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Yellow coloration phenomena of incorporated indomethacin into folded sheet mesoporous materials

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ABSTRACT

Solid-state ^{13}C nuclear magnetic resonance (NMR) spectroscopy that included relaxation time measurement was utilized to evaluate the yellow coloration of evaporated samples (EVPs) of indomethacin (IMC) with commercially available folded sheet mesoporous materials (TMPS). Colorimetric analysis by visible light reflection spectroscopy clarified the color differences in each sample: deep yellow-colored melt-quenched amorphous IMC, a slightly yellow-colored EVP of TMPS-1.5 (pore size: 1.8 nm), and a yellow-colored EVP of TMPS-7 (pore size: 7.3 nm). The color of EVPs changed from yellow to white after washing with ethanol, indicating the reversible coloration without a chemical reaction. Powder X-ray diffractometry and differential scanning calorimetry demonstrated that the EVPs of TMPS-7 entrapped greater amounts of amorphous IMC into the mesopore than TMPS-1.5. The amount of amorphous IMC in the mesopores could affect the strength of yellow coloration. Solid-state ^{13}C NMR spectroscopy that included spin–lattice relaxation time (T_1) measurement revealed that the mobility of the aromatic rings of amorphous IMC in TMPS mesopores was higher than that in melt-quenched amorphous IMC. The difference in color between amorphous IMC in TMPS mesopores and melt-quenched amorphous IMC can be explained by their distinct intramolecular π-conjugation systems.

1. Introduction

Drug coloration phenomena sometimes occur during pharmaceutical processing. Drug coloration is mostly induced by chemical reactions between drugs and excipients, and their subsequent decomposition (Rhee et al., 2008). It is no wonder that colored formulations due to chemical reactions should be avoided because the product quality is lost. Changes in the molecular state of drugs due to intermolecular interaction with excipients could lead to sample coloration as well (Sheth et al., 2005; Braun et al., 2008). There are also the cases where color change of photochromic molecules was induced by its conformational difference (Siewertsen et al., 2009). From formulation development and quality control perspectives, such colored samples without degradation and impurities might be acceptable as formulations, although sample coloration is not desirable. Hence, it is important to understand the coloration mechanisms of drug formulation. There are many reports about coloration phenomena occurring in chemical and engineering organic materials such as solar cells and organic dyes (Morimoto et al., 2003; Shen et al., 2009). However, most studies about coloration in the pharmaceutical field are limited to the quality control measures such as the quantitation of drug decomposition and validation (Siddiqui and Nazzal, 2007; Rhee et al., 2008). Few reports focus on the coloration phenomena of pharmaceutical compounds induced by change in molecular state and not by chemical reactions.

Coloration mechanisms are divided into two types: visible light absorption and visible light emission. For both mechanisms, the coloration of organic compounds depends on the electrical situation, such as the length of π-conjugated systems and/or electric delocalization from molecular structures, crystal structures, and molecular interactions (Braun et al., 2008; Yamamura et al., 2008; Siewertsen et al., 2009). It is necessary to obtain detailed, molecular-level information to analyze coloration phenomena in organic compounds effectively. Single-crystal X-ray analysis is considered the most useful method, although it cannot be applied for powder samples or pharmaceutical formulations, including drugs and excipients. Complementary analytical technologies for drug formulations such as powders, including X-ray diffraction, thermal analysis, solid-state fluorescence, and infrared measurements, can be used to investigate coloration phenomena. In particular, solid-state nuclear magnetic resonance (NMR) spectroscopy including relaxation time measurement, which can assess the atomic-level chemical environment and dynamics, is a powerful technique (Tishmack et al.,

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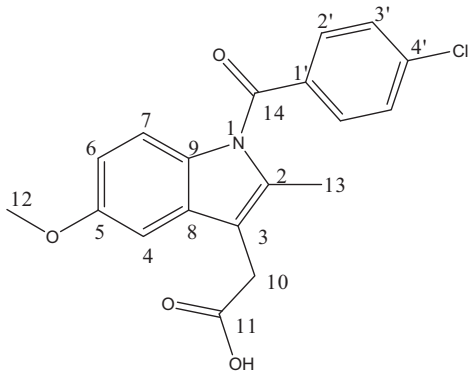

Fig. 1. Chemical structure of indomethacin (IMC).

2003; Geppi et al., 2008; Lubach et al., 2007). Sheth et al. (2005) used solid-state NMR techniques to demonstrate that the yellow coloration phenomenon of piroxicam is due to proton transfer.

Mesoporous silica is a porous honeycomb-like structure with a large specific surface area and highly controlled pore size. Recently, mesoporous materials have been proposed as host materials for improving drug properties such as dissolution and stability (Ambrogi et al., 2007; Mellaerts et al., 2008). We previously reported that various active pharmaceutical ingredients (APIs) (e.g., benzoic acid, salicylamide, flurbiprofen, prednisolone, and mefenamic acid) could be incorporated into the pores of mesoporous silica (Tozuka et al., 2003, 2005a,b; Nishiwaki et al., 2009; Moribe et al., 2010). Some APIs changed from white to colored after the incorporation process. Moribe et al. (2010) investigated the molecular state of mefenamic acid in colored samples using solid-state NMR and reported that changes in the molecular state of mefenamic acid in the pore could affect blue coloration. Reversible coloration is observed when *p*-nitroaniline is incorporated into the pores of ZSM-5, a kind of zeolite (Komori and Hayashi, 2003, 2004). Coloration as a result of the intermolecular interaction between *p*-nitroaniline and Na^+ of ZSM-5 is affected by water adsorption/desorption. However, the direct relationship between reversible coloration and the molecular state of pharmaceutical compounds is unclear.

In this study, we investigated the mechanism of yellow coloration in evaporated indomethacin/commercially available folded sheet mesoporous materials (TMPS). Various analytical techniques, including colorimetric analysis, powder X-ray diffractometry, differential scanning calorimetry, and solid-state NMR spectroscopy (including relaxation time measurements) were utilized to evaluate the coloration mechanism both quantitatively and qualitatively.

2. Materials and methods

2.1. Materials

The γ-form of indomethacin (IMC, 1-(*ρ*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid) was purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). The chemical structure of IMC is illustrated in Fig. 1. IMC has two major polymorphs: the stable γ-form and metastable α-form. The α-form of IMC was obtained using a recrystallization method: a solution of 2 g of IMC in 7 mL of ethanol at 70 °C was rapidly cooled to 4 °C and stored overnight at 4 °C. The precipitated α-form crystals were collected by filtration and dried in vacuo at 40 °C (Masuda et al., 2006). Melt-quenched amorphous IMC was prepared by melting indomethacin at 165 °C and cooling it using liquid nitrogen (Savolainen et al., 2007). Taiyo Kagaku Co., Ltd. (Mie, Japan) kindly supplied TMPS-1.5 and TMPS-7. The mean pore sizes, specific surface areas, and pore volumes of TMPS-1.5 and TMPS-7 were 18 and 73 Å, 1019 and 826 m^2/g, and 0.37 and 1.1 cm^3/g, respectively. The TMPS was ground by mortar and pestle, sieved using a 125-μm sieve, and dried at 120 °C for 3 h in vacuo before use. All other chemicals were of reagent grade.

2.2. Sample preparation

The TMPS and γ-IMC were mixed at weight ratios of 7/3 and 5/5 in a glass vial for 1 min to obtain a physical mixture (PM). The TMPS was dispersed in an ethanol solution containing IMC. Weight ratios of IMC to TMPS in the suspension were 3/7 and 5/5. Then, the solution was sonicated for 3 min and evaporated at 30 °C. The resultant powder was dried at 60 °C for 24 h to obtain an evaporated sample (EVP). The EVP was dispersed in ethanol and sonicated for 10 min. The powder was filtrated and dried at 30 °C for 30 min to obtain washed EVP.

2.3. Colorimetric analysis

Visible light reflection spectra in the 400–780 nm range were obtained using a JASCO FP-6500 spectrofluorometer (Tokyo, Japan) equipped with a JEOL ISF-153 integration sphere (Tokyo, Japan). A sample holder (JASCO PSH-001; Tokyo, Japan) was filled with a powdered sample. The reflectance of a Specralon® white standard plate was used for calibration. The reflectance curve was digitalized using a JASCO V-500 color diagnostics program (Tokyo, Japan) and the data were plotted on an L*a*b* color system.

2.4. Ultraviolet (UV) absorption spectrophotometry

UV absorption spectrophotometry was carried out using a JASCO V-600 spectrometer (Tokyo, Japan). The powdered sample was dispersed in ethanol, sonicated for 10 min, and filtered for UV measurement at 320 nm.

2.5. Powder X-ray diffraction (PXRD) measurement

PXRD patterns were obtained using a Rigaku MiniFlex II powder diffractometer (Tokyo, Japan). The X-ray generator was operated at 30 kV and 15 mA using CuKα radiation. The scans were performed between 3° and 35° with a scanning rate of 4°/min at room temperature.

2.6. Thermogravimetry (TG)

TG measurements were operated using a SII Nanotechnology EXSTAR 6000 TG/DTA 6200 (Chiba, Japan). The operating conditions were as follows: platinum open pan; sample weight, ca. 5 mg; heating rate, 5 °C/min; temperature range, 30–800 °C; air flow rate, 200 mL/min.

2.7. Differential scanning calorimetry (DSC)

DSC measurements were performed using SII Nanotechnology EXSTAR6000 DSC6200 (Chiba, Japan). The operating conditions were as follows: crimped-aluminum pan; sample weight, ca. 5 mg; heating rate, 5 °C/min; temperature range, 30–180 °C; nitrogen gas flow rate, 60 mL/min.

2.8. Solid-state ^{13}C NMR spectroscopy

All solid-state ^{13}C NMR measurements were carried out using a JEOL JNM-ECA600 unit (Tokyo, Japan) with a magnetic field of 14.09 T operating at 150 MHz for ^{13}C. Sample powders were placed