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Review

Pharmaceutical applications of vibrational chemical imaging and chemometrics: A review

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ABSTRACT

The emergence of chemical imaging (CI) has gifted spectroscopy an additional dimension. Chemical imaging systems complement chemical identification by acquiring spatially located spectra that enable visualization of chemical compound distributions. Such techniques are highly relevant to pharmaceutics in that the distribution of excipients and active pharmaceutical ingredient informs not only a product's behavior during manufacture but also its physical attributes (dissolution properties, stability, etc.). The rapid image acquisition made possible by the emergence of focal plane array detectors, combined with publication of the Food and Drug Administration guidelines for process analytical technology in 2001, has heightened interest in the pharmaceutical applications of CI, notably as a tool for enhancing drug quality and understanding process. Papers on the pharmaceutical applications of CI have been appearing in steadily increasing numbers since 2000. The aim of the present paper is to give an overview of infrared, near-infrared and Raman imaging in pharmaceutics. Sections 2 and 3 deal with the theory, device set-ups, mode of acquisition and processing techniques used to extract information of interest. Section 4 addresses the pharmaceutical applications.

Contents

Abbreviations: AH, agglomerative hierarchical; ANN, artificial neural network; API, active pharmaceutical ingredient; ASA, acetylsalicylic acid; ATM, atomic force microscopy; ATR, attenuated total reflection; BSS, blind source separation; BTEM, band target entropy minimization; CCA, cosine correlation analysis; CCD, charge coupled detectors; CI, chemical imaging; CLS, classical least squares; csiFCM, cluster size insensitive fuzzy-C mean; 2D/3D, two-/three-dimensional; DA, discriminant analysis; DAC, directed agglomeration clustering; DCLS, direct classical least squares; DESI-MS, desorption electrospray ionization linear ion trap mass spectrometry; D_2O, deuterium oxide; DR, diffuse reflection; EMSC, extended multiplicative signal correction; EVA, ethylene vinyl acetate; FCM, fuzzy-C mean; FNNLS, fast non-negative least squares; FPA, focal plane array; FFT, fast Fourier transform; FIR, far-infrared; FOV, field of view; FT, Fourier transform; FTIR, Fourier transform infrared; HPLC, high performance liquid chromatography; HPMC, hydroxypropylmethylcellulose; ICA, independent component analysis; IR, infrared; ITTFA, iterative target transformation factor analysis; KM, K-means; KSFA, key-set factor analysis; LCTF, liquid crystal tunable filter; LDA, linear discriminant analysis; LLS, laser light scattering; LUT, look-up table; MBCD, methyl-β-cyclodextrin; MCR-ALS, multivariate curve resolution-alternating least squares; MCT, mercury cadmium telluride; MIA, multivariate image analysis; MIR, mid-infrared; MLF-ANN, multilayer feed-forward-artificial neural network; MLP-ANN, multilayer perception-artificial neural network; MNF, maximum noise fraction; MSC, multiplicative scatter correction; NA, numerical aperture; NIR, near-infrared; NMF, non-negative matrix factorization; OLS, ordinary least squares; OPA, orthogonal projection analysis; PARAFAC:, parallel factor; PAT, process analytical technology; PBS, phosphate buffered saline; PCA, principal component analysis; PDMS, polydimethylsiloxane; PEG, polyethylene glycol; PEO, polyethylene oxide; PLGA, poly(lactic-*co*-glycolic acid); PLS, partial least squares; PMF, positive matrix factorization; RGB, red–green–blue; ROI, regions of interest; SA, salicylic acid; S.D., standard deviation; SIM, spectral identity mapping; SIMCA, soft independent modeling of class analogies; SIMPLISMA, simple-to-use interactive self-modeling mixture analysis; SMCR, self-modeling curve resolution; SNR, signal to noise ratio; SNV, standard normal variate; SVM, support vector machine; UV, ultraviolet; WEFA, window evolving factor analysis.

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1. Introduction

Vibrational spectroscopy encompasses near-infrared (NIR), mid-infrared (MIR) and Raman spectroscopy. Aided by relentless instrumentational advance, these complementary techniques have now entered common use for the study of solid-state samples. They allow both quantitative and qualitative analysis and can also be deployed in-line. They have therefore found many applications in the industrial pharmaceutical setting [1,2].

In 1949, in *Nature*, Barer and Cole reported the acquisition of spatially resolved spectra using a microscope [3]. This publication opened up new opportunities for spectroscopy by allowing microscopic samples to be analyzed. Four decades later, in 1988, Harthcock and Atkin obtained the first chemical map in the MIR range [4] using a microscope and moving stage. By revealing information that is both spectral and spatial, the technique can identify and localize compounds. Subsequent refinements have been exponential. Development of the first microscope-mounted focal plan array (FPA) detectors increased enthusiasm for chemical imaging (CI) [5]. Fast and robust acquisition is now possible in the NIR and MIR ranges and also with Raman spectroscopy. Almost all chemical compounds in a sample can be visualized within minutes. Applications have since increased in various fields, from waste sorting [6] to biological tissue [7] and food quality [8]. More recently, the introduction in 2001 of the concepts of process analytical technology (PAT) [9] and quality by design sparked fresh interest in the pharmaceutical industry. PAT is a generic term for monitoring quality and performance parameters in production-based systems. It has two objectives: (1) it requires the product to be monitored not only at the end of the production line, as at present, but also all along the line, in order to enhance quality; (2) it encourages the development of new process-monitoring methods and systems, thereby enhancing understanding of the process itself. One undeniable factor influencing the physical attributes of solid dosage forms is compound distribution. For example, heterogeneous compound distribution can decrease the rate of tablet dissolution [10] or prompt process troubleshooting over poor powder flow or sticky tablets [11]. CI is an ideal tool for resolving these issues when spatial information is required [12]. Unsurprisingly, publications dealing with hyperspectral imaging have multiplied since 2000.

CI has also raised new data-processing challenges. A single acquisition may record thousands of images across numerous wavelengths. The resulting image stack forms a three-dimensional (3D) matrix, or data cube, spanning two spatial dimensions with a series of wavelengths making up the third (spectral) axis (Fig. 1). There are two challenges: (1) the data cube may be viewed as spatially located spectra, with the processing tools of classical spectroscopy being applied to single spectra; (2) the data may be viewed as images, with image-processing tools being used to extract higher-quality spatial information. CI thus combines the techniques of spectroscopy and signal and image processing, making it a truly multidisciplinary discipline.

This review will not only offer a comprehensive presentation of the pharmaceutical applications of vibrational imaging but also cover and discuss the instrumentation and data-processing techniques available. Section 2 (vibrational spectroscopy theory and instrumentation) encompasses several important aspects of imaging, such as acquisition time, calibration, and resolution (both spectral and spatial). Section 3 presents the processing techniques available for extracting relevant information from data cubes. Both parts refer to publications in other fields, such as agriculture and biology, to corroborate and illustrate the