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Report

Solid-State Interaction of Magnesium Oxide and Ibuprofen to Form a Salt

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During formulation development work involving ibuprofen, a solid-state interaction between MgO and ibuprofen was observed. In this study the interaction of MgO and ibuprofen was investigated for 1:1 and 2:1 *M* mixtures of ibuprofen and MgO, which had been stored at 55°C, using the differential scanning calorimetric (DSC), thermogravic analysis (TGA), and multiple internal reflectance infrared (MIR) techniques. Evidence for the reaction was the disappearance of the melting endotherm at 79°C and appearance of a new endotherm at 161°C after less than 1 day of storage at 55°C and, also, the change in the physical appearance of the mixtures. Comparison of the DSC, TGA, and MIR data for the reacted ibuprofen and MgO mixtures and synthetic $Mg(ibuprofen)_2$ indicated that MgO and ibuprofen react to form the Mg salt of ibuprofen. The interaction of ibuprofen and MgO was also studied at 30 and 40°C, using 1:1 *M* mixtures. At 30°C no significant interaction was observed for up to 80 days; however, at 40°C a reaction was evident on day 1. $NaHCO_3$, K_2CO_3 $1.5H_2O$, CaO, and $Mg(OH)_2$ also showed solid-state reactions with ibuprofen. $MgCl_2$ and $Al(OH)_3$ did not show this reaction.

KEY WORDS: ibuprofen; magnesium oxide; solid-state interaction; thermal analysis; multiple internal reflectance infrared (MIR).

INTRODUCTION

During development of pharmaceutical dosage formulations, excipient compatibility studies are routinely performed to look for possible interactions of the formulation components with the active ingredient. In the literature, interactions between $NaHCO_3$ and tartaric acid and benzoic acid (1,2), phenylephrine hydrochloride and aspirin (3), and picric acid and acenaphthane, β-naphthylamine, and pyrocatechol (4,5) were reported in the solid state.

Ibuprofen is a nonsteroidal antiinflammatory (NSAID) compound. During tablet formulation, a solid-state interaction between ibuprofen and MgO was observed. This suggested the possibility of an acid–base type of reaction between ibuprofen and MgO in the solid state.

In this study, the solid-state interaction of MgO and ibuprofen was investigated using differential scanning calorimetry (DSC). The product of the reaction at 55°C was characterized by thermogravic analysis (TGA) and multiple internal reflectance infrared (MIR) techniques and the data were compared to the data for synthetic $Mg(ibuprofen)_2$. Studies were also performed to determine whether $Mg(OH)_2$, $Al(OH)_3$, $NaHCO_3$, K_2CO_3 $1.5H_2O$, CaO, and $MgCl_2$ interacted in the solid state with ibuprofen.

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MATERIALS AND METHODS

Materials

Ibuprofen was obtained from Mitsubishi International (Japan). $Mg(ibuprofen)_2$ was synthesized by the Chemical Development Department at G. D. Searle & Co. Magnesium ethoxide and ibuprofen were refluxed in ethanol for about 0.5 hr until a clear solution resulted. The solution was filtered and the ethanol was evaporated. The residue was dissolved in hot water and then cooled to precipitate the final product. The elemental analysis of the synthetic salt indicated the presence of at least 0.5 mol of water.

Experiments Involving Incubation of MgO and Ibuprofen

The solid ibuprofen and MgO were mixed at 1:1 or 2:1 *M* ratios in 10-ml glass scintillation vials (total weights of the mixtures were between 2 and 3 g). Studies of the mixtures stored at 40 and 30°C were performed with 1:1 *M* mixtures of ibuprofen and MgO. The vials were capped (without induction seal) and placed into ovens. At each time point, a 50- to 100-mg sample was removed and submitted for analysis. In the studies with CaO, $Mg(OH)_2$, $Al(OH)_3$, $MgCl_2$, $NaHCO_3$, and K_2CO_3 $1.5H_2O$, 1 mol of each chemical was mixed with the mole(s) of ibuprofen and equal to the valance of the cation of the salt, and the mixtures were stored at 55°C (except in the K_2CO_3 $1.5H_2O$, case where 1 mol of ibuprofen was mixed).

Analytical Measurements

Differential Scanning Calorimetry Analysis (DSC). The

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DSC thermograms were obtained using a DuPont 9900 thermal analysis system. The scanning rate was 10°C/min. The sample size varied from 1 to 10 mg. All DSC measurements were performed with an open pan.

Thermogravimetric Analysis (TGA). The TGA thermograms were obtained using a DuPont 9900 thermal analysis system fitted with a thermogravimetric analyzer. The rate of scanning was 20°C/min unless indicated otherwise in the figure legends. The sample size was about 4–10 mg.

Hot-Stage Melting-Point Determinations. The determinations were performed using a Mettler hot-stage melting-point apparatus.

Multiple Internal Reflectance IR (MIR) Analysis. The MIR spectra were obtained using an IBM FTIR-32 instrument equipped with a micro MIR attachment.

HPLC Analysis of Samples. The analysis was performed with a Waters 590 HPLC instrument equipped with a Waters 481 UV detector. An Ultrasphere ODS, 15 cm × 4.6-mm-i.d. column was used. The mobile phase consisted of a mixture of methanol and 0.1% H_3PO_4 (70:30, v/v). The flow rate was 1 ml/min. The detection of column effluent was performed by UV absorption at 230 nm, and peak area measurements were used for quantification. Samples were dissolved in the mobile phase before injection into the HPLC system.

RESULTS AND DISCUSSION

The DSC thermogram of pure ibuprofen is shown in Fig. 1a. As can be seen, there are two endotherms, one around 79°C and another around 261°C. By using a hot-stage melting apparatus with a microscope attachment, the melting point of ibuprofen was detected to occur around 78°C.

The TGA of ibuprofen indicated a major weight loss in the temperature range from 150 to 210°C (Fig. 1b). This weight loss may be due to evaporation of the sample.

In our preliminary investigations with tablet formulations, the stability of various ibuprofen formulations was studied at 55°C, and the interaction between ibuprofen and MgO was detected. Therefore 55°C was initially chosen to determine the mechanism of solid-state reaction between these two chemicals.

After ibuprofen and MgO were mixed at a 1:1 molar ratio as solids and stored at 55°C, the texture of the mixture started changing within a few hours. The sample became softer and stickier. The DSC thermogram of MgO which is given in Fig. 2 does not contain any peaks. The DSC thermogram measured prior to storage of the mixture at 55°C (Fig. 3a) was similar to the DSC thermogram of pure ibuprofen shown in Fig. 1a. However after 1 day of storage at 55°C, the DSC thermogram of the mixture was significantly different (Fig. 3b). The 79°C melting endotherm which is characteristic of pure ibuprofen disappeared and a new endotherm appeared at 161°C. The use of a hot-stage melting apparatus showed that this later endotherm was due to melting of the mixture. DSC studies of the mixture stored at 55°C for up to 12 days did not reveal any further changes (results are not shown).

The water contents of MgO, ibuprofen, and a 1:1 *M* mixture of MgO and ibuprofen (after 1 day of storage at 55°C) were determined as 2.8, 0.2, and 3.1%, respectively

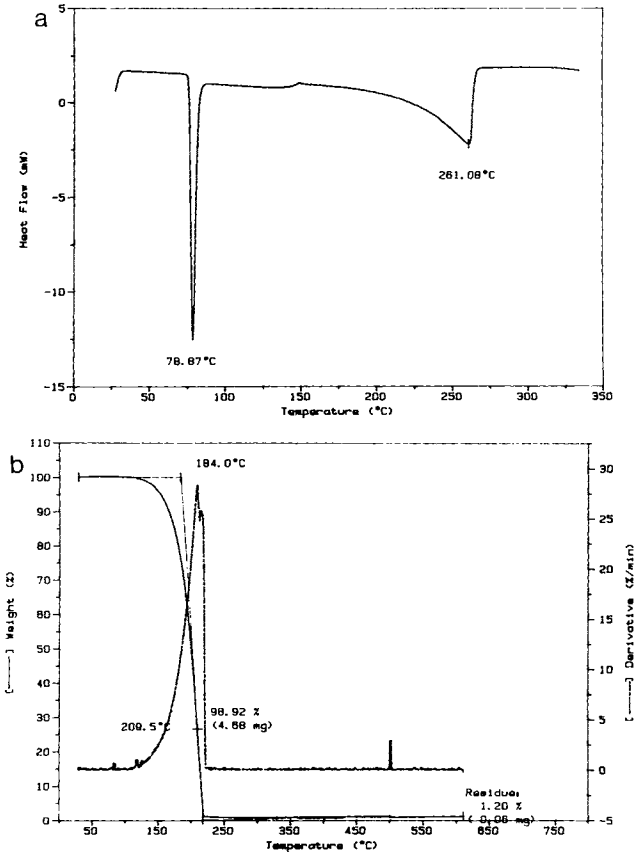

Fig. 1. (a) The DSC thermogram of ibuprofen. (b) The TGA thermogram of ibuprofen. The scanning rate was 10°C/min.

(Karl Fisher method was used). Based on the total weights (for a 1.03-g ibuprofen and 0.2-g MgO mixture), the moisture content of the initial reaction mixture should be only 0.63%. This indicated that water was a product of the reaction between MgO and ibuprofen.

The incubation of 2:1 *M* mixtures of ibuprofen and MgO was also performed. After storage at 55°C for a few hours, the 2:1 *M* mixture also showed similar texture changes. The DSC thermogram of the 2:1 *M* mixture after 1 day of storage at 55°C appeared more complex than the DSC thermogram

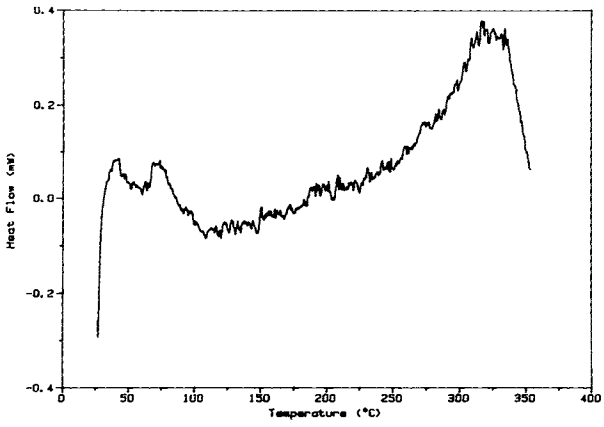

Fig. 2. The DSC thermogram of MgO.

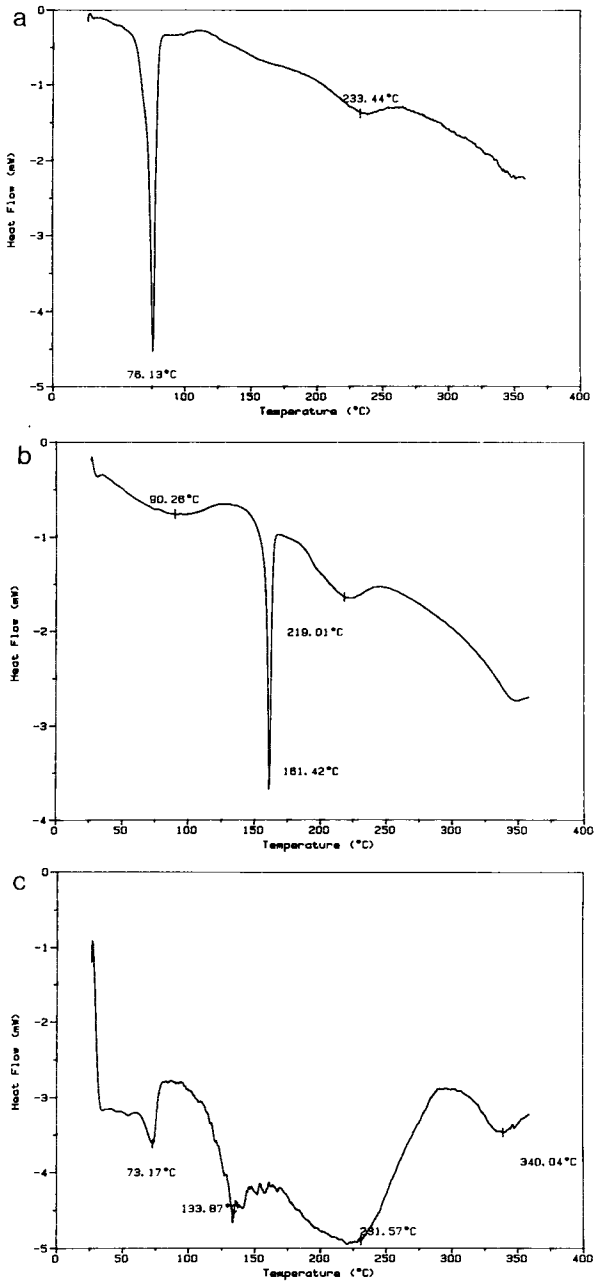

Fig. 3. (a) The DSC thermogram of the 1:1 *M* mixture of ibuprofen and MgO before storage at 55°C. (b) The DSC thermogram of the 1:1 *M* mixture of ibuprofen and MgO after 1 day of storage at 55°C. (c) The DSC thermogram of the 2:1 *M* mixture of ibuprofen and MgO after 1 day of storage at 55°C.

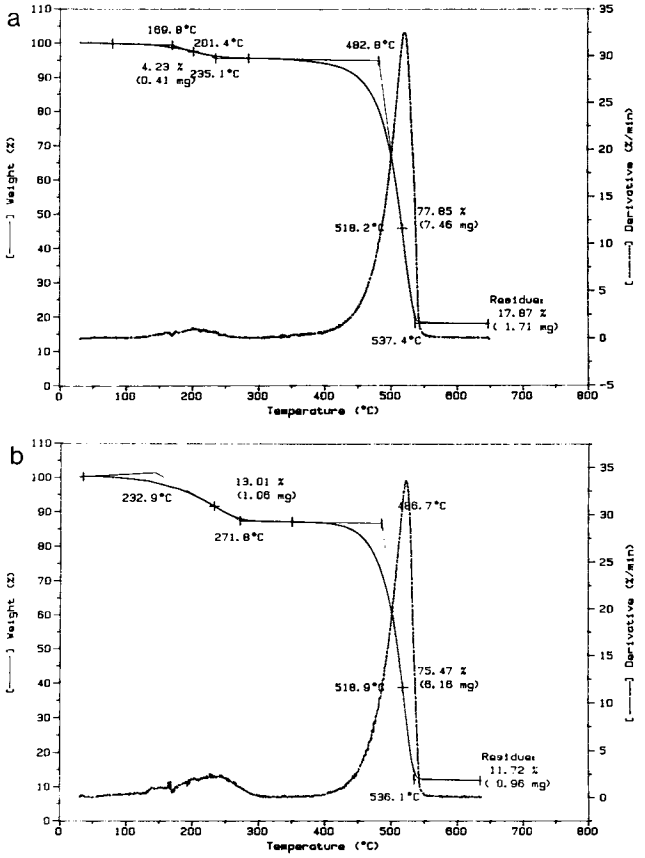

Fig. 4. (a) The TGA thermogram of the 1:1 *M* mixture of ibuprofen and MgO after 12 days of storage at 55°C. (b) The TGA thermogram of the 2:1 *M* mixture of ibuprofen and MgO after 2 days of storage at 55°C.

of the 1:1 *M* mixture (no clear endotherm at 161°C) (Fig. 3c). The DSC analyses of the 2:1 *M* mixture stored at 55°C for up to 6 days did not reveal further changes. The melting endotherm of ibuprofen did not disappear completely in the 2:1 *M* mixture, indicating the presence of some unreacted ibuprofen.

The TGA thermograms of both the 1:1 and the 2:1 *M* mixtures of ibuprofen and MgO (after the reaction was complete, as judged by DSC) are shown in Figs. 4a and b. It is very clear that the temperature at which the major weight loss occurs is now shifted to temperatures above 300°C. There is also some weight loss at temperatures below 300°C in both mixtures, especially in the 2:1 *M* mixture. The lower-temperature weight losses could be due to water, which was shown to be the product of the reaction, and unreacted ibuprofen, which appears to be present at a higher percentage in the 2:1 *M* mixture. The presence of unreacted ibuprofen was also evident in the DSC thermogram of the 2:1 *M* mixture (Fig. 3c).

Since ibuprofen is a weak acid and MgO is a basic oxide, a solid-state acid–base reaction seems to be a good possibility. The product of such a reaction would be the Mg salt of ibuprofen. In order to verify this, $Mg(ibuprofen)_2$ was synthesized and its DSC and TGA thermograms were determined. The results of the DSC measurements for the salt indicated a small endotherm around 175°C (Fig. 5a). By using the hot-stage melting technique, melting of the salt was found to occur from 168 to 180°C. The melting range of the synthetic $Mg(ibuprofen)_2$ salt is about 10°C higher than the melting temperature of the reacted ibuprofen–MgO mixtures. However, it must be remembered that the reacted ibuprofen–MgO mixture is less pure and its physical state is different from that of $Mg(ibuprofen)_2$. The TGA thermogram of the synthetic $Mg(ibuprofen)_2$ salt shows that the major weight loss occurs at temperatures above 300°C (Fig. 5b). This TGA thermogram for the synthetic salt is very similar to

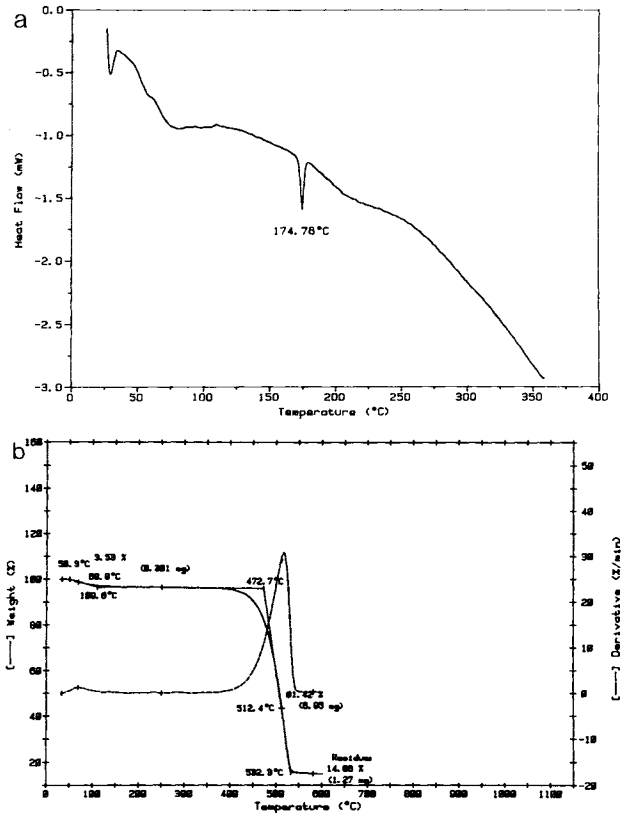

Fig. 5. (a) The DSC thermogram of synthetic Mg(ibuprofen)$_2$. (b) The TGA thermogram of synthetic Mg(ibuprofen)$_2$.

the TGA thermograms of the reacted ibuprofen–MgO mixtures. Comparison of the DSC and TGA results for the synthetic salt and the reacted mixtures suggested that the mechanism of solid-state interaction between MgO and ibuprofen might involve formation of the Mg salt of ibuprofen.

To confirm that the reaction product of ibuprofen and MgO is the Mg salt of ibuprofen, the MIR spectra of pure ibuprofen, MgO, 1:1 and 2:1 *M* mixtures of ibuprofen and MgO, and synthetic Mg(ibuprofen)$_2$ salt were determined (Figs. 6a–e, respectively). Although comparison of the MIR spectra of the 1:1 and 2:1 molar mixtures shows differences in intensities of some bands, the spectra are generally similar (Figs. 6c and d). It is clear that the band due to the carbonyl stretch of the COOH at 1700 cm^{-1} in the spectrum of ibuprofen (Fig. 6b) is significantly weaker in the spectra of the reacted ibuprofen–MgO mixtures. The presence of new bands due to carboxylate carbonyl stretch at about 1400 and 1590 cm^{-1} in the spectra of the reacted mixtures indicates the formation of a salt. The MIR spectra of Mg(ibuprofen)^2 (Fig. 6e) and the reacted ibuprofen–MgO mixtures all contain carboxylate bands, further confirming the formation of the Mg salt of ibuprofen from the reaction of ibuprofen and MgO, in the solid state.

The interaction of ibuprofen and MgO was also investigated at 30 and 40°C, using 1:1 *M* mixtures of MgO and ibuprofen. At 30°C the DSC of the mixture indicated almost no reaction for 80 days. However, at 40°C, the reaction was detected on day 1 and completion was reached within 28 days (results are not shown).

In order to prove that no ibuprofen degradation occurs at 55°C in the presence of MgO, the reacted 1:1 *M* mixture of ibuprofen and MgO was analyzed by HPLC. The results indicated no degradation for ibuprofen (no degradation peaks were observed); also 99.5% of the ibuprofen in the mixture could be accounted for by HPLC.

If the reaction of MgO with ibuprofen involved an acid–base type of interaction as suggested above, then it would be expected that other basic oxides and salts might also interact with ibuprofen. Indeed upon storage at 55°C, the mixtures of ibuprofen with Mg(OH)$_2$, K_2CO_3 1.5H$_2$O, $NaHCO_3$, and CaO also showed interactions. The reaction of ibuprofen with the above chemicals was evident from the change in the texture of the mixture to a softer and stickier state within a few hours of storage, except for the CaO mixture, as was observed for the MgO mixtures. In the case of CaO, the completion of the reaction took several months. DSC thermograms of these mixtures (except CaO case) determined after 4 days of storage at 55°C showed the disappearance of the 79°C endotherm and appearance of new endotherms above 160°C (results are not shown). In the case of CaO–ibuprofen, the change in the DSC pattern of ibuprofen took several months. The incubation of Al(OH)$_3$ with ibuprofen for up to 15 months at 55°C produced no interaction at 55°C. $MgCl_2$ also did not show any interaction with ibuprofen. The lack of interaction between ibuprofen and Al(OH)$_3$ could reflect the lower basicity of this chemical in the solid form. The interaction of $MgCl_2$ would not be expected with ibuprofen, since it is not a basic salt.

In this study the effect of water was not investigated. The observed interaction between ibuprofen and basic oxides, hydroxides, and salts will certainly require the presence of water in the system. Wright and Carstensen (1) studied the solid-state interaction of sodium bicarbonate with substituted benzoic acid derivatives in the presence of very small amounts of moisture (as low as 1.8) and found sodium benzoate formation. In their study, the water content was found to have a pronounced effect on the solid state interaction rate. Water provides a medium for the dissolution and diffusion of the acidic and basic species in the system. In our study, it is suggested that the reaction of MgO and ibuprofen is also driven by water and 0.63% water content of the initial mixture may be enough to start the reaction between MgO and ibuprofen (1:1 *M* mixture). As the reaction proceeds, production of water as a product of the reaction should accelerate the interaction rate between basic oxides and ibuprofen.

The significance of such a reaction in development of dosage forms is manifold. Any solid-state interaction in this nature will certainly affect the physical appearance and stability of formulations. If the reaction occurs very fast as in the case of ibuprofen and MgO, $NaHCO_3$, and K_2CO_3 mixtures, the formulation efforts will be hampered. If the reaction proceeds slowly as in the case of CaO, the properties of formulation will change over time. The production of water will adversely effect the stability of the formulation. Further, the formation of a relatively insoluble salt, such as Mg(ibuprofen)$_2$, will significantly change the dissolution profile of the active component.

In summary, it was found that the weak acid ibuprofen reacts in the solid state with various basic oxides, hydrox-

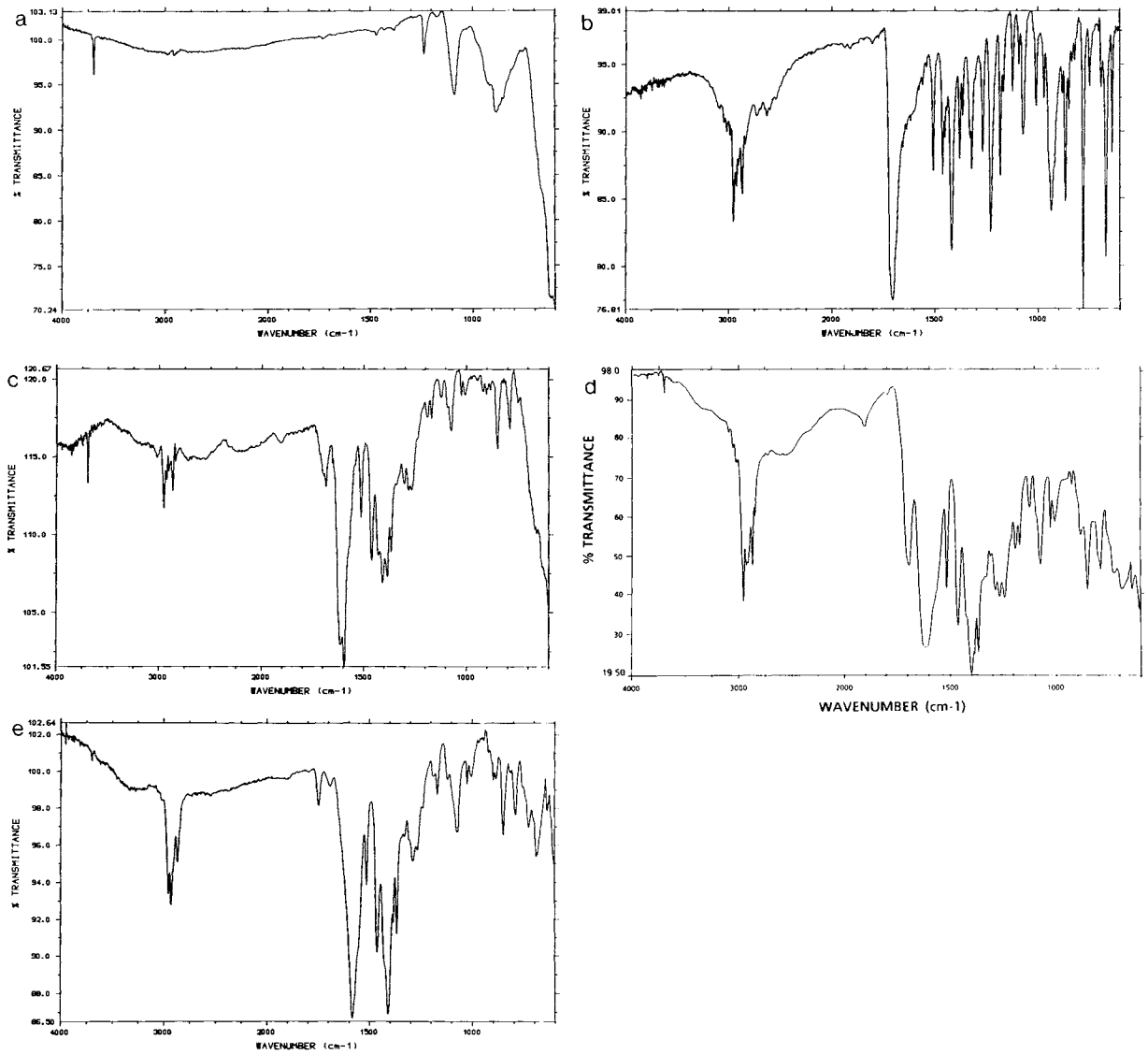

Fig. 6. (a) The MIR spectrum of MgO. (b) The MIR spectrum of ibuprofen. (c) The MIR spectrum of a 1:1 *M* mixture of ibuprofen and MgO after 12 days of storage at 55°C. (d) The MIR spectrum of a 2:1 *M* mixture of ibuprofen and MgO spectrum after 14 days of storage at 55°C. (e) The MIR spectrum of synthetic $Mg(ibuprofen)_2$.

ides, and salts. In the case of MgO, the reaction product appears to be the Mg ibuprofen salt. For the others, the salt formation can also be suggested even though the products of the reaction were not investigated. These reactions can have a significant impact on formulation stability and performance.

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