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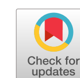
Rapid quantitation of atorvastatin in process pharmaceutical powder sample using Raman spectroscopy and evaluation of parameters related to accuracy of analysis



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ABSTRACT

The purpose of this study was to determine the atorvastatin (ATV) content in process pharmaceutical powder sample using Raman spectroscopy. To establish the analysis method, the influence of the type of Raman measurements (back-scattering or transmission mode), preparation of calibration sample (simple admixing or granulation), sample pre-treatment (pelletization), and spectral pretreatment on the Raman spectra was investigated. The characteristic peak of the active compound was more distinctively detected in transmission Raman mode with a laser spot size of 4 mm than in the back-scattering method. Preparation of calibration samples by wet granulation, identical to the actual manufacturing process, provided unchanged spectral patterns for the in process sample, with no changes and/or shifts in the spectrum. Pelletization before Raman analysis remarkably improved spectral reproducibility by decreasing the difference in density between the samples. Probabilistic quotient normalization led to accurate and consistent quantification of the ATV content in the calibration samples (standard error of cross validation: 1.21%). Moreover, the drug content in the granules obtained from five commercial batches were reliably quantified, with no statistical difference ($p = 0.09$) with that obtained by HPLC assay. From these findings, we suggest that transmission Raman analysis may be a fast and non-invasive method for the quantification of ATV in actual manufacturing processes.

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1. Introduction

Atorvastatin calcium (ATV), a pyrrole and heptanoic acid derivative, is commonly prescribed for the treatment of hyperlipidemia, and it acts by inhibiting 3-hydroxy-3-methylglutaryl Coenzyme A reductase [1]. ATV is usually administered in the tablet dosage form containing 10 to 40 mg of the active compound per tablet. Currently, high-performance liquid chromatography (HPLC) is used to assess the active pharmaceutical ingredient (API) content, including ATV, during the manufacturing process and/or in final products. Despite many advantages, HPLC analysis necessitates establishment of analysis conditions to separate the analyte from the other substances on the chromatogram. Further, the destruction of the samples, and time-consuming pre-treatment processes are needed prior to chromatographic determination [2,3].

Recently, Raman spectroscopy has been applied for the analysis of the drug content in the process sample and/or final pharmaceutical products [4–6]. Raman spectroscopy has the advantages of high chemical specificity; ability to identify polymorphs and drug crystalline state; rapid analysis within 3 s; and non-invasive analyses with minimal and/or no sample pre-treatment [7,8], as opposed to the traditional HPLC technique. The Raman technique may be widely adopted as a process analytical technology (PAT) tool for monitoring manufacturing processes in the pharmaceutical industry, including blending drying, and monitoring the homogeneity of products [9–11]. Griffen et al. [8] successfully predicted the amounts of five pharmaceutical ingredients in a tablet, with individual nominal concentrations ranging from 1% to 85%, by transmission Raman spectroscopy.

Nevertheless, some adjustments and/or corrections are frequently required to boost the accuracy and reproducibility of Raman spectroscopy analysis in actual industrial fields. The Raman intensity depends on a number of factors, including the type of Raman spectroscopy, laser power, radiation frequency, and response of the detection system [12,13]. In addition, since the Raman intensity is proportional to the number of molecules in the sample volume, the granular size and/or packing density of the sample are also important factors [13]. In this regard, physicochemical differences between the calibration samples and test samples may lead to inaccurate predictions and/or poor

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reproducibility. Moreover, the presence of numerous pharmaceutical excipients, especially fluorescence materials, may hamper reliable quantification by causing fluctuations in the spectral baseline. Mazurek and Szostak reported that FT-Raman is effective in the quantification of ATV in tablets, based on partial least squares, principal component regression, and counter-propagation neural networks [14]. However, ATV tablets had to be ground to powder form in order to minimize the physical difference between the calibration sample (powder form) and the test sample (tablet form). Although the approach provided reproducibility in ATV analysis, a simpler pre-treatment method is required for practical use. In another case, the drug content in solid dosage form was simply quantified using the ratio of the intensities of the two peaks attributed to ATV and the excipient in the same spectrum, with limitations in averaging and/or removing interference or noise signals [13].

In this study, Raman spectroscopy was applied to analyze the ATV content in process pharmaceutical samples prepared by wet granulation. To establish an accurate method, we evaluated the effects of 4 parameters on the ATV quantification: type of Raman spectroscopy (back-scattering or transmission Raman spectroscope), calibration sample preparation (simple admixing or wet granulation), sample pre-treatment (pelletization), and spectral pre-treatment using probabilistic quotient normalization (PQN). After establishing the optimal quantitative model, we predicted the actual manufacturing process samples and compared the results with the reference values determined by HPLC.

2. Experimental and Methods

2.1. Chemicals

ATV calcium anhydrous, an active ingredient, was obtained from Kyongbo Pharm. (Seoul, Korea). Microcrystalline cellulose and lactose hydrate were provided by Asahi Kasei Chemicals (Japan) and DMV Fonterra Excipients GmbH & Co. (KG, Germany), respectively. Precipitated calcium carbonate was purchased from Nippon Talc. Co. Ltd. (Japan). All other chemicals were of reagent and/or analytical grade and were used without further purification.

2.2. Raman Spectroscopic Conditions

Back-scattering and transmission Raman spectra of the samples were obtained using Raman Workstation Rxn1 (Kaiser Optical Inc., USA) and Raman TRS100 (Cobalt Light Systems Ltd., UK) systems, respectively. Each powder sample was placed in a 4-mm-thick polystyrene cuvette and tapped more than 100 times to reduce void volume between the particles. Raman spectra of the pelletized samples were obtained without loading in the cuvette. Pelletized samples were prepared by loading 150 mg of the sample into a compressor with a diameter of 8 mm and subsequent compressing at a pressure of 3 tons for 1 min. In back-scattering Raman microscopy, an excitation laser (785 nm, diode laser) was introduced and magnified to form a circular illumination area of 6 mm diameter (area: 28.3 mm^2) to cover a large sample area. To obtain transmission Raman spectra, the excitation laser (830 nm, diode laser) was introduced with a spot diameter of 4 mm. In both Raman modes, a CCD detector (iDUS, Andor, UK) was used to collect spectra over the wavenumber range 50–2500 cm^{-1}. The measurement time was set to 80 s for 40 accumulations, with 2 s of exposure time.

2.3. Calibration Sample Preparation

The weight of the ATV-containing powder per each tablet was fixed to 150 mg. The granules were composed of 9.68% w/w of ATV as an active ingredient, and approximately 40% w/w of microcrystalline cellulose, 20% w/w lactose hydrate, and 20% w/w of calcium carbonate as pharmaceutical excipients. The minor excipients were hydroxypropyl cellulose as a binder, cross-linked sodium carmellose and crospovidone as a disintegrants, and magnesium stearate as a lubricant. To plot the calibration curve, a total of 25 samples of calibration were set from eight raw materials. Among the eight ingredients in the dosage from, the amounts of ATV, microcrystalline cellulose, lactose hydrate, and precipitated calcium carbonate, whose individual concentrations were more than 20% w/w in the granule, were randomized over the range 80% to 120%. This randomization process ensures that there is no correlation between the four independent variables, thus avoiding multicollinearity and achieving linear independence.

These compositions were prepared by two methods. First, a calibration sample was prepared by simply admixing the active ingredient and excipients in an amount corresponding to the respective contents. Second, calibration samples were prepared by wet granulation method, similar to the actual manufacturing process. Briefly, ATV and other raw materials were added to a high-speed mixer with a binding agent at a certain ratio to produce wet granules. The mixer speed was set at 80 rpm with the main impeller and kneading was carried out for 3 min. The ATV-containing granules were dried using a fluid-bed dryer with an inlet temperature of 60 °C. Then, the final granular mixture for tabletization was produced through subsequent sizing using a Comil oscillator by a final mixing process.

2.4. Model Development

The calibration and test sets were explored to establish and/or verify the accuracy and reliability of Raman spectroscopy as an API content prediction model. To establish the calibration model, spectral preprocessing was conducted by the probabilistic quotient normalization (PQN) method. This method compensates for spectral changes caused by differences in the density or particle size of the solid samples. In PQN method, the median quotient is used, which provides a better estimation of the overall scale and is not much influenced by differences in constituent concentrations [15]. After spectral pretreatment, quantitative analysis was conducted with the partial least square (PLS) [16–18], a multivariate regression analysis.

To verify the established model, five test samples containing different amounts of ATV (88.0–112.5%) were further predicted using Raman spectroscopy, after converting granules into pellet form. The predicted values were compared with the actual drug content calculated from the mixing ratio of each component.

2.5. Prediction of ATV Content in Actual Pharmaceutical Powder Sample

In process pharmaceutical powder samples were prepared by the wet granulation method, as described in Section 2.3. A total of 220 kg of drug powders and pharmaceutical excipients was used to produce 2,000,000 tablets per batch. A total of five batches were prepared by the same method with the same manufacturing scale. Then, the drug content in the actual process samples was predicted by the established Raman method for 5 batches. 150 mg of powder sample was withdrawn from each batch and pelletized. The drug content in each pellet was predicted by triplicate Raman measurements, and the mean value was calculated by averaging the individual predictions. For comparison, the drug content in these pellets was analyzed by HPLC, as described earlier.

2.6. HPLC Assay of ATV

The API content in the granules was quantitatively analyzed by HPLC (Waters, USA). The HPLC system consisted of a pump (L-2130), UV detector (L-2400), data station (LaChrom Elite, Hitachi, Japan), and 15 cm C_{18} column (Gemini C18 column). The mobile phase consisted of pH 4.0 buffer solution, acetonitrile, and tetrahydrofuran (53:27:20) with a flow rate of 1.5 mL/min. The UV wavelength was 244 nm, and the sample

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