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A continuous process for solid-state dehydration, amorphization and recrystallization of metoclopramide HCL monohydrate studied by simultaneous DSC-FTIR microspectroscopy

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Abstract The purpose of this study was to investigate the thermal-induced solid-state characterization of metoclopramide hydrochloride monohydrate (MCP H_2O) by using a combination of differential scanning calorimetry (DSC) and Fourier-transform infrared (simultaneous DSC-FTIR) microspectroscopy. The DSC and thermogravimetric (TG) analyses were also carried out. The result indicates that a continuous process of dehydration, amorphization and recrystallization for MCP H_2O in the solid state was easily evidenced via the thermal responsive IR spectral changes by using this simultaneous DSC-FTIR microspectroscopy. In the heating course, one mole of water was first dehydrated from the MCP H_2O sample beyond 77 °C, was then quickly transformed to an amorphous form due to the appearance of weak broad IR bands, and continuously recrystallized from 148 °C by showing the sharp IR bands. This one-step novel simultaneous DSC-FTIR microspectroscopy might be available for studying the changes in the progressive processes of the thermal-dependent solid-state characterizations of drugs.

Keywords Metoclopramide HCl monohydrate · Continuous process · Dehydration · Amorphization · Recrystallization · Solid state · Simultaneous DSC-FTIR microspectroscopy

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Introduction

Solid state characterization and physicochemical property of the active pharmaceutical ingredients (APIs) are fundamental elements in the pharmaceutical development from the beginning of drug discovery to the final market products [1–3]. Awareness of the solid-state properties of APIs should be the first priority in the oral dosage form design [3–6]. Several pharmaceutical unit operations including milling, wet granulation, and/or drying may cause the dehydration/desolvation, hydration/solvation or polymorphic transformation of API in the manufacturing process, leading to the changes in solid-state physicochemical properties and bioavailability of APIs [3–7]. Thus, an analytical study for the manipulation of the solid state characteristics of APIs is an important approach to formulation design of solid dosage form [2, 5–7].

Metoclopramide HCL, chemically known as 4-amino-5-chloro-2-methoxy-*N*-[(-2-diethyl-amino)ethyl] benzamide HCL(MCP, Fig. 1), is commonly used by an oral tablet to treat a short term basis for patients with heartburn, esophagitis, or different symptoms of nausea and vomiting [8, 9]. As an API, three raw materials of metoclopramide such as free base, monohydrochloride or dihydrochloride are currently commercialized in the pharmaceutical market. However, metoclopramide HCL with monohydrate (MCP H_2O) is the most popular one for solid dosage form [10]. Few studies have focused on the investigation of metoclopramide in the solid state after different treatments [11–15], but the detailed mechanism for polymorphic transformation of MCP H_2O is rarely studied.

Recently, a combination of differential scanning calorimetry (DSC) and Fourier-transform infrared (simultaneous DSC-FTIR) microspectroscopy has been extensively applied to investigate the thermal-induced solid-state

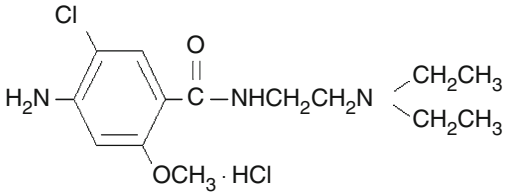

Fig. 1 Chemical structure of metoclopramide HCl (MCP)

characterization of intramolecular cyclization of diketopiperazine of aspartame or enalapril, *trans–cis* isomerization of captopril, lactamization of gabapentin, decarboxylation of 10-hydroxycamptothecin, sublimation of nitroxoline, polymorphic interconversion processes of famotidine and gabapentin; processes of dehydration and rehydration of trehalose [16–24]. The purpose of this study was to explore the detailed mechanism of the changes in solid-state characterization of MCP H_2O before and after thermal treatment by using this novel simultaneous DSC-FTIR microspectroscopy.

Materials and methods

Materials

A pharmaceutical grade of MCP H_2O as an API was purchased from AMSA, Como, Italy. The KBr crystal was of analytical reagent grade and purchased from Jasco Co., Tokyo, Japan.

Thermal analysis of MCP H_2O

The API of MCP H_2O powder was identified by a differential scanning calorimetry (DSC, TA Instruments, Inc., New Castle, DE) with a heating rate of 3 °C/min under an open pan system in a stream of N_2 gas from 30 to 200 °C. Temperature and heat flow of DSC system were calibrated by a standard indium reference sample. Thermogravimetric (TG) analysis (TGA-951, TA Instruments, Inc.) was also carried out by using a heating rate of 3 °C/min to measure the weight loss of MCP H_2O sample. The 165 °C-preheated MCP sample was also prepared by preheating the MCP H_2O powder to the prescribed temperature of 165 °C in the DSC system, and then slowly cooling to room temperature.

Simultaneous DSC-FTIR microspectroscopic study

A trace amount of API or 165 °C-preheated MCP sample was respectively smeared on the surface of one piece of KBr pellet, and then compressed by a hydraulic press under 200 kg/cm^2 for 15 s [16–24]. Each sample disc compressed was placed onto a temperature-controlled microscopy cell (FP 84 HT TA, Mettler, Greifensee Switzerland). This microscopy cell was then directly placed on the stage of a FTIR microscopic spectrometer (IRT-5000-16/FTIR-6200, Jasco Co., Tokyo, Japan) with a mercury cadmium telluride (MCT) detector (simultaneous DSC-FTIR method). The system was operated in a transmission mode. The temperature of the microscopy cell was monitored with a central processor (FP 90, Mettler). The sample disc was equilibrated to the starting temperature of 30 °C and then heated to 200 °C with a heating rate of 3 °C/min. The thermal responsive IR spectra were simultaneously recorded during heating process.

Results and discussion

Identification of MCP H_2O

Figure 2 shows the TG curve and DSC curve of MCP H_2O by using a heating rate of 3 °C/min from 30 to 200 °C. It clearly indicates that the TG curve of MCP H_2O powder showed a weight loss of about 5.01% from 78 to 150 °C, which was almost equal to the loss of 1 mol of water (4.94%) from the MCP H_2O powder. This reveals that one monohydrate was exactly contained in the MCP H_2O structure but it was dehydrated from 78 °C. While two endothermic peaks at 85 and 184 °C and one minor exothermic peak at 105 °C were observed in the DSC curve of MCP H_2O. From the data of TG curve, the former endothermic peak at 85 °C in DSC curve might be owing to the dehydration of MCP H_2O, but the latter endothermic peak at 184 °C was only attributed to the melting point of MCP [10, 13]. On the other hand, an exothermic peak at 105 °C

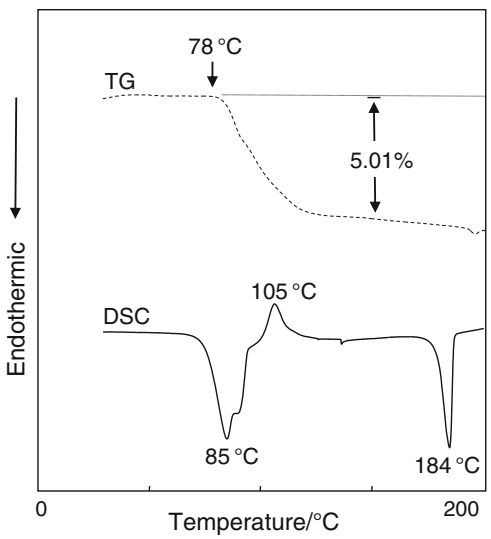

Fig. 2 TG curve and DSC curve of MCP H_2O by using a heating rate of 3 °C/min from 30 to 200 °C

seemed to be related to the recrystallization of amorphous sample [25–27]. Thus it might be proposed that MCP H_2O after dehydration became a fully or partially amorphous form and then recrystallized with temperature.

Thermal FTIR microspectroscopic study

Three-dimensional plot of the FTIR spectra of MCP H_2O within the 3,600–3,100 and 1,700–1,400 cm^{-1} region as a function of temperature is displayed in Fig. 3. It is apparent that several characteristic IR absorption bands and their assignments of MCP H_2O before thermal treatment are listed as follows: 3448 cm^{-1} (OH stretching mode of hydrate), 3396 cm^{-1} (symmetric NH_2 stretching vibration), 3310 and 3197 cm^{-1} (NH stretching mode of amide), 1660 cm^{-1} (OH bending mode of hydrate), 1631 and 1599 cm^{-1} (NH_2 scissoring and/or C=O stretching bands) and 1539 cm^{-1} (amide N–H band), respectively. The peak position and its assignment of IR spectrum for MCP H_2O agreed to the other reports [28, 29].

From the thermal-dependent 3-dimensional IR spectral plot of MCP H_2O in Fig. 3, three marked regions for the changes in peak intensity were clearly observed from the contour profile. It clearly indicates that there was less significant change in the contour profile before 77 °C. Once the heating temperature was beyond 77 °C, all the IR spectral peaks became broader and reduced their peak intensities. However, the sharp IR peak intensities appeared again when temperature was >148 °C. The weak, broad IR bands within 77–148 °C due to the formation of amorphous form after dehydration of MCP H_2O might be attributed to the water molecules, which quickly escaped from the original crystal structure, resulting in the random structure in crystal lattice. The starting temperature at 77 °C was almost consistent with that of the thermal change at 78 °C in TG curve and DSC curve (Fig. 2). The changes in several specific IR peak intensities with temperature might confirm this result, as shown in Fig. 4.

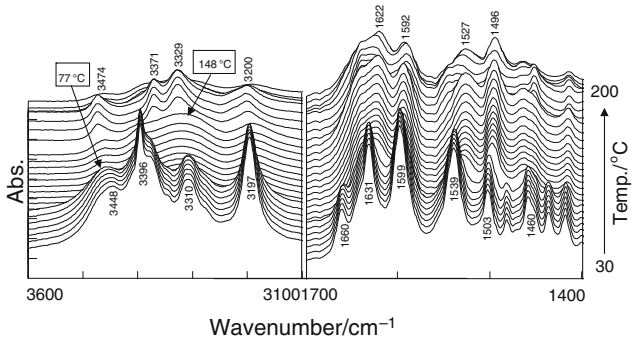

Fig. 3 Three-dimensional plot of the FTIR spectra of MCP H_2O within the 3,600–3,100 and 1,700–1,400 cm^{-1} region as a function of temperature

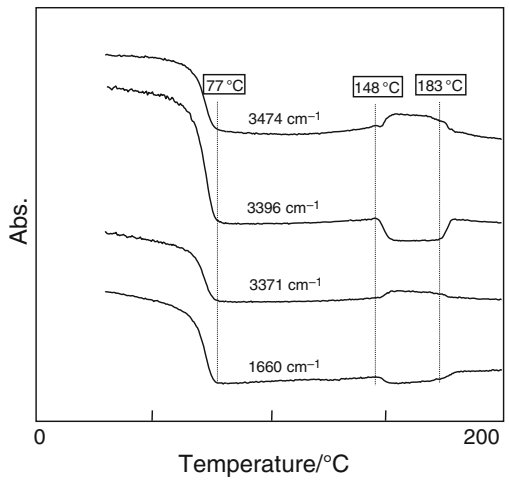

Fig. 4 Temperature-dependent changes in several specific IR peak intensities of Fig. 2

Since the amorphous form of MCP was unstable in the heating process, it was quickly re-crystallized near 148 °C to alter the IR band from broad shape to a sharp one [30–32]. Since the temperature of sample was higher than 148 °C at this time, the IR spectral shifting phenomena were observed for the MCP, as compared with the IR spectral position at the lower temperature.

Obviously, the thermal-dependent three-dimensional plot of the FTIR spectra could clearly evidence both processes of amorphization and recrystallization after dehydration by a one-step determination. However, it was found that the recrystallization temperature at 148 °C recorded by simultaneous DSC-FTIR microspectroscopic determination was significant higher than that of the temperature at 107 °C determined by DSC method. Although both

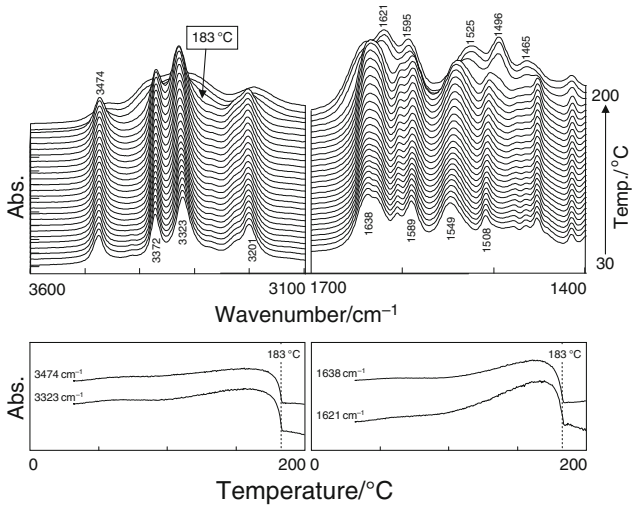

Fig. 5 Three-dimensional FTIR spectral plot of the 165 °C-preheated MCP sample in the 3,600–3,100 and 1,700–1,400 cm^{-1} region with respect to temperature

determination methods were markedly different, further study is needed to explore their difference.

Figure 5 shows the three-dimensional FTIR spectral plot of the 165 °C-preheated MCP sample within 3,600–3,100 and 1,700–1,400 cm^{-1} region with respect to temperature. The changes in several specific peak intensities with the increase of temperature are also shown. A significant difference was obtained between Figs. 2 and 4. Since the 165 °C-preheated MCP sample not only had passed the dehydration process but also preceded the recrystallization in the DSC heating course from 30 to 165 °C, thus the contour profile did not show any obvious change with the increase of temperature until the melting point at 183 °C for MCP.

In conclusion, a continuous process of dehydration, amorphization and recrystallization for the API of MCP H_2O in the solid state was easily determined using a simultaneous DSC-FTIR microspectroscopy. This one-step novel simultaneous DSC-FTIR microspectroscopy might be available for studying the changes in the progressive processes of the thermal-dependent solid-state characterizations of drugs.

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