Journal of Pharmaceutical and Biomedical Analysis 49 (2009) 168–172

Contents lists available at ScienceDirect

Journal of Pharmaceutical and Biomedical Analysis

journal homepage: www.elsevier.com/locate/jpba

Short communication

Quantification of atorvastatin calcium in tablets by FT-Raman spectroscopy

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ARTICLE INFO

Article history:
Received 14 July 2008
Received in revised form 8 October 2008
Accepted 10 October 2008
Available online 1 November 2008

Keywords:
Atorvastatin calcium
Active ingredient quantification
FT-Raman spectroscopy
Chemometrics

ABSTRACT

The FT-Raman quantification of atorvastatin calcium in tablets was performed using the partial least squares (PLS), principal component regression (PCR) and counter-propagation artificial neural networks (CP-ANN) methods. To compare the predictive abilities of the elaborated models, the relative standard errors of prediction (RSEP) were calculated. The application of PLS, PCR and 6 × 6 CP-ANN provided models of comparable quality. RSEP error values in the range of 1.9–2.8% for calibration and validation data sets were obtained for the three procedures applied. Four commercial products containing 10, 20 or 40 mg of atorvastatin calcium per tablet were successfully quantified. Concentrations found from the Raman data analysis correlate strongly with the declared values, with a recovery of 98.5–101.3%, and with the results of reference analysis, with the recovery of 98.9–102.1%, for the different models. The proposed procedure can be a fast, precise and convenient method of atorvastatin calcium quantification in commercial tablets.
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1. Introduction

Atorvastatin calcium (ATC), [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt trihydrate, is a synthetic lipid-lowering agent, an inhibitor of 3-hydroxy-3-methylglutaryl Coenzyme A (HMG-CoA) reductase [1].

Chromatographic techniques such as HPLC [2–6] and LC–MS [7,8] are the most popular analytical methods for this active pharmaceutical ingredient (API) quantification. Other analytical techniques used for ATC quantification include electrophoresis [9] and UV–vis spectrometry [10–12]. The suitability of Raman spectroscopy to the quantitative analysis of ATC polymorphs was also demonstrated [13].

It is well established that Raman spectroscopy is an effective analytical method for quantification of complex mixtures, including pharmaceutical preparations [14,15]. The most important advantage of this technique is probably its simplicity, but the short analysis time and capacity for automation of the analytical procedure are also very important. With this method, there is no need to solvate or extract the API under consideration. In many cases, Raman spectroscopy, supported by chemometrics, enables the analysis of medicines in their unaltered states, without any sample treatment. It is a particularly useful tool in the analysis of products with a high API content [16,17]. Nevertheless, Raman quantification of preparations containing less than 5% by weight of API was also reported [18,19].

ATC is usually administered in the form of tablets containing from 10 to 40 mg of the active compound per tablet. This corresponds to ATC comprising not more than a few percent of the tablet mass. The difficulty of ATC quantification by Raman is compounded by its big formula weight, equal to 1155 Da. It is 6–8 times larger than the formula weights of acetylsalicylic acid and acetaminophen, active ingredients that are known to be easily quantifiable in solid dosage forms by this method [17]. It should be pointed out that the Raman technique is not a very sensitive one and the facts mentioned above may hamper reliable ATC quantification.

The advantage of neural networks over other chemometrics methods such as partial least squares (PLS) and principal component regression (PCR) [20,21] in the modeling of systems for which non-linear signal-answer dependencies are present is well documented [22]. Herein, we present the results of quantification by PLS, PCR and counter-propagation neural networks (CP-ANN) [23,24] data treatment of four commercial atorvastatin calcium tablets containing approximately 5–7% of active compound. The results obtained by the Raman technique are compared with those found from UV–vis measurements.

2. Experimental

2.1. Materials and sample preparation

The substances used, namely atorvastatin calcium and lactose, were of pharmacopoeial purity. The active component was kindly donated by Biofarm. Microcrystalline cellulose, hydroxypropyl

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doi:10.1016/j.jpba.2008.10.015

methylcellulose, magnesium stearate, $CaCO_3$, and TiO_2 were of analytical grade (Sigma). Four atorvastatin calcium preparations, in the form of tablets containing, as declared, 10–40 mg of API, were purchased in a local pharmacy. Methanol used for UV–vis measurements was of HPLC grade (Merck).

Calibration and validation samples were prepared by mixing pure, solid substances in a mortar for several minutes to homogenize the powders properly. Suitable weight ratios of compounds were taken to minimize the colinearity between component concentrations and no significant correlations were observed. The determination coefficients R^2 for the concentration versus concentration plots were in the 0.01–0.16 range. Next, half of the prepared mixture, i.e., approximately 200 mg of powder, was used to prepare a pellet in a way similar to that adopted in IR spectroscopy. The commercial tablets were first ground and then processed further in the same way as the calibration samples.

Reference quantification of atorvastatin calcium preparations was performed according to an adopted spectrophotometric procedure given by Nagaraj et al. [11] and Sonavane et al. [12].

2.2. Apparatus

A Nicolet Magna 860 FT-IR spectrometer interfaced with an FT-Raman accessory with a CaF_2 beamsplitter and indium–gallium arsenide (InGaAs) detector was used to perform the measurements. The samples placed in a rotating sample holder were illuminated by an Nd:YVO_4 laser line at 1.064 μm with a power of 350 mW at the sample, without a converging lens; backscattered radiation was collected. Samples were rotated at a constant speed of ca. 200 rpm. The interferograms were averaged over 256 scans, Happ-Genzel apodized and Fourier transformed using a zero filling factor of 2 to produce spectra in the 100–3700 cm^{-1} range at a resolution of 8 cm^{-1}.

UV–vis spectra of ATC methanol solutions, in the range 200–300 nm with the resolution of 1 nm were recorded using a Carry-5 Varian spectrometer.

2.3. Software and numerical data treatment

Nicolet TQ Analyst ver. 7 chemometrics software was used to construct PLS and PCR models. The neural network simulations were performed with the help of software developed by Zupan [25]. The numerical data were prepared and transformed into an appropriate format using the Matlab (MathWorks) environment. All spectral data were mean centered.

To characterize and compare the predictive abilities of the developed models, the relative standard errors of prediction (RSEP) were calculated according to the following formula [26]:

$$\mathrm{RSEP}(\%) = \sqrt{\frac{\sum_{i=1}^{n}(C_i - C_i^A)^2}{\sum_{i=1}^{n} C_i^{A2}}} \times 100, \quad (1)$$

in which C^A is the actual component content, C is the concentration found from Raman or UV–vis data analysis, and n is the number of samples. The $RSEP_{cal}$ and $RSEP_{val}$ errors were determined for the calibration and validation data sets respectively.

The cross-validation, using leave-one-out technique, was performed to estimate the robustness of the constructed models. The root mean square error of cross validation (RMSECV) was calculated to select an optimal number of factors for the PLS models.

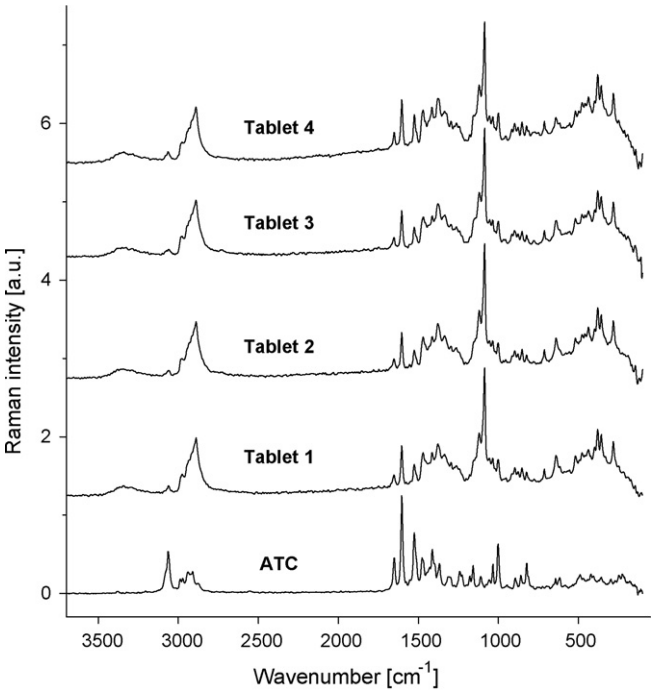

Fig. 1. FT-Raman spectra of atorvastatin calcium and four analyzed tablets.

3. Results and discussion

3.1. Raman analysis

In Fig. 1, the FT-Raman spectra of pure atorvastatin calcium and of the studied commercial preparations are presented. All four analyzed tablets, denoted 1, 2, 3 and 4, besides the active component (5.0–7.0% by weight), contain as additives lactose, cellulose and its hydroxypropyl methyl derivative, magnesium stearate, $CaCO_3$, and TiO_2 in different proportions. Tablets 1, 2 and 3 were produced by the same manufacturer, and the qualitative composition of the tablet mass of these preparations was very similar. The differences between the content of the studied commercial samples originating from the two manufacturers can be attributed mainly to the different composition of the outer layer of the tablets. Although compounds present in tablet coatings are rather weak Raman scatterers, the differences in tablet composition are clearly shown by the scores plots of PCA analysis.

To construct calibration models, the Raman spectra of 36 solid samples (prepared as described above) were used. The mass fraction varied in the 0.03–0.10 range for atorvastatin calcium, 0.17–0.39 for lactose, 0.31–0.55 for cellulose, 0.03–0.19 for hydroxyproplyl methylcellulose, 0.005–0.05 for magnesium stearate, 0.09–0.17 for $CaCO_3$, and 0.005–0.03 for TiO_2. Eight mixtures were chosen for the validation procedure, and the validation data set was selected by the Kohonen mapping. The remaining 28 samples were used as a calibration or training set. This division between calibration and validation samples was preserved for all PLS, PCR and CP-ANN models built. In the construction of the chemometrics model, the 990–1680 cm^{-1} region of Raman spectra was applied. Usually this region was slightly modified for each preparation studied. From the RMSECV plot for ATC presented in Fig. 2 (top left), it follows that it is enough to build the PLS model with the use of 4 factors.

In comparison to the PLS and PCR methods, the optimization of neural networking appears to be more complex because the number of possible network parameters influencing the strength of the

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