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Quantitative analysis of topical gels and ointments by FT-Raman spectroscopy

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ABSTRACT

A method for quantitative determination of ibuprofen (IBU), naproxen (NAP), methyl salicylate (MES) and menthol (MNT) in commercial topical gels and ointments using partial least squares (PLS) models based on FT-Raman spectra is described. The calculated relative standard errors of prediction (RSEP) were found to be in the range of 2.1–3.2% for the calibration and validation data sets. Two commercial topical gels containing 5.0% of IBU and 10% of NAP (w/w), as well as one ointment containing 15% of MES and 10% of MNT (w/w) as active pharmaceutical ingredients (APIs), were successfully quantified using the developed models with recoveries in the 99.2–101.5% range. The proposed procedure can be used as a fast, reliable and economic method for the quantification of APIs in topical gels and ointments.

1. Introduction

Ointments and gels are forms of medicines intended for external use. Depending on the desired area of their application, various types of ointment/gel bases are applied in order to create the optimal chemical environment for the active pharmaceutical ingredient (API) used. Active substances can be dissolved, suspended or emulsified in the base.

Quantitative analysis of these types of medicine is not a straightforward task. The most common methods applied for API quantification in topical gels and ointments are based on laborious and time-consuming extraction followed by chromatographic determination [1–3]. Near infrared (NIR), infrared (IR) and nuclear magnetic resonance (NMR) techniques can also be used for this purpose [4–8].

Transdermal transport of APIs and the expected speed of its absorption through the tissue, determining the bioavailability of the substance, require relatively high water content in these types of medicines; the amount of water in gels/ointments often exceeds 80% (w/w). With regard to the physical state of these medicines and the fact that water is a weak Raman scatterer, Raman spectroscopy seems to be a convenient tool for API quantification in gels and ointments.

In recent years, Raman spectroscopy has gained ground in the analysis of multicomponent systems in the food, cosmetics and pharmaceutical industries [9–11]. It enables rapid quantification of APIs in different forms of pharmaceutical products present on the market [12–15], including medicines with very low API content [13,16], and quantitative analysis of polymorphs [17–21]. Multivariate models constructed on the basis of Raman data can be used for simultaneous determination of several compounds of interest in one product, which significantly shortens and simplifies the analysis [22]. Therefore, according to Food and Drug Administration (FDA) recommendations [23], Raman technique can be widely adopted as a Process Analytical Technology (PAT) tool for monitoring manufacturing processes in the pharmaceutical industry [24,25], including blending [26] and drying [27], controlling the homogeneity of products [28] and their composition [29].

Reports describing API quantification in gels and ointments in their native state are scarce. Chuchuen et al. developed a procedure of tenofovir quantification in gels [30]. Oh and co-workers described quantitative analysis of urea and titanium dioxide in cream formulations using Raman spectroscopy [31,32]. De Beer et al. studied the influence of the mean particle size of salicylic acid on its quantification in ointments by Raman spectroscopy [33].

Here we present the procedures and results of four APIs quantification in two topical gels and one ointment utilizing Raman spectroscopy based on separate calibration systems for

Abbreviation: API, active pharmaceutical ingredient; CLS, classical least squares; IBU, ibuprofen; MNT, menthol; MES, methyl salicylate; NAP, naproxen; PAT, process analytical technology; PC, principal component; PCA, principal component analysis; PCR, principal component regression; PLS, partial least squares; RMSECV, root mean square error of cross-validation; RSEP, relative standard error of prediction; SNV, standard normal variate.

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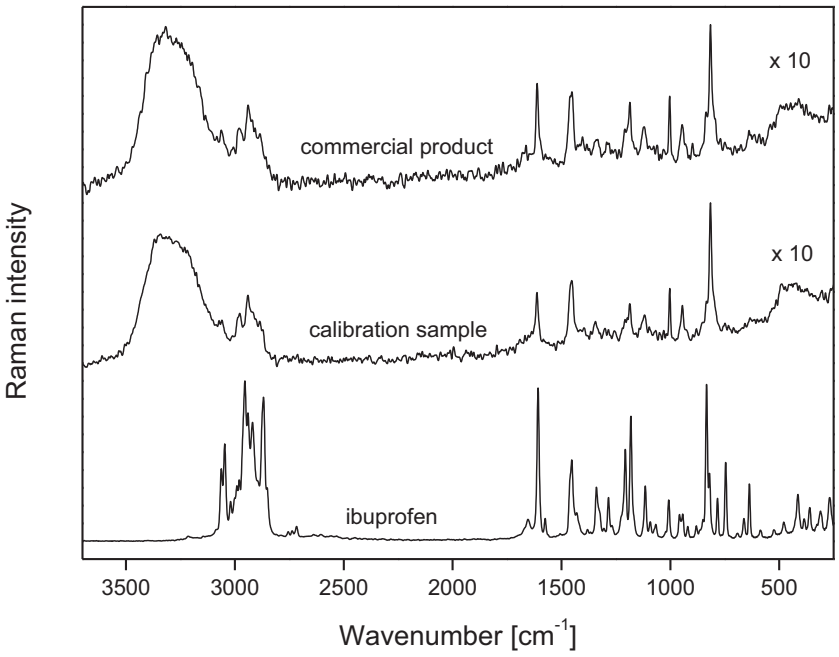

Fig. 1. FT Raman spectra of pure ibuprofen, calibration sample and commercial preparation.

each of the studied commercial products. We report on the analysis of commercial medicines containing active compounds in the 5–15% (w/w) concentration range.

2. Experimental

2.1. Materials and samples

The active compounds used, namely ibuprofen (IBU), naproxen (NAP), methyl salicylate (MES), menthol (MNT) (Fig. S1 in Supplementary material) and their main excipients, i.e. carbomer, hydroxyethyl cellulose, lanolin and polysorbate 85, were of pharmacopoeial purity. The remaining substances – benzyl, ethyl and isopropyl alcohols, glycerol monostearate, stearic acid, NaOH and triethylamine – were of analytical grade and originated from POCh (Gliwice, Poland), Applichem (St. Louis, USA) and Merck (Darmstadt, Germany). Aqueous bases were prepared using purified water (Merck Millipore, Darmstadt, Germany) characterized by a resistivity of 18.2 MΩ cm at 25 °C. Two commercial gels, one containing 50 mg/g IBU and another containing 100 mg/g NAP, and a commercial ointment containing 150 mg/g MES and 100 mg/g MNT, were purchased in a local pharmacy.

2.1.1. Preparation of ibuprofen gels

A defined amount of ibuprofen solution (35%, w/w, in a mixture of isopropyl and benzyl alcohol, 87:13) was added to a base

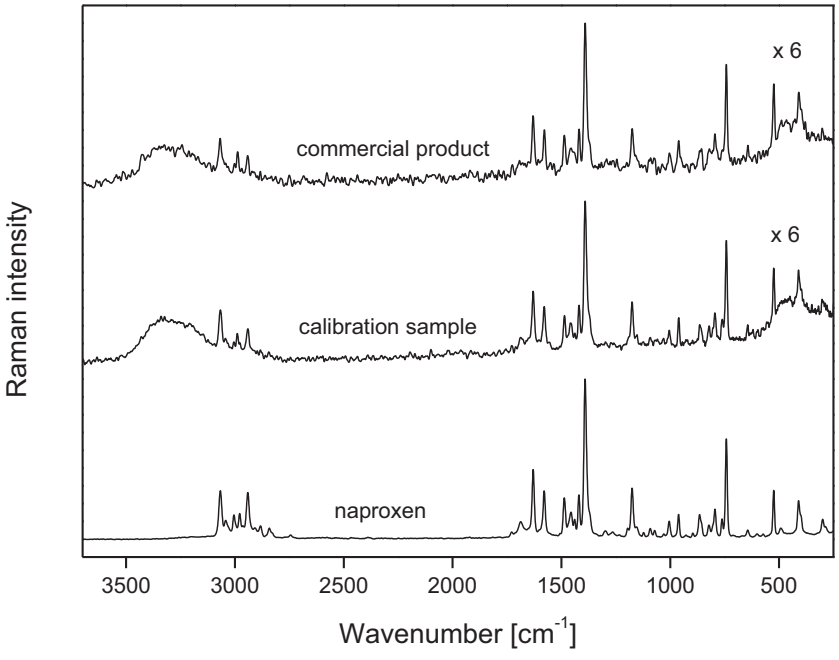

Fig. 2. FT Raman spectra of pure naproxen, calibration sample and commercial preparation.