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Non-invasive *in situ* identification and band assignments of diazepam, flunitrazepam and methadone hydrochloride with FT-near-infrared spectroscopy

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ABSTRACT

Near-infrared spectroscopy (NIR) has evolved into an important rapid, direct and non-invasive technique in drugs analysis. In this study, the suitability of NIR spectroscopy to identify two benzodiazepine derivatives, diazepam and flunitrazepam, and a synthetic opiate, methadone hydrochloride, inside USP vials and probe the solid-state form of diazepam presents in tablets has been explored. The results show the potential of NIR spectroscopy for rapid, *in situ* and non-destructive identification of drugs.

1. Introduction

Near-infrared (NIR) spectroscopic technique has been long accepted as an analytical tool that is capable of accomplishing rapid and non-destructive analysis. In recent years, considerable efforts have been undertaken to apply this technique for determination and identification of the pharmaceutical products [1–12]. It is envisioned that successes on this front can lead to decreased analysis time and cost as well as reduced handling of and exposure of analysts to hazardous chemical materials. More importantly, implementation of this approach can lead to an increased throughput for release analysis thus furnishing improved quality control of the final products [13]. The basic principles and pharmaceutical applications of NIR spectroscopy has been reviewed recently [14].

The vibrational NIR spectroscopic technique offers sampling related advantages similar to Raman, but has no problem with fluorescence. Also NIR instruments with integrated fibre-optic technology are markedly less expensive than the comparable Raman instruments. The price to pay for this convenience is a much less interpretable NIR spectral signature. In spite of the vast amount of literature published on NIR spectroscopy for solid-state analysis of drugs and its apparent advantages within the field, little work has hitherto been done to establish the usefulness of the technique for rapid *in situ* identification of pharmaceuticals and for probing the solid-state forms of drugs present in tablets. Therefore, the applicability of NIR spectroscopy in this context merits closer examination.

The aims of this study were to investigate the analytical potential of NIR spectroscopy to identify two benzodiazepine derivatives, diazepam and flunitrazepam, [15,16] (Fig. 1, a and b) and a synthetic opiate, methadone hydrochloride (HCl), [15,16] (Fig. 1, c) inside USP vials and probe the solid-state form of diazepam presents in tablets.

2. Materials and methods

2.1. Materials

Diazepam, flunitrazepam and methadone HCl specimens were purchased from Sigma Aldrich. The unknown samples (A, B and C) of the studied drugs were generously supplied by Astellas Pharma, Tokyo, Japan. Valium® (diazepam) 5 and 10 mg tablets from Roche were purchased from the local market.

2.2. NIR spectroscopy

Near-infrared spectra were collected in triplicate using a Bruker Optics *MPA*-FTNIR spectrometer with an integrating sphere and auto-sampler along with a fiber-optic probe. The instrument was controlled with OPUS Version 5.0 (Ettlingen, Germany). Integrating sphere specimen vials were placed in the auto-sampler and measured in sequence. Spectra were collected through the base of transparent glass vial and 10 scans (~7 s accumulation times) with a spectral resolution of 8 cm^{-1} in the range of 1100–2500 nm using the reflectance mode. Individual sample vials were rotated between triplicate scans to ensure representative spectra. Triplicate scans were averaged to obtain one spectrum for each sample.

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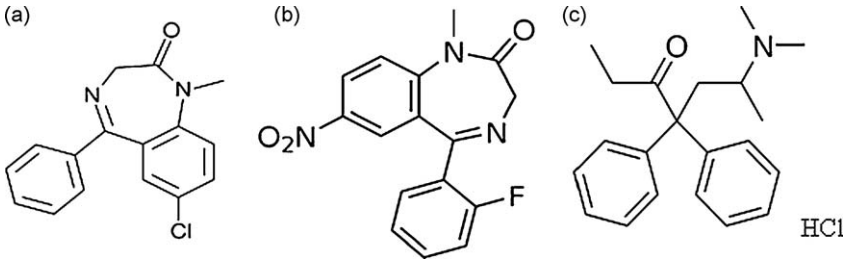

Fig. 1. The chemical structures of diazepam (a), flunitrazepam (b) and methadone HCl (c).

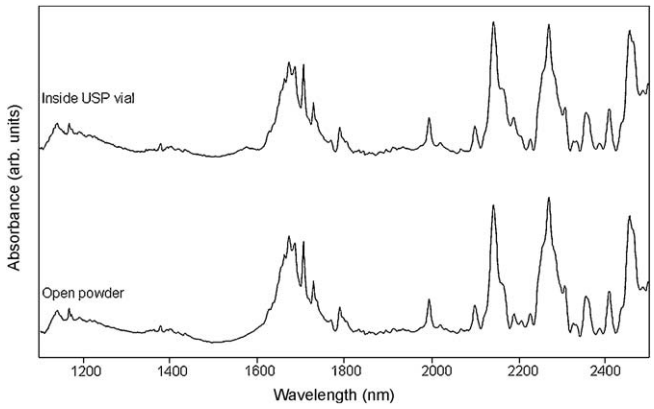

Fig. 2. Baseline corrected NIR spectra of diazepam obtained inside a USP vial and as an open powder (1100–2500 nm).

2.3. Spectral preprocessing

All NIR spectra were exported to the Galactic* SPC format using GRAMS AI (Version 8.0, Thermo Electron Corp, Waltham, MA, USA). The raw spectra suffered from a marked scattering effect observed as a baseline shift as a result of varying shape of the sample material (assessed visually from the powdered samples). In order to best preserve the original features of the NIR spectra and thus allow visual inspection, baseline correction was performed using the GRAMS AI package.

3. Results and discussion

3.1. Non-invasive in situ identification of diazepam, flunitrazepam and methadone HCl

Common glasses (borosilicate, soda, etc.) are virtually transparent to NIR radiation [15] and powdered samples may be measured in glass sample bottles using the reflectance mode.

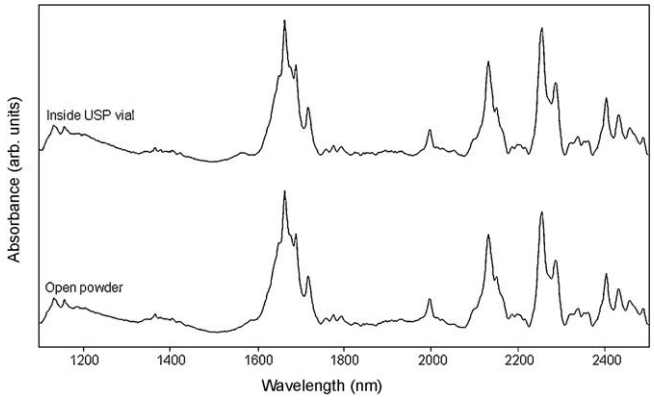

Fig. 3. Baseline corrected NIR spectra of flunitrazepam obtained inside a USP vial and as an open powder (1100–2500 nm).

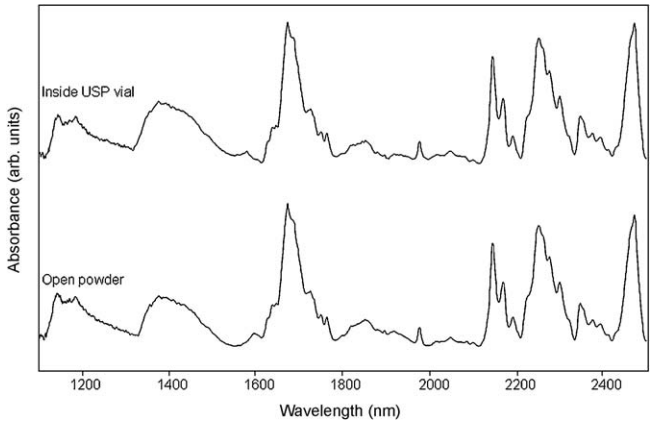

Fig. 4. Baseline corrected NIR spectra of methadone HCl obtained inside a USP vial and as an open powder (1100–2500 nm).

The NIR spectra of the studied drugs over the wavelength range of 1100–2500 nm are shown in Figs. 2–4 as open powders and inside USP vials. It should be noted that the recorded NIR spectra inside vials are almost the same as those obtained as open powders.

NIR spectral wavelengths, nm and proposed assignments for the drugs under study are presented in Table 1.

From the NIR spectroscopic analysis carried out in the present work, it is observed that the NIR spectrum of flunitrazepam is much richer than the NIR spectra of diazepam and methadone HCl with more than 40 well resolved peaks being identified (Table 1). This is due to the anharmonicity of the molecular vibrations in the NIR region which allow overtone absorptions. Thus, a particular vibration can show several absorption characteristics in the NIR spectrum [17].

Band assignment of solid-state NIR spectra, in general, is difficult to carry out and is associated with high ambiguity,

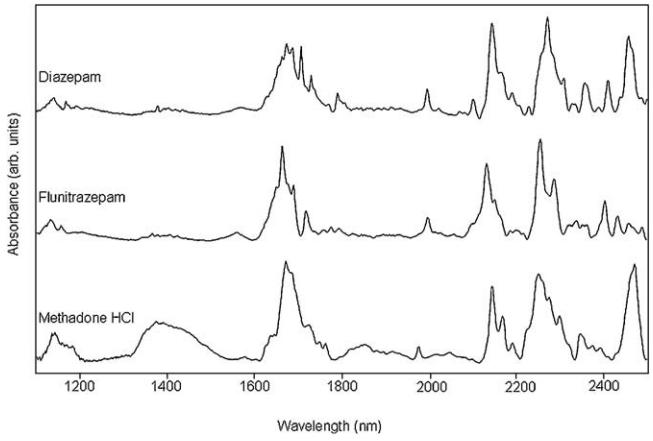

Fig. 5. Baseline corrected NIR spectra of diazepam, flunitrazepam and methadone HCl obtained inside USP vials (1100–2500 nm).