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Near-infrared methods for the identification of tablets in clinical trial supplies*

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Abstract: Near-infrared reflectance analysis (NIR) methods have been developed for the confirmation of the identity of blister-packed tablets for clinical trial supplies. Three approaches are described: (1) presentation of single exposed tablets from blisters directly to the optical window; (2) presentation of unopened opaque blister-packed tablets directly to the optical window of the NIR instrument; and (3) use of a fibre-optic accessory to examine tablets through unopened opaque blister packs. For clinical purposes, all tablets in this trial were manufactured to match the appearance of one another. Tablets containing four strengths of an experimental drug (2, 5, 10 and 20% w/w of the active), a marketed product as a clinical comparator (80% w/w of the active), and a placebo were investigated. The NIR methods were developed by chemometrically building a library with second derivative spectra for each tablet type. Library validation and test data are presented along with a comparison of the three sample presentation techniques. The scope and limitation of each sample presentation technique are discussed.

Keywords: *Near-infrared reflectance analysis (NIRA); identification test; clinical trial materials; noninvasive.*

Introduction

In a clinical trial such as a pharmacokinetic study, dosing each subject with the correct clinical trial material (i.e. active, placebo, or clinical comparator tablet) at the right time to obtain a certain blood level of drug is critical. In some clinical trials, materials may be packaged in blister packs with some cells containing active, and the remainder containing placebo to be taken at specific times. Also, some other blister packs in the same clinical trial may contain only clinical comparator tablets. Because these studies depend on the subject being dosed with the correct tablet at the correct time, identification tests to ensure that the clinical trial materials have been correctly packed are needed.

Near-infrared reflectance analysis (NIRA) has been used to identify pharmaceutical raw materials [1–8] and dosage forms [9–11]. In this work, NIRA was used to develop identification tests to distinguish between tablets containing several strengths of active, a placebo tablet, and a clinical comparator. Three forms of sample presentations to an NIRA instrument were used. One approach was to expose naked (tablets removed from the blister packs) tablets to the NIRA instrument via a direct presentation to the spectrometer window. The second approach was similar to the first in presentation except that the tablet spectra were measured *through the blister pack plastic*. The third approach was to measure the tablet spectra *through the blister pack plastic* with a fibre-optic probe. In the last two cases, the tablet spectra were obtained noninvasively. The merits and drawbacks of these approaches will be demonstrated and discussed.

Experimental

Samples

The tablets used in this work were manufactured to resemble one another regardless of potency or composition. The tablets were manufactured to contain 2, 5, 10 or 20% of an experimental drug, 80% of a marketed drug as a clinical comparator, or to be a matching placebo. The tablets were packaged in five-

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celled blister packs manufactured with white opaque plastic on one side and aluminum foil on the other.

Instrumentation

All spectra were measured with an NIRS Systems Model 6500 near-infrared reflectance spectrometer configured with the aperture slit facing upward. All sample presentation attachments to the spectrometer are commercially available from the spectrometer manufacturer.

Sample presentations

For the window presentation, a horizontal set-up module (HSM) with a detector was attached to the spectrometer. Special templates were used to position the naked tablets and the tablets in the blister pack cells on the window of the HSM. After a zero-absorbance reference spectrum of a ceramic plate was obtained, each tablet spectrum was measured by an automatic average of 32 scans.

For the fibre-optic presentation, a fibre-optic bundle was attached at one end to the spectrometer and the other end was used to collect the spectra of the samples. A zero-absorbance reference spectrum was obtained from an automatic average of 50 scans by inserting the fibre-optic probe (FOP) end into a holder containing a ceramic reflective target disk. The FOP was then attached to a modified arbor press, hereafter referred to as the FOP press, which was used to centre each tablet cell in the blister pack under the FOP (see Fig. 1). Each tablet spectrum was obtained as an automatic average of 50 scans.

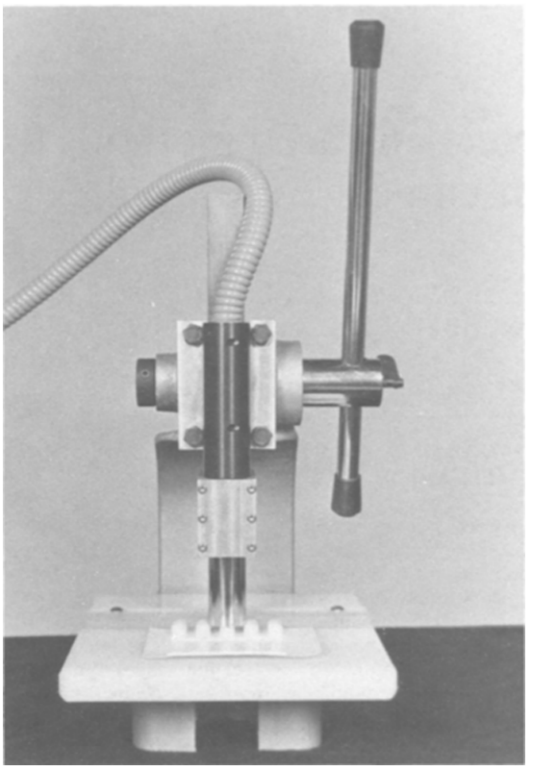

Figure 1
Photograph of the fibre-optic probe positioned on a blister pack tablet cell while being attached to the fibre-optic probe press.

Data processing

The spectra collected for the libraries were mathematically transformed to the second derivative using the system software. Each second derivative spectral library was processed to determine the suitability of the library to perform qualitative analysis by spectral matching. This 'validation' was performed without use of the principal component utility in the NIRA software.

Modes of identification

In the library verification software, the identification tests may be performed as 'identification by correlation' or 'identification by distance'. To perform the 'identification by correlation', the NIRA software computes the correlation coefficient between the unknown spectrum and the average spectrum for each tablet type in the library [12]. A threshold correlation coefficient of 0.85 was used for this work.

In the 'identification by distance' mode, the software first computes a standard deviation value from averaging the spectra for each tablet type [13]. The software performs the identification by computing the maximum distance between the unknown spectrum and the average spectrum for each tablet type in the library in units of standard deviation. The threshold limit is six standard deviations.

Both modes of identification were used to 'validate' and test all spectra in this investigation.

Chemical testing

The identity of each tablet, whether used to create or to test the spectral library, was confirmed using the appropriate wet chemical method for that tablet.

Results and Discussion

Window presentation of the naked tablets

Tablets containing 2, 5, 10 and 20% w/w of an experimental drug, placebo tablets, and clinical comparator tablets were removed from their blister packs and placed on the NIRA instrument using the HSM for the window presentation. Spectra were measured from 400 to 2500 nm. In Fig. 2, plots of the second derivative NIRA spectra for the tablets containing 5, 10 and 20% w/w of an experimental drug, and placebo tablets are shown in the 1466–1480 nm region. The spectra of the tablets containing 2% w/w of experimental drug were virtually indistinguishable from the placebo tablet spectra and hence, were not used.

In this region of the naked tablet spectra, the three strengths of tablets, the placebo, the clinical comparator tablets can be visibly differentiated. However, this ability to differentiate the tablets must be accomplished by the software system to be of practical use. A spectral library built upon these data was then tested with the computer software against the individual spectra in the library to ensure that the library was suitable for performing identification tests. The spectral library passed this internal test and hence, was found to be suitable for performing identification tests on tablets with the potencies stated above.

An external evaluation of this spectral library was then performed using the NIRA identification software by testing spectra collected from naked tablets not included in the library. The spectra from the tablets containing 5, 10 and 20% w/w of the experimental drug, placebo tablets, and clinical comparator tablets were identified correctly in every case. From these results, it was determined that this spectral library was suitable for identifying only tablets containing 5, 10 and 20% w/w of the experimental drug, placebo tablets, and clinical comparator tablets as naked tablets.

Window presentation of the blister-packed tablets

NIRA spectra of blister-packed tablets with different potencies (5, 10 and 20% w/w of experimental drug), placebo tablets, and clinical comparator tablets were measured noninvasively through the blister pack plastic over the 400–2500 nm region using the same window presentation as that for the naked tablets. In Fig. 3, second derivative tablet spectra in the 1466–1480 nm region are plotted with the exception of the clinical comparator

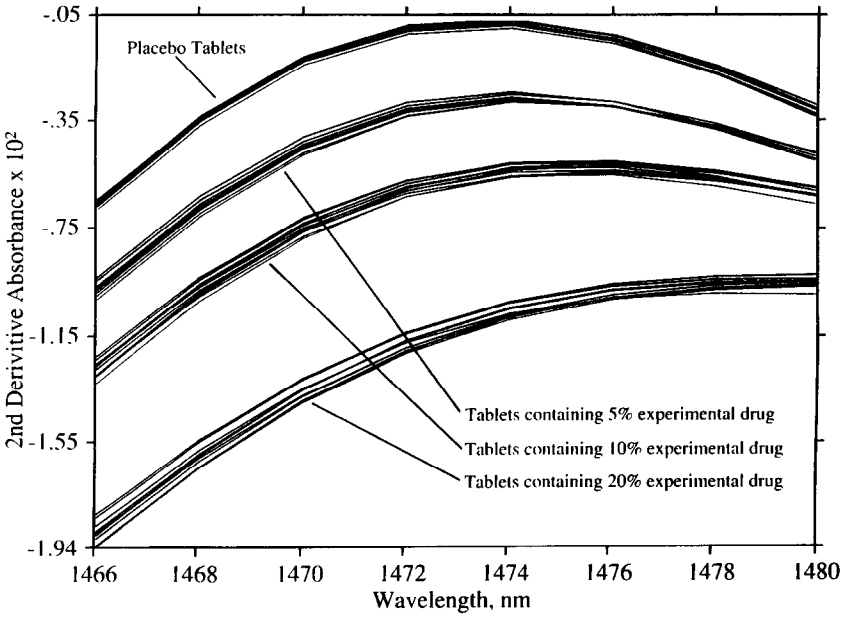

Figure 2
Pertinent region of the second derivative NIRA spectra for tablets containing 5, 10 and 20% w/w experimental drug and placebo tablets. The fundamental spectra of the naked tablets were obtained using the window presentation with the horizontal set-up module.

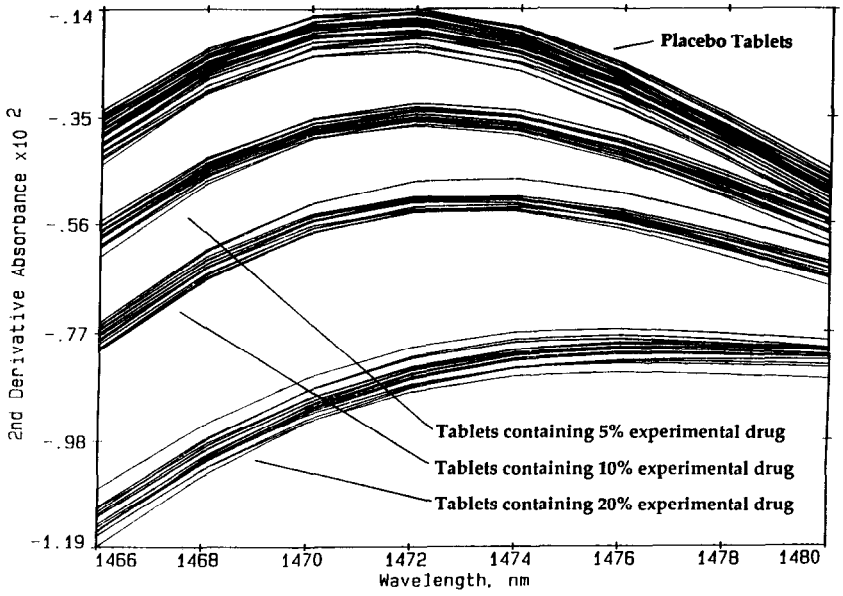

Figure 3
Pertinent region of the second derivative NIRA spectra for tablets containing 5, 10 and 20% w/w experimental drug and placebo tablets. The fundamental spectra of the blister-packed tablet were obtained using the window presentation with the horizontal set-up module.

tablets, which were easily differentiable from the other second derivative tablet spectra.

Again, differences between the three different potencies and the placebo can easily be seen in these spectra. The spectral library built from these spectra was found to be suitable for identifying the blister-packed tablets mentioned above in the window presentation mode by both correlation and distance. Upon testing the library with blister-packed tablets not included in the spectral library, all but the tablets containing 5% w/w of experimental drug could be reliably identified by both correlation and distance. Thus, this spectral library was found to be suitable for identifying only tablets containing 10 and 20% w/w of the experimental drug, placebo tablets, and clinical comparator tablets in this blister pack material.

Fibre-optic presentation of the blister-packed tablets

In the fibre-optic presentation mode, NIRA spectra of blister-packed tablets with different potencies (5, 10 and 20% w/w of the experiment drug), placebo tablets, and clinical comparator tablets were measured noninvasively through the blister pack plastic from 1100 to 2500 nm. The spectra of the tablets containing 5% w/w experimental drug could not reliably be distinguished from those of the placebo tablets. The pertinent portion of the other second derivative tablet spectra (1466–1480 nm) is plotted in Fig. 4.

The differences in the second derivative absorbances for the various spectra facilitate the discrimination between the two experimental drug potencies, the placebo, and the clinical comparator. A spectral library built from these spectra was found to be suitable for identifying blister-packed tablets mentioned above using the FOP by both correlation and distance. Upon testing the library with tablets from blister cards not included in the spectral library, all tablets containing 10 or 20% w/w of experimental drug, the placebo tablets, and the clinical comparator tablets could be reliably identified by both correlation and distance. Thus, this spectral library was found to be suitable for identifying only those tablets containing 10 and 20% w/w of the experimental drug, placebo tablets, and clinical comparator tablets in this blister pack material using a FOP.

Comparison of the presentation modes

All sample presentation methods could rapidly (less than 1 min per tablet) and reliably identify tablets containing 10 and 20% of experimental drug, the placebo tablets, and the clinical comparator tablets. The naked tablet window presentation could also identify tablets

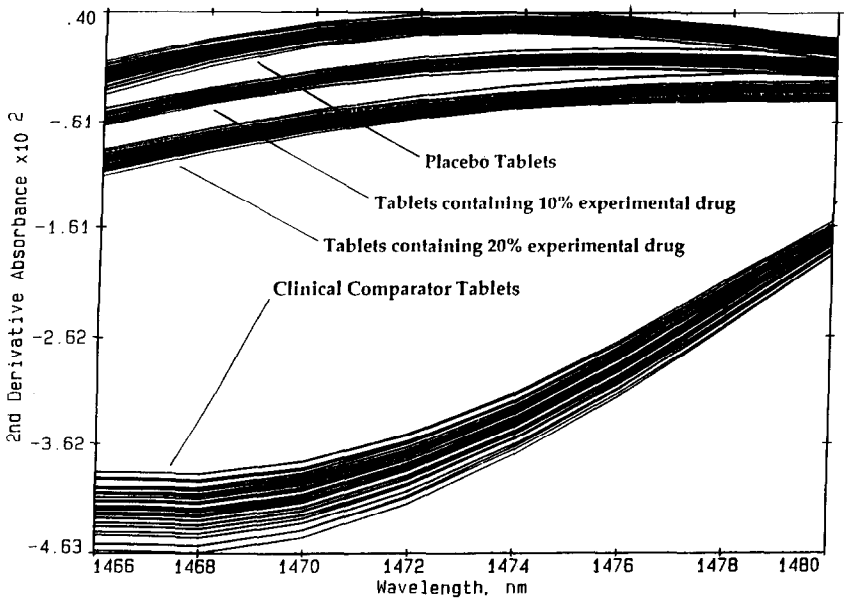

Figure 4
Pertinent region of the second derivative NIRA spectra for tablets containing 10 and 20% w/w experimental drug, placebo tablets and clinical comparator tablets. The fundamental spectra of the blister-packed tablets were obtained using the fibre-optic probe attached to the fibre-optic probe press.

containing 5% of experimental drug in addition to the ones stated above, presumably because these measurements were not made through blister pack plastic. However, this tablet presentation mode is inconvenient to use because it requires tablet removal from the blister packs to perform a measurement.

The two blister-packed presentations maintained the integrity of the blister packs as the spectral measurements were noninvasive, and little difference was seen between these sample presentation methods in terms of ability to identify tablets. The fibre-optic presentation, in conjunction with the FOP press, was found to be quicker and is more amenable to automation. In addition, the FOP press eliminated the need for an analyst to hold the FOP on the tablet-filled cell.

Conclusions

Rapid (result obtained in less than 1 min per tablet), noninvasive identification tests for tablets containing various potencies of an experimental drug, placebo tablets, and clinical comparator tablets were developed using several sample presentation methods to an NIRA spectrometer. While a wider range of potencies for the tablets containing the experimental drug could be identified using the naked tablet window presentation, this mode of presentation was found to be more inconvenient than those in the blister pack because tablet removal is required. The FOP was found to be the most convenient mode of tablet presentation to use with the FOP press, although it was less sensitive than the naked tablet window presentation.

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