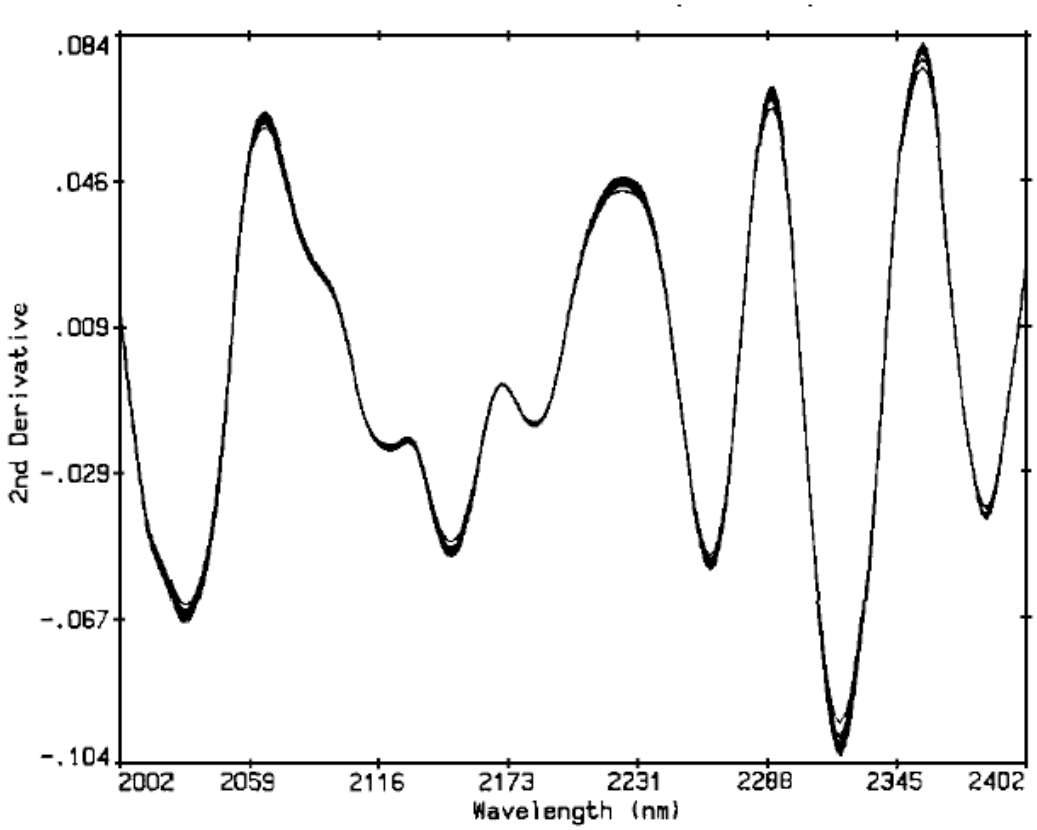
Near-Infrared Spectroscopy Application Note NIR–1

Determination of active ingredients in solid (pharmaceutical) dosage forms utilizing solid-state standard additions



Two of the leading pain remedies, apirin and acetaminophen, are compared with generic samples for content uniformity testing using near-infrared spectroscopy (NIRS). The method of standard addition is used for quantification. To reduce most of the effects that stem from particle size and packing differences, second derivative spectra are used.

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Method description

Introduction

Often an analyst is called upon to determine an analyte where the matrix cannot be eliminated or exactly reproduced in a blank sample. This is often the case in environmental, chemical effluent, or clinical samples. For years, chemists have been dealing with these samples in the techniques of atomic absorption spectroscopy (AAS) and ion-selective electrodes (ISE). The method of choice, in many cases, is the method of standard additions.

In brief, the standard additions technique uses the unknown as a constant matrix wherein controlled amounts of the analyte are added. The total spectrum is now considered and a calibration curve is developed.

The United States Pharmacopeia (USP) and the Food and Drug Administration (FDA) have limits for the content of both prescription and over-the-counter products. Within the shelf life posted upon the bottle, the individual tablets should contain between 90 and 110% of the label claim. Usually, internal specifications are tighter to allow for normal loss of potency during shelf life. Often, these are as tight as 98 to 102% for expensive, volatile (nitroglycerine), or less stable materials.

The actual limits of release can be the major factor in cost. To attain tight limits, extra formulation and pilot plant time must be invested. The actual manufacturing of the product becomes more expensive because of tighter in-process and quality control testing of the finished product. More rejected batches mean higher production costs. Fewer restraints on limits can lower costs.

The near-infrared (NIR) region of the electromagnetic spectrum is from around 700 nm to 2500 nm, between the end of the visible to the start of the traditional infrared. The spectrum consists of overtones and combination bands originating in the mid-range IR. The lower extinction coefficients allow for direct diffuse reflectance measurements without having to first dilute the sample.

Experimental

All work was performed on a FOSS NIRSystems' Model 6500 NIR spectrophotometer equipped with a remote reflectance fiber optic probe. Since this instrument is not available anymore, the NIRS XDS RapidContent Analyzer is recommended. Various sample holders were used: a commercial sample cup, a single tablet holder and a Teflon mini-cup.

All pharmaceutical preparations were purchased over-the-counter: generic aspirin and acetaminophen tablets were supermarket store brands. Tylenol and Bayer products were selected for use as the proprietary products because of ease of purchase and name brand recognition. Pure substances were USP grade and analyzed by a commercial QC department for compliance with USP specifications.

An average weight of each dosage form was ascertained. Ten tablets were weighed with an amount of active representing between 25 and 200% of the amount in the tablets themselves. These mixtures were finely ground and scanned in the spectrophotometer. Three sample holders were used: the larger «closed cup» where far more than one tablet weight was used, the single tablet holder, and the mini-cup with its 1 mm x 10 mm dimple. The «as is» ground tablets were considered to have 100% of the labeled amount of drug present. The following mixtures were then labeled 125%, 150%, etc.

For each experiment, a multiple linear regression calibration was calculated using the second derivative spectra. The second derivative has the ability to cancel most of the effects of particle size and packing differences in the samples. These equations were then used to predict percentages in individual tablets.

Results and discussion

Since aspirin (acetylsalicylic acid, ASA) and acetaminophen (N-acetyl-para-aminophenol, APAP) are two of the leading pain remedies, two leading brands were compared with generic samples for content uniformity testing. Figure 1 shows pure aspirin with an ASA tablet and Figure 2 shows acetaminophen and an APAP tablet.

While it required care to position individual tablets, the variations between repeat scans (and positions, see Figure 3) are much smaller than between different tablets (Figure 4). When the closed cup is used, the single tablet does not completely fill the sample area. Using the single tablet holder and, where necessary, adjusting for any bias, good results are achieved. For the best results, the mini-cup was used. The standard and single tablet surface areas and depths were most easily reproduced. Two, three, and even four component dosage forms are amenable to this approach.

Table 1 lists the results of a batch of 325 mg aspirin tablets (store brand), while Table 2 contains the results of the «name» brand. Table 3 and Table 4 list the results from the analysis of 500 mg APAP tablets, generic and «name» brands, respectively. The procedure gives results comparable to HPLC. In the USP, the reproducibility limit for duplicate injections of a solution HPLC is only 2%. The above described technique was shown to rival that precision.

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Method description

Figure 1
ASPIRIN TAB vs PURE ASPIRIN

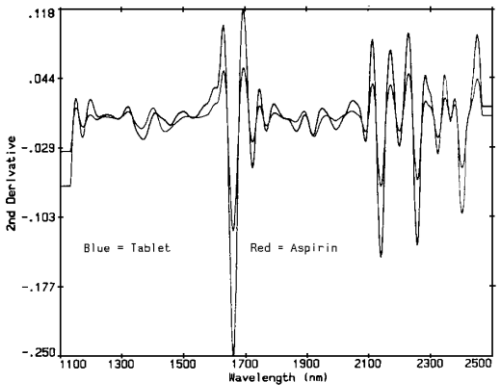

Figure 2
APAP TABLET vs PURE APAP

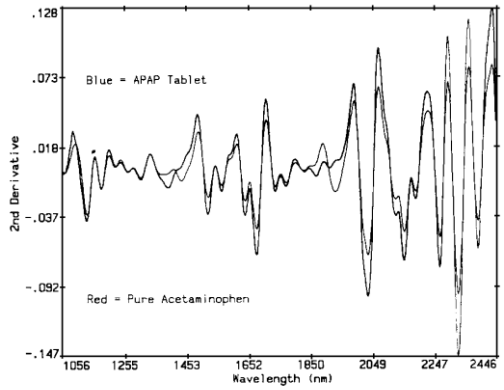

Figure 3
APAP 500mg Tab; Re-Runs

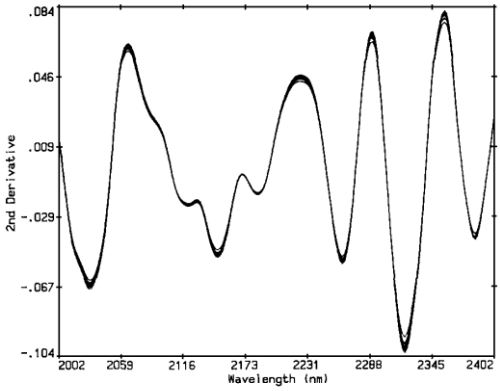

Figure 4
APAP 500 mg GENERIC TABLETS

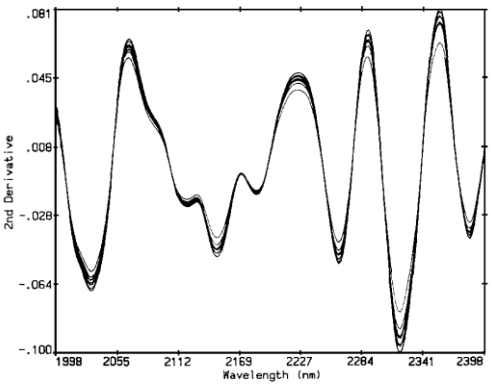

Table 1: Generic aspirin 325 mg, content uniformity

Tablet #	*% Found*
1	96.98
2	97.46
3	103.61
4	99.55
5	99.29
6	102.59
7	96.66
8	101.91
9	104.13
10	106.09
11	102.54
12	91.62
13	99.94
14	98.67
15	108.66
16	108.96
17	98.94
18	99.48

Average = 100.95%

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Method description

Table 2: Bayer 325 mg, content uniformity

Tablet #	*% Found*
1	98.98
2	99.46
3	101.61
4	99.55
5	99.29
6	101.59
7	99.66
8	101.91
9	99.13
10	99.09
11	98.54
12	101.63
13	100.94
14	100.67
15	101.67
16	99.96
17	99.94
18	100.52

Average = 100.23%

Table 3: Generic acetaminophen 500 mg tablets, content uniformity

Tablet #	*% Found*
1	102.23
2	103.48
3	103.27
4	99.74
5	98.46
6	97.62
7	100.24
8	101.77
9	98.69
10	99.66
11	98.39
12	103.70
13	102.47
14	100.19
15	105.53
16	94.98
17	99.10
18	97.59
19	98.25
20	100.82

Average = 100.15%

Table 4: Tylenol 500 mg, content uniformity

Tablet #	*% Found*
1	101.83
2	103.48
3	102.77
4	98.74
5	99.46
6	99.11
7	99.84
8	101.77
9	99.59
10	99.67
11	98.79
12	101.70
13	101.47
14	100.19
15	101.54
16	99.98
17	99.10
18	99.60
19	99.75
20	100.82

Average = 100.46%

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