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Direct comparison of low- and mid-frequency Raman spectroscopy for quantitative solid-state pharmaceutical analysis

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ABSTRACT

This study considers the potential of low-frequency (terahertz) Raman spectroscopy in the quantitative analysis of ternary mixtures of solid-state forms. Direct comparison between low-frequency and mid-frequency spectral regions for quantitative analysis of crystal form mixtures, without confounding sampling and instrumental variations, is reported for the first time. Piroxicam was used as a model drug, and the low-frequency spectra of piroxicam forms β, α2 and monohydrate are presented for the first time. These forms show clear spectral differences in both the low- and mid-frequency regions. Both spectral regions provided quantitative models suitable for predicting the mixture compositions using partial least squares regression (PLSR), but the low-frequency data gave better models, based on lower errors of prediction (2.7, 3.1 and 3.2% root-mean-square errors of prediction [RMSEP] values for the β, α2 and monohydrate forms, respectively) than the mid-frequency data (6.3, 5.4 and 4.8%, for the β, α2 and monohydrate forms, respectively). The better performance of low-frequency Raman analysis was attributed to larger spectral differences between the solid-state forms, combined with a higher signal-to-noise ratio.

1. Introduction

Solid-state forms (including crystalline polymorphs, solvates, salts, cocrystals and the amorphous form) are important in the pharmaceutical industry, because they exhibit distinct physicochemical properties [1]. In drug development and manufacturing, solid-state transformations can occur during processing or storage, and it is possible that mixtures of solid-state forms of the drug are present [2]. Since the solid-state structure(s) can affect many critical quality attributes, such as solubility, stability and mechanical properties, for regulatory and commercial purposes, it can be important to quantify, as well as reliably detect, the potential presence of these different forms. Various analytical techniques with specific advantages and disadvantages are used for solid-state characterization [3]. Some advantages of Raman spectroscopy are rapid, non-destructive, and non-contact analyses, which also make it suitable for in-line measurements and real-time process monitoring [4,5]. Conventional mid-frequency Raman spectroscopy has been used to quantify the compositions of solid-state form mixtures of pharmaceuticals [6,7].

Low-frequency (terahertz) Raman spectroscopy can probe solid-state structure on a level that cannot be obtained by traditional mid-frequency Raman spectroscopy [8]. Low-frequency Raman bands correspond to polarizability changes associated with lattice vibrations produced by collective translational or rotational motions of molecules in the unit cell. These vibrations, also called phonon modes, are directly defined by the molecular packing arrangement and intermolecular forces, such as hydrogen bonds and π-π stacking interactions of aromatic rings, and therefore reflect the solid-state form [9]. Such low-frequency Raman bands appear close to the laser line, typically below 130 cm^{-1} for organic molecules, and they are often difficult to detect with conventional Raman systems where the Rayleigh-rejection filters also block the low-energy scattered photons [9]. The development of specialized optical filters (ultra-narrow band notch filters

Abbreviations: CSD, Cambridge Structural Database; FT-Raman, Fourier-transform Raman spectroscopy; LF-785, low-frequency Raman with 785 nm excitation; LF-830, low-frequency Raman with 830 nm excitation; PLSR, partial least squares regression; RMSEE, root-mean square error of estimation; RMSEP, root-mean square error of prediction; SNV, standard normal variate; XRPD, X-ray powder diffractometry.

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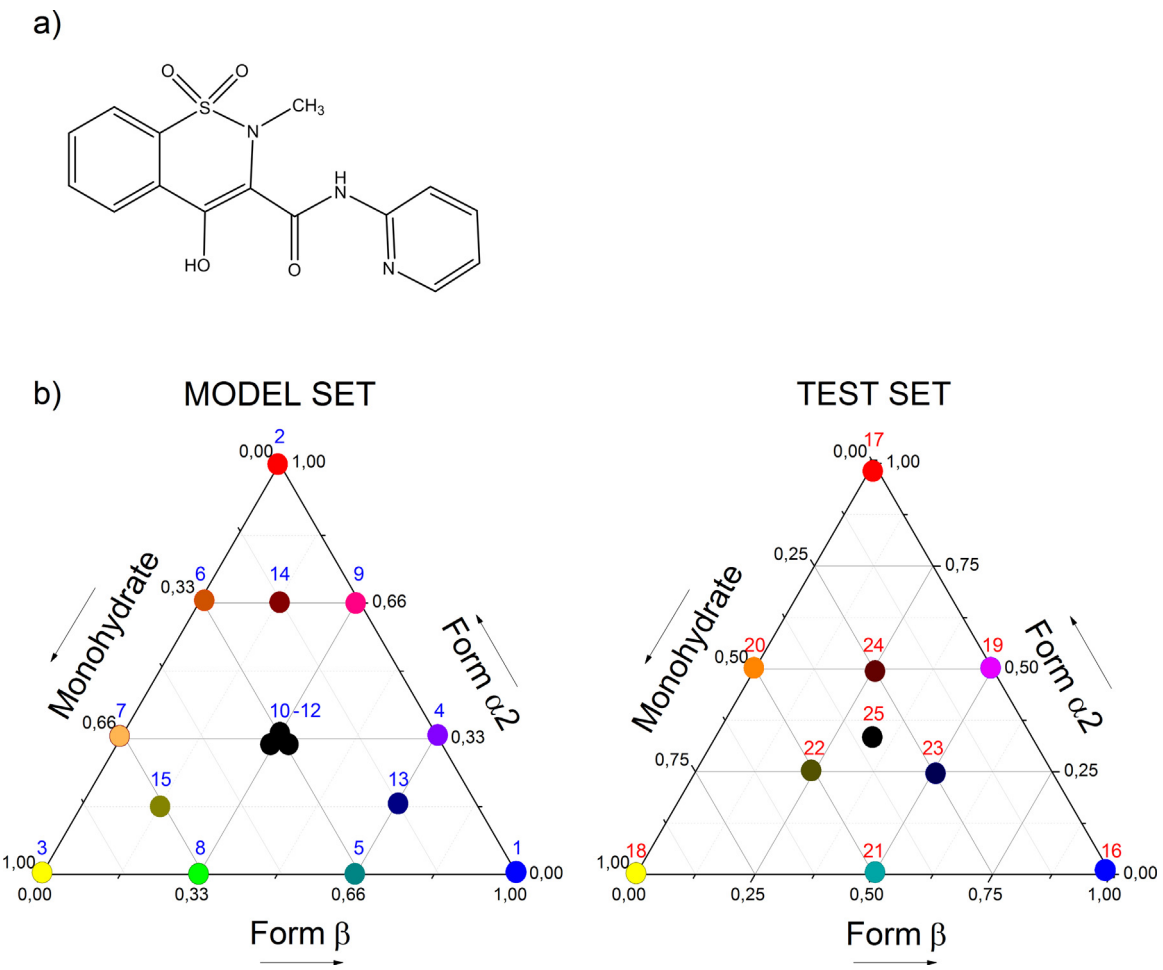

Fig. 1. a) Molecular structure of piroxicam and b) Mixture designs for the model (calibration) set and the test (validation) set.

and volume holographic grating technology) has enabled access to the low-frequency spectral range with routine dispersive Raman instruments, and made the technique attractive for pharmaceutical research applications [10,11]. Terahertz (pulsed) spectroscopy, the low frequency analogue of (mid-)infrared spectroscopy, also probes lattice vibrations. Instead of polarizability changes, the technique is sensitive to dipole moment during such vibrations. While terahertz spectroscopy is also highly sensitive to solid-state structure and has been successfully used to quantify mixtures and transformations of solid state forms in pharmaceutics [3,12], low-frequency Raman has some advantages such as insensitivity to atmospheric water, flexible sample interfacing for e.g. in-line analysis, as well as the same core technology as for mid-frequency Raman setups (with potential for adaptation).

Low-frequency Raman spectroscopy has been used for various pharmaceutical solid-state analytical purposes, including identification of polymorphs [9,13,14], solid-state form composition analyses of tablets by Raman imaging [15] and transmission Raman spectroscopy [16], as well as evaluation of crystallization of amorphous systems and other solid-state transformations [17,18]. For the quantitative applications, both univariate [17] and multivariate data analysis [16,18] methods have been used.

Despite such studies demonstrating the feasibility of low-frequency Raman spectroscopy for quantitative solid-state analysis, an important consideration is whether such analysis provides better results than could be obtained with established mid-frequency Raman setups. There are currently no studies directly comparing conventional mid-frequency and the low-frequency Raman capabilities for quantifying crystal form mixtures without setup sampling differences associated with different instruments. Such a comparison requires simultaneous access to the full low- and mid-frequency ranges in the same instrument. The purpose of this work was to directly compare these spectral regions to get insight into any additional value of low-frequency Raman equipment over mid-frequency setups.

In this work, piroxicam, a widely available non-steroidal anti-inflammatory drug, was used as a model drug (Fig. 1**a**). Piroxicam has low aqueous solubility and high permeability, therefore it is a Biopharmaceutics Classification System class II drug with the solid-state form potentially mattering therapeutically. Crystalline piroxicam exhibits polymorphism, with five anhydrous crystal forms and the monohydrate described in the Cambridge Structural Database (CSD), with additional polymorphs having been reported [19]. Ternary mixtures of piroxicam forms were prepared for the spectral data comparison because 1) ternary mixtures are less widely studied and quantitative models more challenging to establish than with binary mixtures, and 2) they are potentially more valuable, since in many industrial processing and even storage situations, three rather than two solid-state forms may be likely to appear [7]. The solid-state forms used in the mixtures were the monohydrate (CSD: CIDYAP02 [20]) and the two anhydrate forms β (CSD: BIYSEH13 [20]) and α2 (CSD: BIYSEH06 [21]), because they are the most commonly observed forms, while the other solid-state forms appear in more extreme conditions or are very unstable. The forms used in this study can also be distinguished using conventional mid-frequency Raman systems [22], which is most common for pharmaceutical solid-state analysis, and therefore makes the comparison between the regions relevant and