Vapor Phase Alkyne Coating of Pharmaceutical Excipients: Discrimination Enhancement of Raman Chemical Imaging for Tablets

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ABSTRACT: Raman chemical imaging has become a powerful analytical tool to investigate the crystallographic characteristics of pharmaceutical ingredients in tablet. However, it is often difficult to discriminate some pharmaceutical excipients from each other by Raman spectrum because of broad and overlapping signals, limiting their detailed assessments. To overcome this difficulty, we developed a vapor phase coating method of excipients by an alkyne, which exhibits a distinctive Raman signal in the range of 2100–2300 cm^{-1}. We found that the combination of two volatile reagents, propargyl bromide and triethylamine, formed a thin and nonvolatile coating on the excipient and observed the Raman signal of the alkyne at the surface. We prepared alkyne-coated cellulose by this method and formed a tablet. The Raman chemical imaging of the tablet cross-section using the alkyne peak area intensity of 2120 cm^{-1} as the index showed a much clearer particle image of cellulose than using the peak area intensity of 1370 cm^{-1}, which originated from the cellulose itself. Our method provides an innovative technique to analyze the solid-state characteristics of pharmaceutical excipients in tablets. © 2015 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 104:4093–4098, 2015

Keywords: analytical chemistry; excipients; formulation; imaging methods; particle size; preformulation; Raman spectroscopy; solid dosage form; solid state; tableting

INTRODUCTION

Chemical imaging or chemical mapping is a widely used technology that visualizes the localization of components in solids. In the field of pharmaceutical science, the particle size as well as dispersion of active pharmaceutical ingredients (APIs) or excipients in solid formulations have been reported using chemical imaging. Common methods used to obtain chemical information at a certain point include vibrational spectroscopy such as infrared (IR),[1,2] near-infrared,[3–5] Raman, or terahertz[6,7] spectroscopy. Of these methods, Raman chemical imaging appears to be superior in many aspects. The advantages of Raman imaging are that the Raman spectrum usually consists of clear signals, which help to discriminate not only the chemical structure,[8] but also the crystal form[9–12] or crystal face,[13] of APIs, and that high-resolution images can be obtained at a single-micrometer resolution. There have been many reports regarding the use of Raman imaging to analyze particle size and the dispersion of APIs in tablet cross-sections.[14–19]

Active pharmaceutical ingredients and low molecular excipients such as lactose or magnesium stearate usually exhibit clear Raman spectra with strong and sharp signals, which make the chemical imaging of these materials easier. However, polymeric excipients such as cellulose, starch, and their derivatives, which are frequently added to solid formulations, show very broad Raman spectra, and it is generally difficult to discriminate these polymeric excipients by Raman imaging.[20] For the quality control of formulations, it is essential to understand the solid-state properties of not only APIs but also the excipients in the tablets. For example, the function of some sustained release formulations is often dependent on the solid-state properties of the excipients. Proper control of the excipients in such formulations will become a key factor to guarantee the dissolution rate of APIs. Therefore, it is necessary to develop a novel technique to enhance the discrimination of the excipients to use Raman imaging to thoroughly assess tablet properties such as particle size and the dispersion of polymeric excipients.

The alkyne-tag technique is one of the promising methods to enhance Raman discrimination. Stretching vibrations of the triple bond of alkyne provides a strong and sharp signal in the range of 2100–2300 cm^{-1} without interference by other groups; therefore, the alkyne group shows an enhanced discrimination in Raman imaging. There are many reports on increasing the detection ability using the alkyne-tag technique, particularly in the field of live cell imaging.[21–26]

In this study, we applied the alkyne-tag technique for the discrimination of polymeric excipients. Chemically tagging the excipients with an alkyne group by a liquid-phase reaction may result in a great change in the solid-state characteristics such as particle size or morphology after resolidification. Therefore, we tried to develop a vapor phase alkyne coating for the excipients, which would be easier to prepare, have fewer limitations pertaining to the materials, and influence the particle characteristics less than the liquid-phase reaction. Of the combinations of alkynes and amines tested, we found that propargyl bromide and triethylamine formed a thin, nonvolatile, and Raman-detectable alkyne coating on the excipient. Furthermore, we formed tablets containing the alkyne-coated material and used Raman imaging to assess the discrimination of the components in the cross-section of these tablets.

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EXPERIMENTAL

Materials

Microcrystalline cellulose (CEOLUS PH-101) and silica gel (Wakosil C-200) were purchased from Asahi Kasei Chemicals (Tokyo, Japan) and Wako Pure Chemical Industries (Osaka, Japan), respectively. Propargyl bromide (stabilized with MgO) and propargyl chloride were purchased from Tokyo Kasei (Tokyo, Japan). Lactose monohydrate, starches, amines, and solvents were obtained from standard suppliers.

Raman Spectra Measurement

The Raman spectra of materials used in this study were recorded on an inVia Raman microscope system (Renishaw Plc., Gloucestershire, UK) equipped with a Leica microscope and a 785 nm, 300 mW excitation laser. A 20× objective lens was used for the measurement.

Vapor Phase Reaction

Three gram of material was spread evenly in a glass chamber ($110 \times 100 \times 45$ mm^3) for thin layer chromatography (TLC). One milliliter of alkyne and 1 mL of amine were separately poured into small vials without a cover and placed them in the chamber. The vapor phase reactions were performed at room temperature for 4 h or overnight.

Extraction of the Coating Component and Structural Analysis with Nuclear Magnetic Resonance and High-Resolution Mass Spectrometry

Two-hundred milligram of silica gel was applied to the overnight vapor phase reaction and then transferred to a new vial. One milliliter of dimethylsulfoxide-d_6 was added to the silica gel. This mixture was stirred for 1 h at room temperature, and following this the extract was obtained by filtration. ^{1}H- and ^{13}C-nuclear magnetic resonance (NMR) spectra of the extract were recorded at 25°C on an ECA500 spectrometer with Delta software (JEOL, Tokyo, Japan). After lyophilization of the NMR sample followed by dissolution in acetonitrile/water, high-resolution mass spectrometry (HR-MS) was recorded on LC/MS Synapt G2 HDMS (Waters, Milford, Massachusetts).

Scanning Electron Microscopy

Scanning electron microscopy (SEM) images of cellulose with or without alkyne coating was obtained using a NeoScope JCM-6000 (JEOL) in the low-vacuum mode.

Tablet Formation

One gram of lactose monohydrate, 1 g of corn starch, and 1 g of alkyne-coated or noncoated cellulose were mixed thoroughly in a glass bottle. A part of this mixture was applied in compression molding to form tablets (ϕ 5 mm) using a Tablet Press 6B-2 (Kikusui, Kyoto, Japan). As for the discrimination experiment between the two starches, 1 g of lactose monohydrate, 1 g of alkyne-coated corn starch, and 1 g of noncoated potato starch were mixed and tableted in the same manner.

Raman Chemical Imaging

The tablet was fixed on a glass plate with an instant glue and milled with a milling machine (Proxxon GmbH, Niersbach, Germany) to expose the cross-section. Raman imaging was carried out with Renishaw StreamLine™ Plus high-speed Raman line-mapping technology[14–16] under a 785-nm excitation laser. 2500×500 μm^2 area, extending from an edge to the center of the tablet in a cross-section, was applied to Raman imaging in a spatial resolution of 7.1 μm (25,063 data points in total). Data collection and analyses were performed with Wire 4.1 software (Renishaw Plc.).

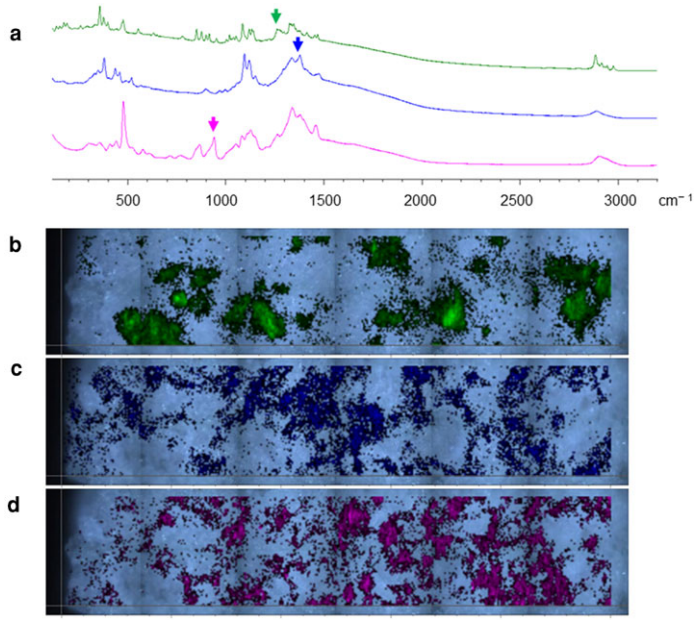

Figure 1. Raman chemical imaging of model tablet containing lactose monohydrate, microcrystalline cellulose, and cornstarch. (a) Raman spectra of lactose monohydrate (green), cellulose (blue), and cornstarch (magenta). Arrows indicate Raman signals used as the index in Raman chemical imaging. (b–d) Images of individual material; lactose monohydrate (b, green), cellulose (c, blue), and cornstarch (d, magenta).

RESULTS AND DISCUSSIONS

Raman Spectra of Pharmaceutical Excipients

Lactose monohydrate, microcrystalline cellulose, and corn starch are the carbohydrates frequently used as excipients in solid formulations. The Raman spectra of these materials are shown in Figure 1a. The overall appearances of these spectra are similar to each other because the molecules consist of common bonds such as C–C, C–H, C–O, and O–H, and Raman spectra are created by a stretching or a bending vibration of these bonds. Most of the signals overlapped; therefore, it was rather difficult to pick a distinctive signal for each material. Furthermore, the polymeric excipients such as cellulose and corn starch exhibited broader signals than lactose. This makes the discrimination of these excipients more difficult when using Raman chemical imaging for solid formulations.

Raman Chemical Imaging of Tablet Cross-Section Containing Unmodified Excipients

We performed Raman chemical imaging of the cross-section of a tablet that contained lactose, cellulose, and corn starch in the same proportions. We used the peak area of the relatively distinct Raman signal of each material (arrows in Fig. 1a) as the index for chemical imaging. As a result, we obtained imaging pictures with a lot of noise, particularly for cellulose imaging