Characterization of Ibuprofen-Loaded MgO by One-Step Mid- and Far-FT-IR Spectroscopy

Takuya Ehiro

Research Division of Polymer Functional Materials, Osaka Research Institute of Industrial Science and Technology; 2–7–1 Ayumino, Izumi, Osaka 594–1157, Japan.
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One-step mid- and far-Fourier-transform (FT)-IR spectroscopy is a facile and powerful tool that provides various information regarding chemical and crystal states. However, its potentially high applicability has not been sufficiently demonstrated. In the present study, ibuprofen (IB)-loaded MgO samples are prepared via different methods, and they are evaluated using scanning electron microscopy (SEM), thermogravimetry-differential thermal analysis (TG-DTA), X-ray diffraction analysis (XRD), N₂ adsorption-desorption measurement, CO₂ temperature-programmed desorption technique (CO₂-TPD), and FT-IR spectroscopy. The obtained results indicate that IB becomes ionized, amorphous, and/or dispersed by using MgO. Since the CO₂-TPD result shows that MgO possesses basic surfaces, it is considerable that acid–base interactions cause the above different chemical states. Furthermore, the FT-IR spectra in mid- and far-IR regions also suggest that the above physical and chemical properties of IB-loaded MgO changes through the interactions. Therefore, the characterization results suggest that one-step mid- and far-FT-IR measurements can provide valuable information regarding the chemical and crystal states.

Key words one-step Fourier-transform (FT)-IR; far-IR; drug delivery system; ibuprofen; drug carrier

Introduction

Drug delivery systems (DDSs) have been studied extensively for the enhancement of drug efficacy, reduction of adverse effects, and/or improvement in drug compliance. For instance, MgO-containing inorganic drug carriers have been investigated to control drug release rate, sustain drug efficacies, and avoid rapid changes in blood drug concentrations due to the burst release of drugs.¹⁻³ In these DDSs, controlled releases are achievable through acid–base interactions between a drug and its carrier.

In addition to controlled release, water solubility must be enhanced in many drug formulations because often drugs are not highly water soluble; hence, only a small portion of drugs reach the target organs. So far, various techniques have been used to improve the water solubility of drugs, such as amorphization, size reduction of drug particle, and co-crystallization.⁴⁻⁷

Fourier-transform (FT)-IR spectroscopy has been performed extensively in mid-IR regions to evaluate the functional groups of drugs. Unlike mid-IR regions, far-IR or terahertz (THz) regions can provide different information, such as crystal polymorphism,⁸⁻¹⁰ owing to their lower electromagnetic energies. In particular, THz spectroscopy has gained significant attention in various fields recently, including the pharmaceutical industry.⁹⁻¹² For instance, it has been reported that the THz time domain spectra of nitrofurantoin and melamine were obviously different from that of their hydrated co-crystal form with hydrogen bonding interactions.¹³ Although THz spectroscopy is extremely useful and promising for analyzing the crystal states, co-crystal structural changes, and the hydrogen bonding effects, the direct evaluation of functional groups is difficult. By contrast, one-step mid- and far-FT-IR measurements are facile methods for simultaneously evaluating the functional groups and crystal states of drugs. However, its applications have not yet been sufficiently demonstrated.

In the present study, ibuprofen (IB)-loaded MgO samples were prepared using three different methods. Subsequently, they were evaluated using various characterization techniques. As stated above, MgO with solid basicity can be a key material to control drug releasability and enhance drug adsorption capacity. Furthermore, IB was used as an acidic model drug owing to its extensive usage as an analgesic and anti-inflammatory drug.¹⁴

Experimental

MgO was prepared by calcining magnesium acetate tetrahydrate (FUJIFILM Wako Pure Chemical Corporation, Osaka, Japan) at 823 K for 3 h. IB (Tokyo Chemical Industry Co., Ltd., Tokyo, Japan) was loaded via adsorption, impregnation, and physical mixing. Adsorption and impregnation were performed using the same procedure as previously reported,¹⁵ and the obtained IB-loaded MgO samples are denoted as IB/MgO(50)-ads and IB/MgO(50)-imp, respectively. During physical mixing, equivalent weights of IB and MgO were loosely mixed using a spatula for 5 min. This sample was labeled as IB/MgO(50)-phy-0 min. Subsequently, IB/MgO(50)-phy-0 min was ground in an agate mortar for 2, 5, 10, or 15 min. The obtained samples were labeled as IB/MgO(50)-phy-x min (x = 2, 5, 10, or 15). Additionally, MgO samples containing 90 wt% IB were prepared by impregnation and physically mixing for 0 and 15 min. The obtained samples were denoted as IB/MgO(90)-imp, IB/MgO(90)-phy-0 min, and IB/MgO(90)-phy-15 min, respectively. To prepare a reference sample, magnesium ethoxide [Mg(OEt)₂, FUJIFILM Wako Pure Chemical Corporation] and IB at 2 to 1 M ratio were reacted in ethanol (Amakasu Chemical Industries Co., Ltd., Tokyo, Japan).¹⁶ After filtering the solution, the filtrate was evaporated to obtain Mg(ibuprofen). The obtained sam-
ple was labeled as Mg(IB)$_2$-syn.

One-step mid- and far-FT-IR were performed using Vertex 70 (Bruker Corp., MA, U.S.A.) in the range of 80–2000 cm$^{-1}$. The FT-IR spectra were obtained via the attenuated total reflectance (ATR) method. Thermogravimetry-differential thermal analysis (TG-DTA), X-ray diffraction (XRD) analysis, scanning electron microscopy (SEM), N$_2$ adsorption-desorption measurement, and CO$_2$ temperature-programmed desorption (CO$_2$-TPD) were performed by referring a previous report.\textsuperscript{15)

Results and Discussion

Figure 1 shows the SEM images of the prepared samples. Although the raw IB particles were relatively large, they were rarely observed even in IB/MgO(50)-phy-0 min. Instead, the external surfaces of the MgO particles were partially coated with IB. In addition, the IB-coated surfaces were more apparent as the grinding time was longer. By grinding the sample for more than 5 min, the originally rough MgO surfaces were covered and embedded with IB. Additionally, as the physical mixing time was longer, the sample became stickier and some larger particles were observed. In contrast, such IB-coated smooth surfaces were not observed in IB/MgO(50)-ads and IB/MgO(50)-imp. This may suggest that the IB molecules diffused into the insides of the MgO particles during the adsorption and impregnation steps.

According to the previous research,\textsuperscript{1)} MgO-modified submicron mesoporous silica [MgO/SBA-15 (Si/Mg = 5)] showed a high Brunauer–Emmett–Teller (BET) specific surface area (569 m$^2$/g) and 32.2 wt% of IB adsorption capacity, owing to its mesoporosity and alkalinity. Therefore, it was conceivable that the present MgO with a lower BET specific surface area (59 m$^2$/g) could have indicated a saturation of IB adsorption and a lower IB adsorption capacity. Moreover, chemical and crystal states of IB adsorbed on MgO could be different from those of IB impregnated on MgO. Hence, the adsorption method was also performed in order to investigate the effects of IB-loading methods on chemical and crystal states.

However, as shown in Fig. 2A, the TG results indicate that the IB content of IB/MgO(50)-ads was estimated to be approx. 50 wt% and almost equal to those of IB/MgO(50)-imp, IB/MgO(50)-phy-0 min, and IB/MgO(50)-phy-15 min. The TG curve of IB/MgO(50)-ads shows that most of the added IB was loaded in the adsorption method because the maximum adsorption amount was 50 wt% in the present conditions. Moreover, its IB adsorption capacity was higher than that of MgO/SBA-15 (Si/Mg = 5).\textsuperscript{1)} Considering the lower BET specific surface area of the present MgO, its higher IB adsorption capacity (approx. 50 wt%) implies that a part of IB reacted with MgO in its bulk phase owing to its reactivity with IB.\textsuperscript{16)} As a result, the saturation of IB adsorption was not observed for MgO in the present study, while it was confirmed for...
15 wt% MgO-modified SBA-15 under the same conditions.\textsuperscript{15)}

In the TG-DTA analyses, it was confirmed that the IB decomposition temperature shifted to high temperature regions owing to MgO. In addition, an endothermic peak at approximately 354 K, which was likely due to IB melting,\textsuperscript{19} was obviously detected in the DTA curve of IB/MgO(50)-phy-0 min, whereas apparent endothermic peaks were not observed for IB/MgO(50)-ads and IB/MgO(50)-imp (Fig. 2B). The disappearance of the endothermic peaks implied that the large portion of IB interacted with MgO.

As stated above, the BET specific surface area of MgO were estimated to be 59 m\(^2\)/g, which was higher than that of an industrial MgO (25.1 m\(^2\)/g).\textsuperscript{17} Additionally, solid basicity of MgO was confirmed using CO\(_2\)-TPD (Fig. 3). In CO\(_2\)-TPD measurements, CO\(_2\) is used as an acidic probe gas to the basic sites. After CO\(_2\) adsorption on the surface, CO\(_2\) desorption is promoted by heating under an inert gas flow. Therefore, a peak in a spectrum represents CO\(_2\) desorption from basic sites and the peak area corresponds to the number of basic sites. Additionally, a high desorption temperature represents strong basicity. Therefore, the peaks in low and high temperature regions indicate basic sites of MgO, which has been widely investigated as a relatively strong solid base.\textsuperscript{18,19} Hence, it was assumed that these surface properties of MgO contributed to the acid–base interaction and changed the morphologies and the thermal behaviors (Figs. 1, 2).

Figure 4 shows the XRD patterns at low and high diffraction angles. The calcined magnesium acetate tetrahydrate showed characteristic peaks due to MgO (PDF#01-071-1176) at approximately 42.8, 62.2, 74.6, and 78.5° (not shown). By contrast, in the 2θ regions shown, MgO did not exhibit any characteristic diffraction peaks, whereas the peaks were detected for raw IB. At high diffraction angles, the crystallinity of IB decreased as the grinding time increased [Figs. 4B(b)–(f)]. However, no IB peaks were detected for IB/MgO(50)-ads and IB/MgO(50)-imp [Figs. 4B(g) and (h)]. These results suggest that IB was more amorphized and/or dispersed on the MgO surfaces by adsorption and impregnation. In addition to the high diffraction angles, XRD patterns at low diffraction angles were obtained by changing the analytical system and conditions. As the grinding time was prolonged, the original IB peaks tended to decrease and a broad peak appeared at approximately 5° [Figs. 4A(b)–(f)]. Regarding IB/MgO(50)-ads and IB/MgO(50)-imp, the original diffraction peaks due to IB were not detected at all diffraction angles, whereas broad peaks appeared at approximately 4.5° [Figs. 4A(g) and (h)]. Although these new diffraction peaks at low diffraction angles were broad and weak, their relative intensities tended to be stronger as the physical mixing time was prolonged (Table 1). Considering the high intensity of Mg(IB)\textsubscript{2}-syn at approx. 4.4° [Fig. 4A(j)], the peaks that emerged at low diffraction angles suggest that IB crystals restructured through interactions between IB and the basic MgO surfaces. The interactions sug-

Table 1. Relative Intensities of the Diffraction Peaks at Low Diffraction Angles

| Sample                  | 2θ/deg. | Relative intensity |
|-------------------------|---------|--------------------|
| IB/MgO(50)-phy-0 min    | 4.9     | 100                |
| IB/MgO(50)-phy-2 min    | 4.9     | 112                |
| IB/MgO(50)-phy-5 min    | 4.9     | 152                |
| IB/MgO(50)-phy-10 min   | 5.0     | 164                |
| IB/MgO(50)-phy-15 min   | 5.0     | 164                |
| IB/MgO(50)-ads          | 4.6     | 344                |
| IB/MgO(50)-imp          | 4.5     | 366                |

Fig. 3. CO\(_2\)-TPD Spectrum of MgO

Fig. 4. XRD Patterns of IB and IB-Loaded MgO Carriers at (A) Low and (B) High Diffraction Angles; (a) IB, (b) IB/MgO(50)-phy-0 min, (c) IB/MgO(50)-phy-2 min, (d) IB/MgO(50)-phy-5 min, (e) IB/MgO(50)-phy-10 min, (f) IB/MgO(50)-phy-15 min, (g) IB/MgO(50)-ads, (h) IB/MgO(50)-imp, (i) Mg(OEt)\(_2\), and (j) Mg(IB)\textsubscript{2}-syn
ggested via TG-DTA may have been related to the changes in the XRD patterns.

Figure 5 shows the FT-IR spectra in the mid- and far-IR regions. According to the previously reported paper, \(^{1,10}\) the band at 1711 cm\(^{-1}\) might belong to the \(\nu(C=O)\) stretching vibration, whereas the bands at 1506 and 1462 cm\(^{-1}\) is attributable to the ring vibrations of organic molecules. As shown in Fig. 5A, the band at 1711 cm\(^{-1}\) shifted to lower wavenumbers when IB was loaded on MgO. These band shifts imply that –COOH groups were partially ionized through the acid–base interaction, as discussed previously. \(^{1,20,21}\) Because the acid–base interaction can affect drug releasability, it is crucial to confirm these band shifts. Moreover, the band shifts of IB/MgO(50)-ads and IB/MgO(50)-imp were greater than those of IB/MgO(50)-phy-x min (x = 2, 5, 10, and 15). Considering the results of SEM, XRD, and TG-DTA analyses, the greater peak shifts of IB/MgO(50)-ads and IB/MgO(50)-imp appeared reasonable.

In the far-IR regions, IB showed weak absorption bands, whereas MgO showed a single band at approximately 370 cm\(^{-1}\) (Fig. 5A). Notably, broad bands appeared at approximately 220 cm\(^{-1}\) by loading IB on MgO. Considering that far-IR often corresponds to the vibration energy levels of inorganic or organic crystals, the broad bands above at approximately 220 cm\(^{-1}\) might suggest that different crystal states were induced in MgO, as shown in Fig. 4A. Moreover, according to the previously reported paper, \(^{16}\) MgO is reactive with IB and can form Mg(ibuprofen)\(_2\). Therefore, it was considerable that the new band at approximately 220 cm\(^{-1}\) originated from the formation of Mg salts of IB.

Although it is difficult to evaluate the ionization behaviors using XRD, Fig. 5B indicates that the carboxylic acid groups ionized gradually, and the crystal states changed as the physical mixing time increased (Figs. 4, 5B). Additionally, it was confirmed in the mid- and far-IR regions that the weak IB absorption bands disappeared, suggesting that IB crystallinity had reduced. However, compared to the adsorption and the impregnation methods, the changes in the XRD patterns and the far-FT-IR spectra were relatively moderate in the physical mixing method.

When increasing the IB content from 50 to 90 wt%, the FT-IR spectrum of IB/MgO(90)-imp were different from those of IB/MgO(90)-phy-0 min and IB/MgO(90)-phy-15 min (Fig. 6). The FT-IR spectra of IB/MgO(90)-phy-0 min and IB/MgO(90)-phy-15 min showed similar absorption bands to raw IB, implying that the chemical states of IB did not change significantly. This is presumably because chemical interactions between IB and MgO were limited by the external surfaces of MgO particles in the physical mixing method.

On the other hand, the absorption band of IB/MgO(90)-imp due to –COOH groups shifted in mid-IR regions and the new absorption band was observed in far-IR regions. Therefore, it was speculated that a large portion of IB in IB/MgO(90)-imp interacted with MgO. Although the peak positions of IB/MgO(90)-imp in far-IR regions may appear different from IB/MgO(50)-emp (Figs. 5, 6), it would be mainly caused by the overlap of absorption bands and the different IB contents. Figure 7 shows the difference FT-IR spectra between IB/MgO(50)-emp and IB/MgO(50)-phy-0 min and between IB/MgO(90)-emp and IB/MgO(90)-phy-0 min. Although the absorbances were different, their spectra varied similarly. These results indicate that the impregnation method would induce the similar interaction between IB and MgO, in spite of the different IB contents. Moreover, it was also suggested that Mg(ibuprofen)\(_2\) salts were formed by impregnation since IB/MgO(90)-imp and Mg(1B)_2-syn showed the similar FT-IR spectra.
spectra [Figs. (6e) and (g)].

Figure 8 shows the TG curves of the samples. The results showed that each sample contained approximately 90 wt% of IB. Moreover, the steps corresponding to the weight losses at around 473 K became smaller by impregnation and physical mixing for 15 min. These TG curves also suggested the interactions between IB and MgO. As shown in Fig. 8(a), 28.3 wt% of IB/MgO(90)-phy-0 min dropped from 673 to 793 K, regardless of the present loose contact method with a spatula. This weight loss at a high temperature suggested that a part of IB interacted with the MgO surfaces even through the loose contact mixture. Given that the FT-IR spectra were collected in ATR method which is sensitive to surface information, it may be understandable that the MgO surface interacting with IB was detected as peak shifts at around 370 cm$^{-1}$ [Figs. 6(b)–(d)].

Therefore, these results suggest that mid- and far-FT-IR spectroscopy can be used to quickly evaluate chemical and crystal states of drugs and carriers which may be influential on their drug properties, such as releasability and water solubility. Furthermore, it was revealed that the effects of the IB-loading methods on the chemical and crystal states can be evaluated using one-step mid- and far-FT-IR measurements.

Conclusion

In the present study, IB-loaded MgO samples were prepared by adsorption, impregnation, and physical mixing methods. The results obtained from various characterization techniques confirmed that MgO interacted with IB. Unlike other characterization techniques, one-step FT-IR spectroscopy in mid- and far-IR regions enabled the evaluation of the chemical and crystal states of IB on MgO without changing the analytical system and conditions. Therefore, the potentially high applicability of one-step mid- and far-FT-IR measurements was demonstrated by evaluating IB-loaded MgO carriers.

**Conflict of Interest** The author declares no conflict of interest.

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