [4,5]. These mixtures are stored at 60–80 °C and 60–80% RH for 1–3 months. Each sample is then extracted with a suitable solvent and HPLC methods are applied to detect any possible loss in potency as well as the formation of any degradation products. However, this practice is not suitable for acid–base reactions that only involve proton transfer since solvation will facilitate the proton transfer and confound the results. Alternatively, we propose methods to detect these reactions by exploiting a combination of solid-state characterization techniques, such as X-ray powder diffraction (XRPD), IR spectroscopy, and solid-state NMR, which have demonstrated great utility in studying the acid–base reaction between indomethacin and sodium bicarbonate in the solid-state. To our knowledge, this is the first report to use the combination of these techniques to study acid–base reactions of solid pharmaceutical compounds.

Indomethacin, 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indole-3-acetic acid, is a non-steroidal anti-inflammatory agent and was used as a model compound in this study.

2. Experimental

2.1. Materials

γ-Indomethacin, 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indole-3-acetic acid, was purchased from Sigma Chemical Co. (St. Louis, MO). α-Indomethacin was prepared by dissolution of the γ form in hot ethanol followed by rapid precipitation with the quick addition of water at room temperature, as previously described [6]. Both samples were passed through a 170-mesh sieve (90 μm) and dried under vacuum overnight before use. Sodium bicarbonate, reagent grade from J.T. Baker, Inc. (Phillipsburg, NY), was used as received. Potassium bromide was purchased from Sigma Chemical Co. (St. Louis, MO) and dried in a vacuum oven before using. Crystalline sodium indomethacin trihydrate was a gift from Drs. George Zografi and Ping Tong, University of Wisconsin at Madison.

2.2. Preparation of the physical mixture

Sodium bicarbonate was uniformly mixed with an equal weight of α-indomethacin in an agate mortar without grinding using a spatula. The resulting mixtures were kept at 40 °C over a saturated aqueous solution of either potassium bromide (80% RH), potassium iodide (66% RH), or lithium chloride (11%) [7]. Aliquots of the stored mixtures were removed for analysis at scheduled time intervals.

2.3. Infrared spectroscopy

Approximately 1 mg of solid sample was carefully ground with 50 mg of dry potassium bromide and pressed into a pellet. No variation was observed owing to the sample preparation. IR spectra were measured on a Perkin-Elmer Spectrum 1600 Fourier-transformed infrared spectrophotometer (Shelton, CT) with a resolution of 4.0 cm^{-1}. Spectra were collected in the region of 4000–650 cm^{-1} for 64 scans. A background spectrum using potassium bromide as the blank was collected under the same experimental conditions as the test samples to subtract the absorptions owing to the ambient conditions (atmospheric carbon dioxide and water). Data acquisition and analysis were performed with *GRAMS/32*© (Galactic Industries Corp., Salem, NH). An identical baseline correction was performed for the series of spectra by manually entering the baseline points at fixed frequencies.

2.4. X-ray powder diffraction

All diffraction patterns were measured on a Shimadzu XRD-6000 diffractometer (Shimadzu Scientific Instruments Inc., Columbia, MD) equipped with a vertical goniometer in $\theta/2\theta$ geometry. The copper Kα radiation was generated at a power of 40 kV and 40 mA. Approximately 0.1 g of powder sample was placed in the well of a glass sample holder and gently compacted using a glass slide to ensure that the sample surface and holder surface were coplanar. A continuous scan was recorded for all samples from 4° to 36° 2θ with a step size of 0.02° 2θ and a scanning rate of 2° 2θ min^{-1}.

2.5. Solid-state nuclear magnetic resonance spectroscopy

^{13}C cross-polarization (CP/MAS) NMR spectra with magic-angle spinning were obtained at 62.9 MHz on a Bruker AC250 FT-NMR spectrometer (Bruker BioSpin Corp., Billerica, MA). The proton decoupling frequency was 250.13 MHz. The same level of power was used for the proton 90° pulse, the cross-polarization, and decoupling.

3. Results

3.1. Infrared spectroscopy of reactants

Fig. 1 shows the reference IR spectra for α-indomethacin, γ-indomethacin, and sodium bicarbonate as well as the proposed reaction product, sodium indomethacin trihydrate. α-Indomethacin and γ-indomethacin have distinct absorption bands in the carbonyl region because each exhibits different crystal packing and hydrogen bonding. γ-Indomethacin has characteristic absorption bands at 1717 and 1692 cm^{-1}. The 1717 cm^{-1} absorption band in γ-indomethacin is assigned to the carbonyl stretch of the carboxylic acid dimer. The 1692 cm^{-1} absorption band is assumed to be the carbonyl

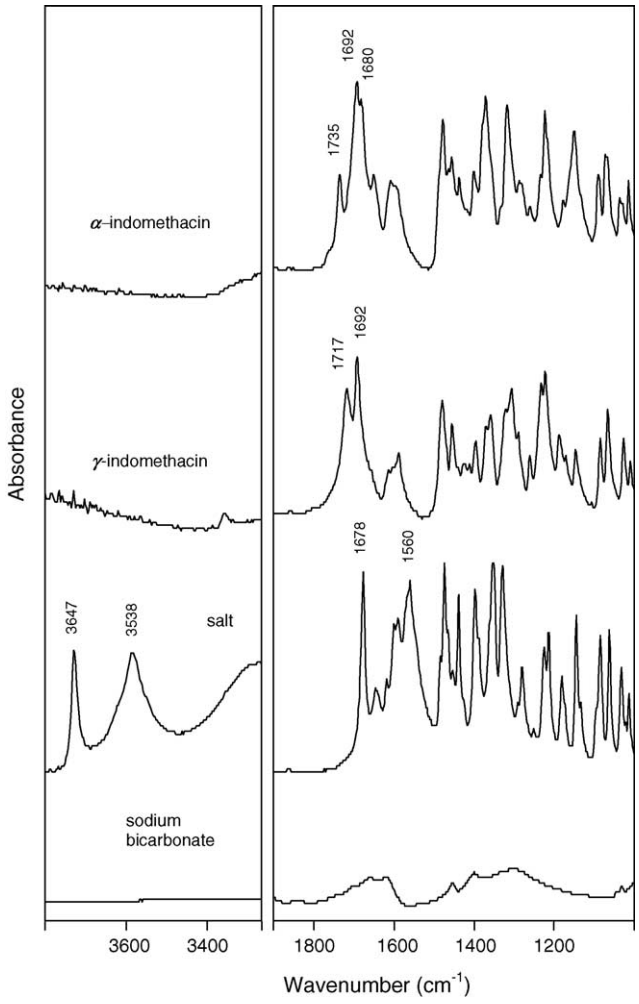


Fig. 1. IR spectra of α-indomethacin, γ-indomethacin, sodium indomethacin trihydrate, and sodium bicarbonate. Wavenumbers are listed above the absorption bands of interest.

stretch of the non-protonated amide. α-Indomethacin has characteristic absorption bands at 1735, 1692, and 1680 cm^{-1}, which is related to its crystal structure [8]. The asymmetric unit of α-indomethacin contains three molecules (designated A, B, and C), each with different conformations. Two of these molecules (A and B) form a typical carboxylic acid dimer while the carboxylic acid of the remaining molecule (C) hydrogen bonds to an amide carbonyl of the dimer. The 1735 cm^{-1} absorption band in α-indomethacin is assigned to the non-dimer involved carboxylic acid carbonyl (Molecule C) while the absorption band for the carboxylic acid dimer is presumed to be the unresolved shoulder near 1717 cm^{-1}. The 1692 cm^{-1} absorption band in both forms is assumed to be the carbonyl stretch of the non-protonated amide while the absorption band at 1680 cm^{-1} is assigned to the protonated amide (Molecule B). The absorption band at 1560 cm^{-1} in sodium indomethacin trihydrate is assigned to the asymmetric carboxylate stretch by analogy to Silverstein and Webster's assignment for the ammonium salt of benzoic acid [9]. Because of the new chemical environment, the amide carbonyl absorption band shifts to 1678 cm^{-1} in the sodium salt, presumably from hydrogen bonding with one or more of the water molecules.

Sodium indomethacin trihydrate has two other characteristic absorption bands at 3647 and 3538 cm^{-1} from water hydroxyls, which are typical for a hydrate. Sodium bicarbonate, the other starting material, shows little interference in the carbonyl region of indomethacin and sodium indomethacin trihydrate. Thus, IR is a very sensitive method for detecting the interaction between indomethacin and sodium bicarbonate that is expected to produce a sodium salt of indomethacin. The characteristic peaks of the hydrate are useful to distinguish the exact physical form of the product.

All IR spectra were collected as potassium bromide pellets. No variation was observed owing to sample preparation. The spectra of reactants and mixtures were also collected as Nujol® mulls (data not shown). Since the spectra from both techniques were nearly identical (excluding the absorption bands of Nujol®), the KBr pellet technique was selected for this investigation.

3.2. Indomethacin and sodium bicarbonate at 40 °C and 80% relative humidity

Fig. 2 shows the reaction progress at 40 °C and 80% RH as monitored by IR spectroscopy. Indomethacin reacts with sodium bicarbonate under these conditions. The spec-

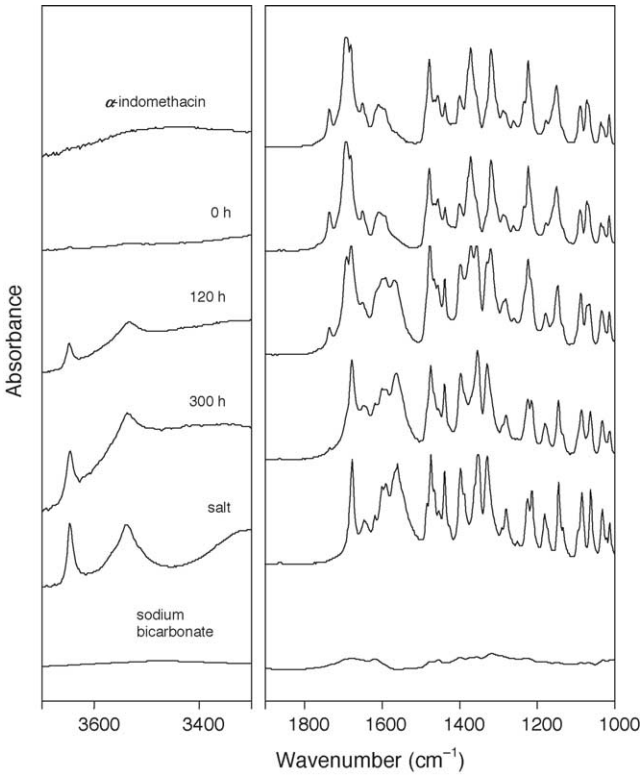


Fig. 2. IR spectra of indomethacin and sodium bicarbonate as well as physical mixture maintained at 40 °C and 80% RH for 0, 120, and 300 h.

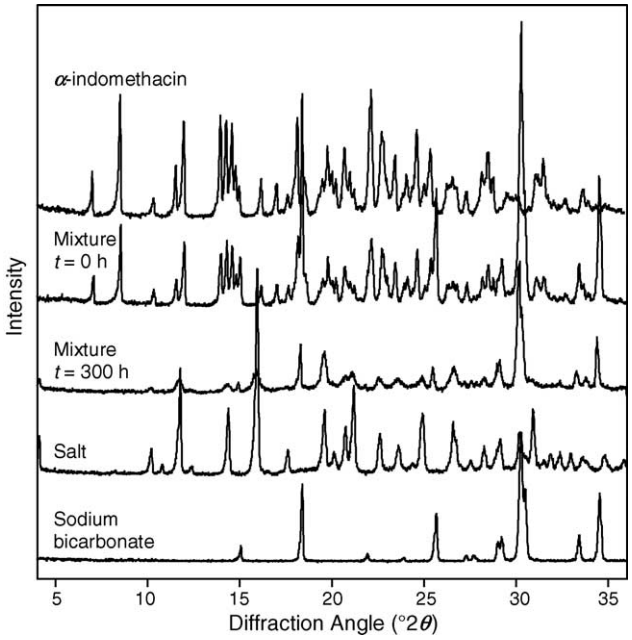
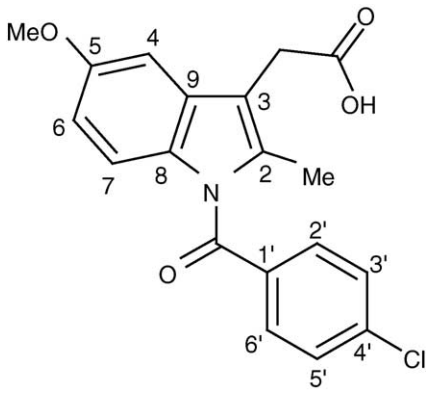


Fig. 3. XRPD patterns of pure indomethacin, indomethacin and sodium bicarbonate physical mixtures before and after storing at 40 °C and 80% RH, pure sodium indomethacin trihydrate (salt), and pure sodium bicarbonate.

trum of the physical mixture of α-indomethacin and sodium bicarbonate at $t = 0$ is nearly identical to that of pure α-indomethacin. A sample taken after 120 h at 40 °C and 80% RH shows a decrease in the absorption band intensities at 1735 and 1692 cm^{-1} and new absorption bands at 1678 and 1560 cm^{-1}. These two characteristic peaks of sodium indomethacin are dominant after 300 h and the characteristic peaks of α-indomethacin totally disappear. It is also observed that the two hydroxyl peaks of water at 3647 and 3538 cm^{-1}, typical of a hydrate, become more intense as time progresses. Pure reactants alone show no distinct change under the same condition. No physical transformation to γ-indomethacin was detected. Therefore, it can be concluded that α-indomethacin reacts with sodium bicarbonate to form sodium indomethacin trihydrate at 40 °C and 80% RH.

XRPD gives additional evidence concerning the reaction progress and the identity of the product formed. Fig. 3 shows the diffraction patterns of physical mixtures before and after reaction; these compare with the pure starting materials and the proposed reaction product. After about 300 h, all of the characteristic diffraction peaks for α-indomethacin disappear in the physical mixtures. In addition to the diffraction peaks from some residual sodium bicarbonate, the resulting diffraction pattern matches that of sodium indomethacin trihydrate. The low diffraction intensity is probably due to the formation of microcrystalline product.

Solid-state NMR further confirms the identity of the reaction product. The spectra of physical mixtures of indomethacin and sodium bicarbonate at $t = 0$ are identical to the spectra of pure α-indomethacin (data not shown). Note that the crystal structure of α-indomethacin contains



Scheme 1. Chemical structure of indomethacin with numbering scheme.

molecules in three different conformations and hence the solid-state NMR spectrum of α-indomethacin consists of multiple resonances for some carbon atoms, such as the carboxylic acid carbon and the methyl carbon attached at C2 of the indole ring (Scheme 1; Fig. 4).

It is clear that a transformation occurs in the mixtures during the 300 h at 40 °C and 80% RH. Compared to the starting material, the carboxylic acid carbon is shifted to lower ppm values and the methylene carbon adjacent to the carboxylic acid group is shifted to higher ppm values. The spectra of the mixtures after 300 h at 40 °C and 80% RH are identical to the spectrum of sodium indomethacin trihydrate.

In summary, the chemical and physical nature of the reaction product between indomethacin and sodium bicarbonate is clearly elucidated by the alliance of IR spectroscopy, XRPD, and solid-state NMR analysis.

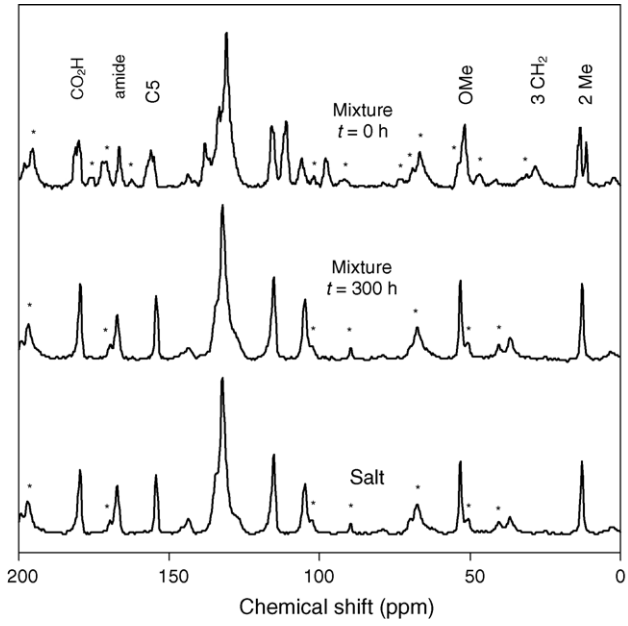


Fig. 4. ^{13}C CP/MAS spectra of indomethacin and sodium bicarbonate physical mixtures before and after storing at 40 °C and 80% RH for 300 h as well as sodium indomethacin trihydrate (salt) [asterisks (*) indicate spinning side bands].

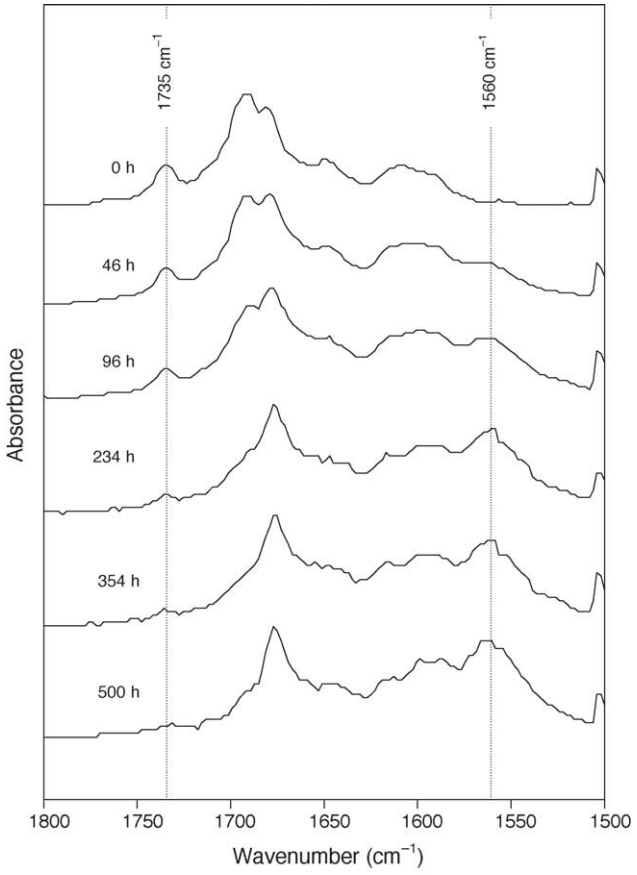


Fig. 5. IR spectra of indomethacin and sodium bicarbonate mixtures kept at 40 °C and 66% RH for 0, 46, 96, 234, 354, and 500 h.

3.3. Indomethacin and sodium bicarbonate at 40 °C and 66% relative humidity

When the relative humidity is 66%, the reaction between indomethacin and sodium bicarbonate is less than at 80% RH as illustrated by the IR spectra in Fig. 5. The reaction is nearly complete for the α-indomethacin samples after 500 h at 40 °C and 66% RH as evident by the disappearance of the characteristic absorption band at 1735 cm^{-1}. The absorption band at 1560 cm^{-1} corresponding to the nonprotonated carboxylic acid carbonyl grows more intense as the reaction time progresses. The peak height ratio between the carboxylic acid carbonyl absorption band of the starting material and the carboxylate carbonyl absorption band of the product was selected to quantify the extent of the reaction.

3.4. Quantifying the reaction using infrared spectroscopy

According to the Beer–Lambert law, the absorbance at any wavenumber for a specific compound is linearly related to the concentration of the compound, as defined in Eq. (1).

$$A = \varepsilon bc \quad (1)$$

IR spectroscopy can be used to quantify a drug substance in a mixture if the drug substance has distinct absorption bands that are well separated from the absorption bands of other components. The simplest case is a binary mixture. It is assumed that Compounds 1 and 2 have characteristic absorption bands at wavenumbers x and y, respectively. According to the Beer–Lambert law, $A_x = \varepsilon_x bc_1$ and $A_y = \varepsilon_y bc_2$. Therefore, there is a linear relationship between the absorption band intensity ratio (A_x/A_y) and the molar concentration ratio (c_1/c_2). This strategy has been used in this study since indomethacin and sodium indomethacin trihydrate have well separated characteristic absorption bands.

Because the other reactant, sodium bicarbonate, has no appreciable IR absorption in the 1400–1800 cm^{-1} region, binary mixtures of α-indomethacin with sodium indomethacin trihydrate were used to construct calibration curves. Indomethacin and sodium indomethacin trihydrate were mixed in various molar ratios and the IR spectrum of each mixture was acquired. The absorption band intensities at 1735 cm^{-1} for α-indomethacin and 1560 cm^{-1} for sodium indomethacin trihydrate were determined using *GRAMS/32*© software [11] following a background subtraction. The absorption band intensity ratios between indomethacin and sodium indomethacin trihydrate were plotted versus the molar ratio of indomethacin in the sample. Least-squares analysis of the calibration curve for the mixtures containing α-indomethacin gives correlations with R^2 of 0.9942 (Fig. 6). Moreover, the standard deviation for three separate samples for each data point is very small, indicating that the peak-ratio quantitative method is appropriate for this study.

The reactions at 40 °C and 66% RH were quantified using the calibration curve and plotted in Fig. 7. The reaction is

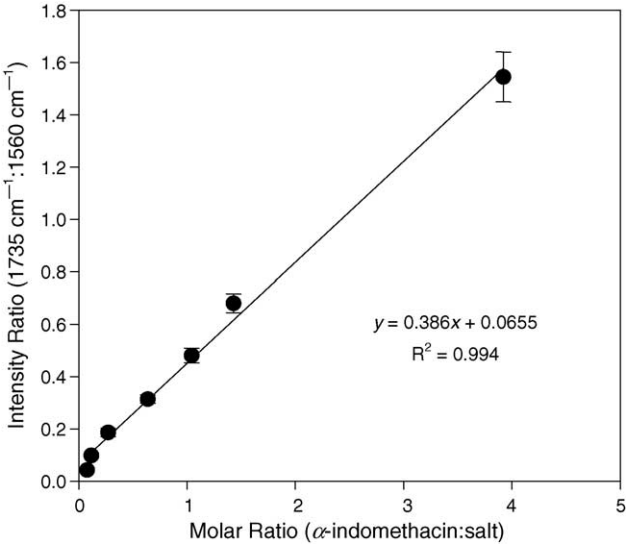


Fig. 6. Calibration curve to quantify either form of indomethacin from mixtures with sodium indomethacin trihydrate (salt) by comparing IR absorption band intensity ratios ($n = 3$ for standard deviations).

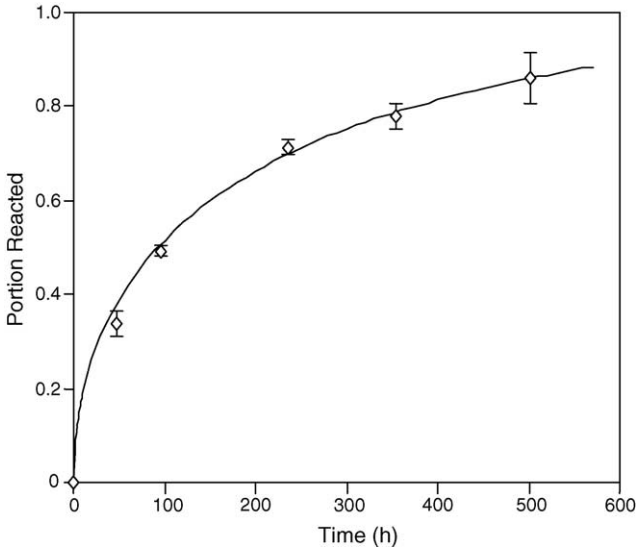


Fig. 7. Mixtures of indomethacin and sodium bicarbonate stored at 40 °C and 66% RH. The extent of the reaction was quantified by IR spectroscopy ($n = 3$ for standard deviations).

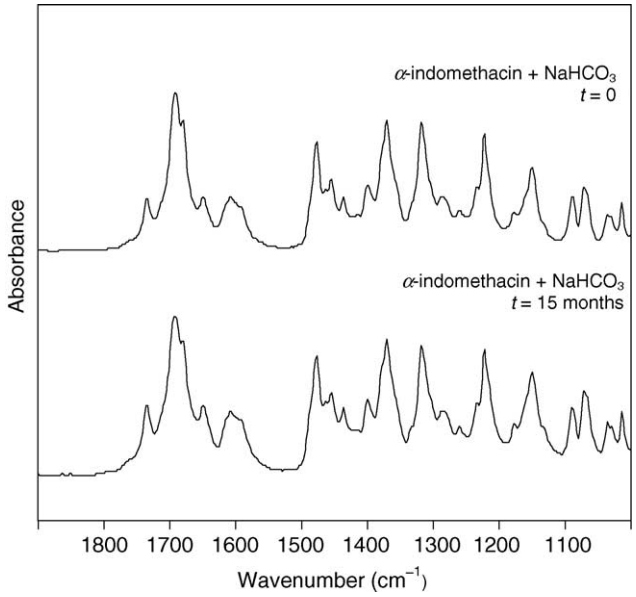


Fig. 8. IR spectra of indomethacin and sodium bicarbonate mixtures before and after 15 months at 40 °C and 15% RH.

deceleratory without an induction period. About 86% of indomethacin reacted with sodium bicarbonate after 500 h. The reaction data were fitted to different solid-state reaction models (Table 1). Nucleation and phase boundary based models fit the kinetics data poorly. However, the diffusion-based models fit much better, especially the three-dimensional diffusion models. The correlation for the Jander equation is 0.997. It is consistent with the hypothesis that the reaction between indomethacin and sodium bicarbonate is controlled by diffusion. The barrier for diffusion is suggested to be the product layer formed after reaction.

Table 1
Fitting of reaction data to different kinetic models

Equations	Integral form $\gamma(\alpha)$[a]	R^2
Prout–Tomkins	$\ln(\alpha/(1-\alpha))$	0.945
Avrami–Erofeev, $n = 2$	$(-\ln(1-\alpha))^{1/2}$	0.786
Avrami–Erofeev, $n = 3$	$(-\ln(1-\alpha))^{1/3}$	0.652
Avrami–Erofeev, $n = 4$	$(-\ln(1-\alpha))^{1/4}$	0.566
One-dimensional phase boundary (zero order)	$1-\alpha$	0.808
Two-dimensional phase boundary	$1-(1-\alpha)^{1/2}$	0.897
Three-dimensional phase boundary	$1-(1-\alpha)^{1/3}$	0.923
One-dimensional diffusion-controlled	α^2	0.953
Two-dimensional diffusion-controlled	$(1-\alpha)\ln(1-\alpha)+\alpha$	0.982
Three-dimensional diffusion-controlled	$1-2\alpha/3-(1-\alpha)^{2/3}$	0.990
Jander equation	$(1-(1-\alpha)^{1/3})^2$	0.997
Power law, $n = 1/2$	$\alpha^{1/2}$	0.599
Power law, $n = 1/3$	$\alpha^{1/3}$	0.497
Power law, $n = 1/4$	$\alpha^{1/4}$	0.441
First-order	$-\ln(1-\alpha)$	0.830
Second-order	$1/(1-\alpha)-1$	0.985

[a] Reference [10].

3.5. Indomethacin and sodium bicarbonate at 40 °C and 15% relative humidity

There is no detectable reaction for either α-indomethacin at 40 °C and 15% RH, even after 15 months as illustrated in Fig. 8. This indicates that the acid–base pair is relatively stable if the relative humidity level can be kept low. Water facilitates the reaction between indomethacin and sodium bicarbonate at temperatures close to ambient conditions. This may be due to the fact that water facilitates diffusion through the product layer.

4. Discussion

Acid–base reactions are a common type of drug–excipient interaction in the solid-state. Screening such interactions in a compatibility study is very critical to establish the correct formulation. However, traditional solution chemistry is not feasible for such analysis. On one hand, most solution chemistry requires solvent extraction. The free form and salt form of the analyte may have very different solubility in a given solvent, especially an organic solvent. If an excipient is even slightly soluble in the selected solvent, it will be impossible to avoid proton transfer from the acidic or basic excipient during sample preparation. In addition, the residual moisture content in the solvent may further facilitate the proton transfer. On the other hand, it will be a very challenging analytical task to quantitatively determine the ionized and free forms by HPLC analysis since the composition of typical mobile phases for reverse-phase HPLC analyses contain some amount of water and will thus, facilitate the speciation between ionized and free forms. Last but not least, any solvent extraction will disrupt the physical information involved in such a reaction

with solid material; this will make it impossible to elucidate the interaction between the drug substance and the excipient. Because of the analytical challenges, it is not surprising that most acid–base reactions studies of solid materials involve studies of effervescent systems [12–18]. The progress of the reaction can be followed simply by monitoring the weight loss since the reaction product is a gas. In our study on the reaction between indomethacin and sodium bicarbonate, we demonstrate that solid-state characterization techniques are powerful tools to detect acid–base type interactions in solid materials. Some of them may be suitable for quantification purpose, such as XRPD and IR spectroscopy.

The potassium bromide pellet technique has been used widely for qualitative and quantitative IR analysis [19–23]. A few milligrams of sample is thoroughly mixed with about 100 mg of dry potassium bromide (or other suitable alkali halide), which is ground further with a suitable mortar and pestle for both particle-size reduction and intimate mixing. A portion of the mixture is transferred to a special die and compressed into a transparent disk. The reproducibility of the spectrum relies on the intimacy of mixing and the consistency in the reduction of particle size, which will affect the absorption band intensities. To overcome the variation from sample preparation, internal standards are typically used for quantitative purpose. Inorganic thiocyanate salts or organic compounds containing a cyano group are common choices. However, adding one more component to the mixture increases the difficulty of mixing intimately as well as increasing the measuring error. Quantitative measurements without internal or external standards were applied successfully in mixtures of hexane and cyclohexane [24]. These measurements are based on the intensity ratios of absorption bands unique to each component at various mixing ratios. The same strategy was used in our study to negate the sample preparation variation. The calibration curve shows good linearity. If the two components have distinct spectra, this quantitative technique is very useful for mixture analyses and acid–base type of drug–excipient interactions.

Without transport via the vapor phase or a solution-mediated reaction, solid–solid reactions should be initiated only when the reactants are in direct contact. It is estimated that only $\sim 10^{-6}$ of the total surface is within the range of possible influence of the chemical forces of neighboring particles. This implies that the onset of product formation is restricted to a very small fraction of the surface. Since bulk diffusion through those contact points is very limited, fast solid–solid reactions, in some cases, could not be explained. Surface migration has been proposed to be the first step of the organic solid–solid reactions of 8-hydroxyquinoline with phthalic anhydride, maleic anhydride, succinic anhydride, catechol, and resorcinol [25,26]. A yellow product layer is formed for those reactions. The kinetics were studied using capillary methods and fit very well with the one-dimensional diffusion equation. The activation energies measured are 45–156 kcal/mol. The activation energy was interpreted in terms of surface migration. Since bulk diffusion is necessary to bring reactants together after the formation of a product layer, the reaction is hypothesized to be diffusion-controlled. Thus, diffusion through channels and cracks in crystal grains is proposed as the main mechanistic pathway for this reaction. The low crystallinity of reaction product layer may facilitate diffusion due to the increased mobility in some amorphous area.

As presented in Table 1 and Fig. 7, the reaction between indomethacin and sodium bicarbonate at 66% RH is also diffusion-controlled and fits well with the Jander equation. The Jander equation describes the kinetics if the reaction is controlled by diffusion from the surface of a spherical particle [10]. Numerous solid–solid powder reactions in alloys and ceramic syntheses are governed by three-dimensional diffusion and are expressed well by the Jander equation [27], such as the solid-state reactions between BaO_2 and Fe_2O_3 [28], Fe and Si [29], tin and copper chloride [30], as well as copper ferrite and copper chromite [31]. The build-up of product layer around the reactant particles becomes a diffusion barrier for reactants and limits the progress of the reactions. It is not quite clear how the reactants diffuse and in what physical state they exist in the diffusion layer. However, it is obvious that the reaction requires the presence of water. Some water may be absorbed by the reactants due to presence of defects, cavities or small amounts of amorphous material. Kuu et al. [32] reported that at a temperature of 40 °C sodium bicarbonate starts to decompose slightly at 75% RH whereas negligible decomposition takes place at and below 48% RH. At and above 75% RH a mass decrease with storage time was observed which was explained by the decomposition of the substance to water, carbon dioxide and sodium carbonate. Even though no deliquescence of sodium bicarbonate occurs at and below 89% RH [32], it can be assumed that the water released by this decomposition reaction in addition to the small amounts of moisture adsorbed at the surface of the particles is sufficient to dissolve the reactants partly forming a reaction layer. The reaction to sodium indomethacin provides further water which remains at the hydrophilic product layer. With increasing vapor pressure of the atmosphere, more water is mobilized in the product layer and consequently the reaction rate increases.

5. Conclusions

This study demonstrates that solid-state characterization techniques provide powerful tools for the detection of acid–base reactions in solid materials. Solid-state NMR, IR spectroscopy, and XRPD all revealed that sodium indomethacin trihydrate is formed when a mixture of indomethacin and sodium bicarbonate is kept at 40 °C and 80% RH. The progress of this type of reaction is dictated by the relative humidity. The reaction at 80% RH reaches completion in 300 h. If the relative humidity is lowered to 66%, the reaction with α-indomethacin is 86% complete after 500 h. No detectable change in mixtures of sodium bicarbonate with

indomethacin kept at 15% RH for 15 months is detected using IR spectroscopy.

A quantitative IR spectroscopic method was employed using the ratio between the acid carboxylic carbonyl and the deprotonated carboxylic carbonyl peaks. The reaction at 66% RH was evaluated using the developed IR spectroscopy method. The reactions appear to be deceleratory and expressed well by the Jander equation, a three-dimensional diffusion mechanism.

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